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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Reviewer Name(s)	Arthur Simone, MD, PhD
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Established Name	Neostigmine Methylsulfate Injection, USP
(Proposed) Trade Name	(b) (4)
Therapeutic Class	Cholinesterase Inhibitor
Applicant	Éclat Pharmaceuticals LLC
Formulation(s)	Injectable solution
Dosing Regimen	30-70 mcg/kg intravenously
Indication(s)	Reversal of neuromuscular blocking agents after surgery
Intended Population(s)	Patients requiring reversal of paralysis induced with nondepolarizing neuromuscular blocking agents

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

An approval action is recommended for this application provided the Chemistry, Manufacturing and Controls review team upon completion of their evaluation do not identify any issues that could potentially affect patient safety and an agreement can be reached between the Agency and the Applicant on the labeling of the product.

1.2 Risk Benefit Assessment

The benefits of neostigmine are predicated on its ability to reliably and substantially hasten the recovery from paralysis induced by nondepolarizing neuromuscular blocking agents. Specifically, recovery from neuromuscular blockade may reduce anesthetic and surgical risks to patients by allowing earlier:

- cessation of exposure to anesthetic agents required to maintain unconsciousness
- return of spontaneous ventilation and maintenance of a patent airway, permitting discontinuation of mechanical ventilation and extubation of the trachea
- evaluation of neurological function, e.g., assess patients' ability to move extremities, peripheral sensation, speech and cognitive function, following surgical procedures that can affect the nervous system, e.g., spine surgery, carotid endarterectomy

The extent of the benefit depends on an individual's medical condition, surgical procedure, type of anesthesia and the difference in recovery time between neostigmine-induced reversal and spontaneous recovery. The difference in recovery times has been demonstrated to range from 10 minutes to 1 hour depending on a number of factors.

The risks associated with neostigmine include relatively rare allergic reactions (anaphylaxis has been reported) and, more commonly, adverse events related to the drug's mechanism of action, which affects cholinergic receptors outside the neuromuscular junction as well as within it. The use of anticholinergic agents, in particular, glycopyrrolate and atropine, have been demonstrated to reduce or prevent most of the adverse events associated the anticholinesterase activity of neostigmine.

Indeed, the standard of care in anesthesia practice is to co-administer one of these agents with neostigmine.

The extent to which the benefits of neostigmine are realized in clinical practice has not been demonstrated in any clinical study reported in the literature. Therefore, these benefits need to be considered as "potential" in a benefit-risk analysis. However, the risks associated with neostigmine have been well documented; many of them can be prevented, mitigated, or treated with administration of anticholinergic agents. Furthermore, they tend to occur soon after the administration of neostigmine and, therefore, in clinical settings where they are easily monitored and effectively treated. Based on these considerations, the benefits of neostigmine are considered to outweigh the risks.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Based on the safety information reported in the literature that was provided by the Applicant, the review and analysis by the Applicant and the Office of Surveillance and Epidemiology of the neostigmine reports in the AERS database, and the long history of (unapproved) neostigmine use in this country, there is no indication that Postmarket Risk Evaluation and Mitigation Strategies are needed for this application.

1.4 Recommendations for Postmarket Requirements and Commitments

The literature provides adequate evidence of efficacy, safety and general dosing requirements for the entire patient population likely to need the drug in the clinical setting. Therefore, there are no recommendations for clinical postmarketing requirements or commitments that should be incorporated into an approval action.

2 Introduction and Regulatory Background

2.1 Product Information

First synthesized in 1931, neostigmine is an anticholinesterase agent that competes with acetylcholine for binding to acetylcholinesterase and thereby inhibits the hydrolysis of acetylcholine at sites of cholinergic transmission. At neuromuscular junctions, the neostigmine-induced reduction in the breakdown of acetylcholine facilitates neuromuscular transmission. Clinically, this effect of neostigmine has been used for the treatment or prevention of post-operative non-obstructive abdominal distention, i.e., adynamic ileus, the symptomatic treatment of myasthenia gravis and the reversal of nondepolarizing neuromuscular blocking agents (NMBAs).

Neostigmine was first approved by the FDA in 1939 as Prostigmin Ophthalmic Solution (NDA 000654) for the treatment of glaucoma. The NDA was withdrawn in 1995 when the Applicant ceased marketing. In 1940 three additional neostigmine NDAs were approved:

1. Prostigmin and Atropine for injection (NDA 002449) for the treatment of adynamic ileus. This NDA was discontinued in 1954 for undocumented reasons.
2. Morphine-Prostigmin tablets and injectable solution (NDA 00574), which was dormant since approval and discontinued in 1948.
3. Prostigmin and Pantopan injection (NDA002575) for analgesia; however, it was never marketed and withdrawn in 1972.

(b) (4)

Neostigmine is associated with direct postsynaptic cholinomimetic effects that may be severe enough to warrant treatment with an anticholinergic agent such as atropine or glycopyrrolate. As the neostigmine-induced inhibition of acetylcholinesterase is fully reversible, in contrast to organophosphates, its cholinomimetic effects have limited duration.

The proposed clinical use of neostigmine, i.e., reversal of neuromuscular blockade due to the administration of nondepolarizing blocking agents, is predicated on its pharmacological action. Specifically, nondepolarizing NMBAs induce paralysis by competing with acetylcholine at the postjunctional nicotinic receptors where they prevent changes in ion permeability of the skeletal muscle endplate and thereby prevent depolarization and subsequent contraction. Neostigmine, by inhibition of acetylcholinesterase, increases the amount of acetylcholine at the junction, which can

compete with the NMBA and ultimately restore impulse transmission and skeletal muscle function.

There is a long history of the clinical use reflected by substantial evidence in the literature in the form of case reports, dose-response studies, and controlled clinical studies that support the proposed indication of neostigmine. Neostigmine is also specifically mentioned for the proposed use in the approved labels of non-depolarizing muscle relaxants, including pancuronium bromide, vecuronium bromide, rocuronium bromide (Zemuron) and cisatracurium besylate (Nimbex).

Neostigmine has also been used as a primary efficacy and safety comparator to sugammadex in recently published, placebo- and active-controlled, randomized clinical studies submitted to the FDA as part of the NDA for sugammadex.

2.2 Currently Available Treatments for Proposed Indications

Edrophonium chloride (Enlon; ANDA 088873) and edrophonium chloride with atropine sulfate (Enlon-Plus; NDA 019678) contain the cholinesterase inhibitor edrophonium. They, like neostigmine, function at the neuromuscular junction sites of cholinergic transmission and reverse the effects of drug-induced neuromuscular blockade. They are approved for the following indications, quoted from their respective labels:

> ENLON is recommended for the differential diagnosis of myasthenia gravis and as an adjunct in the evaluation of treatment requirements in this disease. It may also be used for evaluating emergency treatment in myasthenic crises. Because of its brief duration of action, it is not recommended for maintenance therapy in myasthenia gravis.
>
> ENLON is also useful whenever a curare antagonist is needed to reverse the neuromuscular block produced by curare, tubocurarine, gallamine triethiodide or dimethyl-tubocurarine. It is not effective against decamethonium bromide and succinylcholine chloride. It may be used adjunctively in the treatment of respiratory depression caused by curare overdosage.
>
> ENLON-PLUS (edrophonium chloride, USP and atropine sulfate, USP) Injection is recommended as a reversal agent or antagonist of nondepolarizing neuromuscular blocking agents. It is not effective against depolarizing neuromuscular blocking agents. It is

also useful if used adjunctively in the treatment of respiratory depression caused by curare overdosage.

According to the product labels, intravenous edrophonium chloride, in doses of 0.5 to 1.0 mg/kg, achieves the maximum antagonism of nondepolarizing muscle relaxants within 1.2 minutes and has a sustained effect for 70 minutes.

Intravenous atropine sulfate, a parasympatholytic (anticholinergic) drug, is combined with edrophonium in Enlon-Plus to counteract the effects of edrophonium at the sites of muscarinic cholinergic transmission occurring at the parasympathetic, postganglionic receptors of the autonomic nervous system. Anticholinesterase activity at these sites is associated with bradycardia, bronchoconstriction, increased secretions, and other parasympathomimetic side effects, which are reduced or prevented by the inclusion of atropine sulfate in the drug product. Atropine sulfate has an immediate effect on heart rate which reaches a peak in 2 to 16 minutes following intravenous administration and lasts 170 minutes after an average 0.02 mg/kg dose.

Pyridostigmine is another anticholinesterase product. It was first approved as Mestinon (NDA 009830) in 1955, and later approved as Regonol (NDA 017398). Mestinon is used most often in the treatment of myasthenia gravis. Regonol, however, is indicated "as a reversal agent or antagonist to the neuromuscular blocking effects of nondepolarizing muscle relaxants."

2.3 Availability of Proposed Active Ingredient in the United States

Neostigmine methylsulfate, although unapproved by FDA, is currently manufactured and marketed in the United States. The active ingredients are, therefore, expected to be readily available into the near future.

2.4 Important Safety Issues with Consideration to Related Drugs

The edrophonium product labels contain the following warnings, some of which may be relevant to neostigmine methylsulfate:

1. It should be used with caution in patients with bronchial asthma or cardiac arrhythmias.
2. Cardiac arrest has been reported to occur in digitalized patients as well as in jaundiced subjects receiving cholinesterase inhibitors.

3. In patients with cardiovascular disease, given anesthesia with narcotic and nitrous oxide without a potent inhalational agent, there is increased risk for clinically significant bradycardia.
4. In patients receiving beta-adrenergic blocking agents there is increased risk for excessive bradycardia from unopposed parasympathetic vagal tone.
5. Isolated instances of respiratory arrest have also been reported following the administration of edrophonium chloride.
6. With drugs of this type, muscarine-like symptoms (nausea, vomiting, diarrhea, sweating, increased bronchial and salivary secretions and bradycardia) often appear with overdosage (cholinergic crisis).
7. An important complication that can arise is obstruction of the airway by bronchial secretions.
8. Overdosage should be managed by:
    - Maintaining adequate respiratory exchange
    - Monitoring cardiac function
    - Treatment with atropine sulfate in doses of 0.4 to 0.5 mg intravenously every 3-10 minutes as needed
    - Instituting appropriate measures to treat shock or convulsions if they occur

The pyridostigmine product labeling contains the following warnings:

1. It is contraindicated for patients with intestinal and urinary obstructions of mechanical type.
2. It should not be used in neonates as it contains benzyl alcohol.
3. It should be used with particular caution in patients with bronchial asthma or cardiac dysrhythmias.
4. Transient bradycardia may occur and be relieved by atropine sulfate. Atropine sulfate should also be used with caution in patients with cardiac dysrhythmias.
5. When large doses of pyridostigmine bromide are administered, as during reversal of muscle relaxants, prior or simultaneous injection of atropine sulfate or an equipotent dose of glycopyrrolate is advisable.
6. Because of the possibility of hypersensitivity in an occasional patient, atropine and antishock medication should always be readily available.
7. When used as an antagonist to nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance, and there should be continuous patient observation. Satisfactory recovery may be judged by adequacy of skeletal muscle tone, respiratory measurements, and by observation of the response to peripheral nerve stimulation. A patent airway should be maintained and manual or mechanical ventilation should be continued until complete recovery of normal respiration is assured.

As an anticholinergic drug, neostigmine has been associated with similar safety issues, and these need to be incorporated into the product's labeling.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Division met with the Applicant on three occasions to discuss issues related to this NDA submission. The meetings were held in 2011 and 2012; meeting packages were submitted to FDA under PIND 111853. The key discussion points for each of the meetings are summarized below.

On June 30, 2011, a Type B meeting was held to discuss issues related to a 505(b)(2) NDA submission. At that meeting, the Applicant clarified that the neostigmine product they intend to market contains phenol as a preservative, (b) (4) Based on this information, the following points were made at the meeting regarding the requirements for an NDA submission and the product's approval:

1. The nonclinical information, in the meeting package, did not appear to be adequate to support an NDA application; however, if a detailed review of the clinical literature did not reveal an unexpected toxicity issue, no further nonclinical studies would be needed.
2. The existing data do not appear to contain adequate information regarding the mutagenic potential and impact on reproductive and developmental toxicity of neostigmine, these studies may be necessary as postmarketing requirements.
3. Any new or novel excipients in the drug product must be adequately qualified for safety.
4. Any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per (ICHQ3A(R2), ICHQ3B(R2)).
5. Impurities that contain a structural alert for genotoxicity or are demonstrated to be genotoxic or carcinogenic must be either reduced to NMT (b) (4) in the drug substance and drug product or adequate safety qualification must be provided.
6. A toxicological evaluation to determine the safe level of exposure to any leachables and extractables needs to be included in the NDA.
7. T_4:T_1 ratios ≥ 0.9 are the most clinically relevant values for the indication sought. Therefore, attention should be focused on the studies reported in the literature which used these values as endpoints to establish efficacy and determine appropriate dosing. The studies evaluating T_4:T_1 ratios of 0.7 as an endpoint could be used to support a finding of efficacy; however, they would not be of much use in establishing appropriate dosing.
8. The characterization of the risk profile for neostigmine should take into consideration the following issues:

- the correlation between dose and adverse events
- the role of atropine and glycopyrrolate and the doses in the mitigation of adverse reactions
- comparison of occurrence of adverse events with placebo or other doses of neostigmine is more informative than simple listings of adverse events noted with the administration of neostigmine
- sugammadex is not an approved product at this time; therefore, safety comparisons with this agent are not meaningful as the Agency has not made a final assessment of its safety profile

If there are gaps in the extent to which the safety profile of neostigmine for the to-be-labeled dose(s), can be characterized by the literature, a small study to provide the needed information may be necessary.

9. The published efficacy data appeared to be of the type that would support the proposed indication. Two points will be especially important in the review process for determining their adequacy:
   - The support provided for the selection of the primary endpoint limits for T_4/T_1, i.e., 0.7 to 0.9.
   - The quality, types and, to a lesser degree, the quantity of the data available, e.g., how the studies were designed to capture adverse events, the doses of neostigmine evaluated, the types and duration of monitoring, demographics of subjects evaluated, and their underlying medical conditions.
10. An important consideration in determining the quality of the data, and thus its adequacy, is the availability of the original protocols and original data from each of the studies. A good-faith effort to obtain this information should be made and documented.
11. It must be verified that the information from the studies cited in the literature is in the public domain or that a right of reference to it has been obtained.
12. An exploration of the AERS data for neostigmine should be performed by the Applicant.
13. Dosing paradigms for co-administration of atropine or glycopyrrolate used in conjunction with neostigmine need to be provided in the NDA, and if neostigmine is to be mixed in the same syringe with either agent, data on physical and chemical compatibility will be needed.

On September 16, 2011, a Type B meeting was held to provide the Applicant with the Agency's input on questions related to the manufacturing, control and stability of neostigmine methylsulfate. The following key points were made at that meeting:

1. The proposed specification of NMT (b) (4) was not acceptable as it appears this compound contains a structural alert for genotoxicity. Therefore, data to show that this chemical does not contain a structural alert for mutagenicity need to be

provided. If it contains a structural alert, the specification needs to be reduced to NMT (b) (4) or adequately qualified via negative results in an in vitro Ames assay. If the compound does not contain a structural alert for genotoxicity, the specification needs to be reduced to NMT (b) (4) or adequate safety qualification needs to be provided.

2. The Applicant noted that the impurity specifications have been provided by the DMF holder and are in the DMF submitted to the Agency. The Division clarified that a letter of authorization (LOA) is needed before it can review the DMF.
3. In addition to other attributes for multidose sterile injections, the total impurities in the drug product specification should be based on batch test data and controlled.
4. To justify the choice of an appropriate sterilization method, it was recommended studies of drug product stability using (b) (4)
5. Based on a presumed maximum daily dose of 5 mg neostigmine, the maximum dose of phenol via the proposed formulation (22.5 mg/5 mL) appears to be higher than any FDA-approved intravenous drug product. Therefore, the safety of the proposed level of phenol must be adequately justified as a new excipient.
6. 12 months stability data should be provided at the time of NDA submission. Expiry dating period will be assessed as per ICH Q1E, based on the real time stability data provided.
7. Leachable and extractable studies for the product are required as part of the NDA submission.
8. Any identified leachable material must be adequately justified for intravenous safety via a toxicological risk assessment.
9. The six months stability data are not sufficient to completely assess trends for primary closure extractables, and it would be ideal if leachable data from the stability studies closer to the requested expiry were provided in order to confirm that there is no increase in leachables with time.
10. If data from shorter term stability assessments demonstrate upward trending of extractables or leachables, it could impact the shelf-life of the product.
11. The safety of the hypotonic drug product solution will need to be justified.

An End-of-Phase 2 meeting was held on May 16, 2012. The following are the key points that were discussed at that meeting:

1. The Applicant confirmed (b) (4) in both humans and animals following both oral and parenteral dosing. (b) (4) (b) (4)

(b) (4) The Division considered this an appropriate justification for the proposed specification provided the Applicant had reduced the lowest levels possible based on their manufacturing capability. The Division also noted that negative results in a standard genetic toxicology study battery would provide definitive data to support the conclusion that the (b) (4) does not represent a genotoxicity safety concern.

2. Genetic toxicology studies for neostigmine will likely be a post-marketing commitment; however, having the data during the review cycle would be useful for addressing any concerns that arise with respect to potential drug substance impurities and drug product degradants.
3. The Applicant provided a rationale for the safety of the level of phenol in their product based (b) (4) Anzemet. The Division noted that (b) (4) the maximum daily exposure to phenol following use of neostigmine (b) (4) of phenol) exceeds that which would be administered via the labeled dose of Anzemet (b) (4) of phenol). Furthermore, there was concern on the Division's part that the Applicant was making reference to an older version of the Anzemet label, and that the current label calls for lower total daily doses, likely, though not explicitly stated in its label, due to concerns related to QT prolongation. Therefore, the Agency's previous finding of safety for Anzemet may be adequate to address the concern for the local tissue toxicity of phenol, but it does not address the concern for the total daily intravenous dose of phenol. The safety of the drug product formulation in terms of local tissue irritation and potential formation of thrombi must be addressed in your NDA, either by reference to existing clinical experience with a comparable drug product, by toxicological data, or by a weight of evidence justification based on literature or other data. The Applicant noted that the specific concentration of phenol was chosen (b) (4) The Division responded that this information would be considered as part of the weight-of-the-evidence risk benefit analysis, but noted that it would be unlikely that the presence of slight irritation would outweigh the benefit of the drug.
4. The Applicant addressed the Division's concerns related to the safety of the hypotonicity of their product by noting that cisatracurium besylate (Nimbex®, NDA 20551) as an FDA-approved product and is a hypotonic solution with a calculated osmolality of approximately 10 mOsmol/L. They noted that the product is administered as a bolus dose of 0.2 mg/kg, which for a 50 kg adult, would result in administration of 5 mL of drug. By contrast, neostigmine at a

maximum dose of 5 mg would result in administration of 5 mL of a 55 mOsmol/L solution, a substantially less hypotonic solution. The Division indicated that this was an acceptable rationale.

5. The Applicant noted there are seven substances that have the potential to leach into the drug product (b) (4) Because the levels of the (b) (4) and (b) (4) are not expected to pose a safety concern, they plan to monitor only for (b) (4) in the planned leachables analysis, and at the time of NDA filing, will provide a justification for these seven extractable substances as well as leachable data related to (b) (4) from the stability analysis at the 6-month time point. Leachable data from the stability analysis at the 12-month time point will be submitted to the NDA during the review cycle. The Division concurred with the proposed approach to safety qualification of the leachables and noted that the shelf life for the drug product will depend upon the stability data submitted in the NDA.

2.6 Other Relevant Background Information

There is no other relevant background information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The information contained in the submission and the access to it were adequate to allow a comprehensive review of safety and efficacy.

3.2 Compliance with Good Clinical Practices

The Applicant neither conducted clinical studies nor obtained original protocols for the studies reported in the literature that provided the clinical evidence of safety and efficacy for this NDA. Therefore, it is not possible to determine the extent to which the data were derived from studies conducted in compliance with Good Clinical Practices regulations.

3.3 Financial Disclosures

No clinical studies were conducted by the Applicant in support of this NDA. Therefore, financial disclosures were neither required nor submitted.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

The Chemistry, Manufacturing, and Controls (CMC) review was performed by Drs. Arthur Shaw, Olen Stephens, and Prasad Peri. They have recommended that the application be approved.

4.2 Clinical Microbiology

Neostigmine is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required and not submitted for this application.

4.3 Nonclinical Pharmacology/Toxicology

The Pharmacology Toxicology review was conducted by Drs. Huiqing Hao and R. Daniel Mellon. The information below is taken from their joint review in which they note that no new toxicology studies for neostigmine were required to support approval of this NDA due to its long history of clinical use. The pharmacology toxicology review, therefore, focused on the safety of the drug substance impurities, drug product degradants, the container closure system, and the drug product excipients.

The team indicated that adequate data were available to support the safety of the container closure system, the drug substance impurity specifications, and the drug product degradant specifications. They noted that, regarding excipient safety qualification, the total daily dose of the preservative phenol in this drug product formulation exceeds that of previously approved drug products administered as a single bolus injection. They defer to the clinical team to determine if adequate clinical experience exists to justify the safety of the phenol levels in this product.

Reviewer's Comments
Neostigmine methylsulfate is currently marketed, without FDA approval, in the United States by APP Pharmaceuticals/Fresenius Kabi. In their label, dated April 2008 and the Material Safety Data Sheet (MSDS) both concentrations of the product (0.5 mg/mL and 1 mg/mL) are listed as containing 4.5 mg/mL of phenol. This formulation has been

marketed for > 20 years. In contrast, two other marketers of the product in the United States, West-Ward Pharmaceuticals (formerly Baxter Healthcare Corporation's US Multi Source Injectables) and American Regent, sell formulations that do not contain phenol.

The Drug Utilization Data Analysis Team in the Division of Epidemiology II within the Office of Surveillance and Epidemiology provided U.S. sales data for each of these manufacturers from 2008 through 2012. During that time period, the APP formulation (b) (4) (b) (4) however, during that period, a total of (b) (4) were sold in this country with each unit containing 10 multidose vials. Over a 20 year period, this would translate to more than (b) (4) vials in the U.S. alone. Based on this information, if any safety issues exist, related to the bolus administration of the amounts of phenol in the product, they would likely have been apparent by this point in time. It should also be noted that the safety concern is related to the bolus administration of phenol as the same dose is contained in approved products that are administered intravenously but by infusion rather than as a bolus. Therefore, adequate clinical experience does exist to justify the safety of the phenol levels in this neostigmine product.

The team also note that the Applicant was informed that the standard battery of genetic toxicology studies and reproductive and developmental toxicology studies would be required to be completed post-marketing unless adequate data could be identified in the literature to inform labeling. The Applicant has submitted sufficient information to render a recommendation for approval; however, the Pharmacology-Toxicology team considers the data in the published literature inadequate to inform labeling. Therefore, they recommend that these studies be conducted as postmarketing requirements, if the product is approved.

4.4 Clinical Pharmacology

The information in the following subsections is taken directly from the Clinical Pharmacology review by Drs. Naraharisetti and Xu. In the review, they conclude that, "from a clinical pharmacology perspective, the information submitted in the NDA is acceptable, pending agreement on the labeling language." They have made recommendations for the product's labeling which are incorporated into the clinical recommendations in section 9.2 below. The team has no recommendations for post-marketing commitments.

4.4.1 Mechanism of Action

Neostigmine inhibits the hydrolysis of acetylcholine by competing with acetylcholine for binding to acetylcholinesterase at sites of cholinergic transmission. By reducing the

breakdown of acetylcholine, neuromuscular transmission is facilitated. Neostigmine also has direct postsynaptic cholinomimetic effects, which can be managed clinically by the co-administration of atropine or glycopyrrolate. Neostigmine inhibition of acetylcholinesterase is fully reversible.

4.4.2 Pharmacodynamics

The Clinical Pharmacology review did not comment on the pharmacodynamics of neostigmine. Neostigmine's onset and duration of action, relative to the duration of action of the neuromuscular blocking agent, are described and discussed in section 6 below.

4.4.3 Pharmacokinetics

Based on the current clinical pharmacology standards, none of the data in the submitted literature were considered adequate to definitively characterize the pharmacokinetics of neostigmine and were not optimal for informing the label in this regard. However, Clinical Pharmacology team notes that the following information is consistent among studies in the literature, regardless of the analytical methods used, and therefore, may suffice for labeling the product.

1. Neostigmine's half life ranged from 24 to 113 minutes after a single intravenous administration.
2. No information was submitted to characterize neostigmine's pharmacokinetics by race or gender.
3. The pharmacokinetic interaction between neostigmine and other drugs has not been studied.
4. The pharmacokinetics of neostigmine in patients with hepatic impairment has not been studied. Neostigmine is metabolized by microsomal enzymes in the liver; therefore, the Clinical Pharmacology team recommends that it be used with caution when it is administered with other drugs which may alter the activity of metabolizing enzymes or transporters.
5. The clearance of neostigmine in patients with impaired renal function is lower compared to patients with normal renal functions; therefore, the Clinical Pharmacology team recommends that it should be used with caution in patients with impaired renal functions including elderly patients who are likely to have declining renal function.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

All of the clinical information used to evaluate the safety and efficacy of neostigmine methylsulfate and to derive dosing recommendations was derived from studies reported in the literature. The bibliography includes all of the citations used for these purposes, both those referenced by the Applicant and additional citations referenced in this review. The sources used specifically for the evaluation of efficacy and safety are listed in tabular form in sections 6 and 7 of this review.

5.2 Review Strategy

The Applicant is relying solely on published literature for evidence of efficacy and safety and for the determination of appropriate dosing regimens. A search of the literature was conducted by this reviewer to assess the adequacy of the Applicant's efforts and to determine whether additional information was available that needed to be considered as part of the benefit-risk analysis.

The publications submitted in support of efficacy were screened based on whether they described controlled studies. Controlled studies in which spontaneous recovery, placebo or the approved reversal agents, edrophonium and pyridostigmine, were a comparator were considered as providing the most meaningful efficacy data as were studies in which multiple doses of neostigmine were evaluated and studies in which the timing of administration of a fixed dose of neostigmine was varied. Therefore, these studies were the focus of this review and served as the basis for the assessment of efficacy and the determination of appropriate dosing.

The evaluation of safety was based on both the findings in the submitted literature and a review of the data in the Agency's Adverse Event Reporting System (AERS). All of the literature submitted by the Applicant was reviewed for safety considerations. However, the data derived from placebo-controlled and edrophonium-or pyridostigmine-controlled studies were weighed most heavily in the characterization of the risk profile as they allowed a comparison in incident rates. The AERS database was reviewed by both the Applicant and the Division of Pharmacovigilance II (DPVII) in the Office of Surveillance and Epidemiology. Although the AERS data do not permit estimates of the incidences of adverse events, they do aid in the identification of infrequently occurring adverse events and may provide insight into the associated patient characteristics, clinical

settings and successful treatments of these events, similar to case reports in the literature.

5.3 Discussion of Individual Studies/Clinical Trials

The studies reported in the literature used to determine the safety and efficacy of neostigmine are summarized in sections 6, 7 and 8 below. The individual studies that were considered pivotal for the determination of the dosing regiment and the evaluation of efficacy are described and commented upon in greater detail in section 9 of this review.

6 Review of Efficacy

Efficacy Summary

The Applicant was able to identify five prospective, randomized, appropriately controlled trials in the literature that support a finding of efficacy for the ability of neostigmine to reverse the paralysis induced by neuromuscular blocking agents (NMBAs) in adult patients undergoing surgical procedures. These "pivotal" trials had a common primary endpoint, a return of the train-of-four twitch ratio to 90% ($TOF_{0.9}$), but they evaluated a range of neostigmine doses (10 mcg/kg - 70 mcg/kg), its ability to reverse several different NMBAs (rocuronium, vecuronium, atracurium, cisatracurium, and mivacurium), and its efficacy when administered at varying points of spontaneous recovery ($TOF_{0.4}$, $TOF_{0.6}$, 5 minutes following the administration of rocuronium or , at 1%, 10% or 25% recovery of the first twitch in the TOF (T_1)). A number of supportive studies were also identified; these generally had primary efficacy endpoints of $TOF_{<0.9}$.

Based on the findings in the pivotal trials, the Applicant drew the following conclusions regarding dosing:

1. Dosing ranging studies have indicated that neostigmine 30 µg/kg produced faster recovery to $TOF_{0.9}$ than doses of 10 µg/kg or 20 µg/kg.
2. Neostigmine doses of 50 µg/kg work only marginally faster than 30 µg/kg doses.
3. Neostigmine doses of 40 µg/kg had superior recovery times compared to spontaneous recovery
4. Neostigmine doses of 70 µg/kg have been demonstrated to be more efficacious than lower doses.
5. The pivotal trials were conducted within the last 20 years and therefore reflect current conditions of surgical and anesthetic practice.

The Applicant favors a dosing recommendation of (b) (4) and an upper limit of 70 µg/kg, which they note are consistent with those reported in standard anesthesia texts. They also note that several studies have demonstrated the intuitive finding that reversal of neuromuscular block, either spontaneously or with the addition of neostigmine, will take longer from deeper levels of block compared to shallower block. They believe that it is reasonable to acknowledge the fact that reversal time should be anticipated to be longer when neostigmine is administered at the time of deep residual block, and suggest that additional neostigmine dosing can be considered; however, there are insufficient quantitative data to recommend any adjustment to standard, initial dosing with neostigmine based on depth of block.

The Applicant's evaluation of data in pediatric, non-elderly adults, and elderly adult populations suggested that spontaneous and neostigmine-assisted recovery is more rapid in children than adults, and slightly slower in elderly adults, but the data do not

support any change to standard dosing recommendations for either of these subpopulations.

The Applicant's proposed language for the product label related to dosing, administration, special populations and clinical studies is as follows:

(b) (4)

8.4 Pediatric Use

(b) (4)

8.5. Geriatric Use

(b) (4)

8.6. Renal Impairment

(b) (4)

8.7. Hepatic Impairment

(b) (4)

14. CLINICAL STUDIES

(b) (4)

Reviewer's Comments

In multiple studies, neostigmine has been demonstrated to reverse the effects of nondepolarizing neuromuscular blocking agents (NMBAs). These studies have evaluated neostigmine's efficacy against a broad range of NMBAs and included spontaneous recovery, placebo (blinded, spontaneous recovery) and alternative doses of neostigmine as comparator treatment arms. All of the studies relied on twitch monitoring, i.e., measuring the contractile force of a muscle following the application of an electrical stimulus to the motor neuron supplying it, as the method for evaluating efficacy. The findings were consistent across studies and robust. However, using the data generated by these studies to develop precise dosing guidelines is limited by a number of confounding factors:

1. The timing of neostigmine administration, based on factors such as the time after last dose of the NMBA or the level of spontaneous recovery, varied substantially across studies.

2. The dose of neostigmine needed to reverse the blockade depended on the extent of recovery that had occurred at the time neostigmine was to be administered.
3. The extent of neuromuscular blockade was influenced by other medications commonly used in the perioperative period, most notably, volatile anesthetic agents and certain antibiotics.
4. The twitch monitoring devices used to assess neuromuscular function in the research setting are much more sensitive and reliable than the devices used in clinical practice. This can impact timing of neostigmine administration, and therefore, the dose required, as well as the ability to determine the extent to which neuromuscular blockade has been reversed.
5. None of the studies correlated twitch monitoring findings to clinically meaningful outcomes related to reversing NMBA activity, e.g., ability to discontinue artificial ventilation and extubate the patient, or ability of the patient to maintain a patent airway and ventilate adequately.

Furthermore, the ability to hasten recovery from neuromuscular blockade has not been demonstrated to have a clinical benefit.

In the sections that follow, these issues are addressed in more detail, but based on the data available, the following recommendations can be made for the use of neostigmine to reverse paralysis induced by nondepolarizing NMBAs:

1. A peripheral nerve stimulator should be used throughout the surgical procedure to monitor the patient's twitch response following NMBA administration in order to:
    a. assess the need for additional doses of the NMBA
    b. determine if sufficient spontaneous recovery from the NMBA has occurred to assure the block is reversible
    c. estimate the dose of neostigmine required to reverse the block
    d. monitor the reversal of the block after neostigmine administration
    e. evaluate the need for additional doses of neostigmine

2. Using train-of-four (TOF) stimuli, preferably applied to the ulnar nerve at the level of the wrist, neostigmine should only be administered if there is a detectable twitch response to the first impulse of the TOF, i.e., if the first twitch, T_1, is present.

3. The dose of neostigmine should be determined based on the responses to the TOF stimuli with lower doses administered if more twitches are present and higher doses administered if only T_1 is detected.

4. The recommended dose range is 30 mcg/kg to 70 mcg/kg. A dose of 40 mcg/kg has been found to be efficacious when T_1 has recovered to 25% of its baseline, i.e., the strength of the contraction prior to the administration of the NMBA.
    a. Although there is evidence that weight-based dosing < 30 mcg/kg is efficacious, the amount of data is limited to support such a recommendation. In addition, the inability to precisely determine the timing of $TOF_{0.4}$ and $TOF_{0.6}$ in clinical practice and the additional efficacy (albeit small) observed with the 30 mcg/kg dose that had no apparent increase in risk associated with it, favor recommending a minimum weight-based dose of 30 mcg/kg. [See section 6.1.4 for more detailed information.]
    b. The recommendation of 70 mcg/kg as the upper limit of dosing is based on the lack of data to support higher weight-based dosing and some evidence in the literature that excessive doses of neostigmine, based on the level of neuromuscular blockade at the time of its administration and possibly the NMBA being reversed, may result in prolonged blockade or paradoxical weakness. [See section 6.1.10 for more detailed information.]

5. Recovery times vary depending on the degree of neuromuscular blockade at the time neostigmine is administered, the dose of neostigmine administered, and other factors, e.g., the types of anesthetic agents in use at the time of reversal, the patient's body temperature. Generally, recovery to the point where the ratio of the contractile strength of the fourth twitch to the first twitch, T_4/T_1, is 90% ($TOF_{0.9}$) occurs over a period of about 10 minutes.

6. Adequacy of the reversal of the neuromuscular block needs to be based on a clinical assessment of the patient and not TOF responses alone.

7. Patients should be monitored for clinical signs of residual blockade (e.g., difficulty maintaining a patent airway, generalized weakness, inadequate ventilatory effort) following cessation of the anesthetic and extubation. The duration of monitoring should take into account the duration of action of the NMBA used and of neostigmine, which is estimated to be 20–30 minutes.

These points should be incorporated into the product labeling.

The clinical utility of neostigmine lies in its ability to substantially reduce the recovery time from NMBAs. No clinical studies have been reported in the literature demonstrating a meaningful benefit for the reductions in recovery times observed with neostigmine. Several potential benefits can be postulated and may be reasonably incorporated into the benefit risk analysis. These include reducing the risks associated with:

1. Patient movement during the final stages of the surgical procedure including wound closure because the ability to reverse an NMBA permits maintaining paralysis through the end of surgery.

2. Exposure to anesthetic agents required to maintain unconsciousness as they may be discontinued once paralysis has been reversed.

3. Mechanical ventilation and the presence of an endotracheal tube as well as other airway management devices as they can be discontinued with return of spontaneous ventilation and maintenance of a patent airway.

4. Delays in evaluation of neurological function, i.e., assess a patient's ability to move extremities, peripheral sensation, speech or cognitive function, following certain surgical procedures that can affect the nervous system, e.g., spine surgery, carotid endarterectomy.

6.1 Indication

The Applicant seeks the following indication for this product:

> (b) (4) is a cholinesterase inhibitor indicated for the reversal of the effects of non-depolarizing neuromuscular blocking agents after surgery.

Reviewer's Comments
In the subsections that follow, analysis of the efficacy data from the literature strongly support the proposed indication. Although these data are derived from patients undergoing surgical procedures performed under general anesthesia, it may be possible to consider the use of neostigmine for the reversal of the effects of non-depolarizing neuromuscular blocking agents in other settings as well, most notably in the Intensive Care Unit (ICU) setting.

Generally, in the ICU, neuromuscular blockade is utilized to facilitate mechanical ventilation of patients. When a patient's medical condition has improved to the point where mechanical ventilation is no longer required, the neuromuscular blocking agent (NMBA) is discontinued. The effects of the NMBA are then either reversed or permitted to spontaneously resolve. Reversal of the NMBA has several advantages over spontaneous recovery; most are related to the substantial reduction in recovery time, e.g., reduced exposure to sedative agents. The dosing requirements, the timing neostigmine administration and the monitoring of recovery are determined in the ICU setting the same as they are immediately after surgery. Whether neostigmine poses any additional risks to ICU patients compared to spontaneous recovery is unknown. A PubMed search did not identify any studies dealing with such use. Given that the ICU population tends to be sicker than the general population, in whom the post-surgical studies were conducted, and likely to be more vulnerable to the cardiovascular effects of neostigmine, the indication should be limited as proposed.

6.1.1 Methods

Based on the discussions at presubmission meetings, it was decided that studies using twitch responses to peripheral nerve stimulation would provide adequate evidence of efficacy for reversal of NMBA-induced neuromuscular blockade. For reasons described

in section 6.1.4 below, it was decided that the ratio of the last to first twitch heights in response to a train-of-four electrical stimuli, or the train-of-four (TOF) ratio, would an acceptable endpoint for demonstrating efficacy. It was also decided that a TOF ratio of 90% ($TOF_{0.9}$) would be the most suitable ratio for a primary endpoint. Although studies utilizing of $TOF_{0.9}$ would be weighed more heavily than studies using $TOF_{<0.9}$, the latter studies could be considered supportive with their TOFs weighed similar to secondary endpoints. Furthermore, those studies for which original protocols and source data could be submitted in the NDA for the Division's review would be given more weight than those lacking these resources.

The Applicant conducted a thorough review of the literature using PubMed, but they limited that search to reports of randomized, controlled trials. In addition, they provided documentation of their efforts to retrieve original protocols and data from the authors of the articles which met their search criteria. Unfortunately, they were not able to retrieve any of the source information.

The Applicant identified randomized, prospective studies that met the following criteria as the adequate and well-controlled studies to support the NDA:

1. Employed a control group (spontaneous recovery or placebo),
2. Statistically analyzed the effects of neostigmine versus the control group
3. Used an endpoint of time to a TOF ratio of 0.7 to 0.9 as determined by objective monitoring (i.e., acceleromyography, electromyography, or mechanomyography)

They found that five studies (one placebo-controlled and four spontaneous recovery-controlled) utilized $TOF_{0.9}$ and considered these as "pivotal" studies to support efficacy. An additional 13 studies that employed $TOF_{0.7}$ or $TOF_{0.8}$ were identified and used to provide supportive evidence of efficacy. Additional prospective, randomized studies employing a spontaneous recovery control group that used clinical endpoints other than these measures were also considered supportive and included in the NDA submission.

The literature submitted by the Applicant is summarized and evaluated for efficacy in two ways: first, to assess whether neostigmine is efficacious at reversing NMBA-induced paralysis and second, to determine when following NMBA discontinuation and at what dose neostigmine should be administered to effectively reverse the neuromuscular blockade.

Reviewer's Comments

The approach taken by the Applicant was consistent with the advice provided by the Division during presubmission meetings.

6.1.2 Demographics

The Applicant provided summaries of demographic information in their review of individual trials but did not integrate these data as the efficacy and demographic information for individual subjects or groups of subjects were not available with the exception of age. Several studies in the literature evaluated the dose-response of neostigmine in pediatric versus adult patients and in younger versus older adult patients. The findings of these studies are considered below in section 6.1.7 - Subpopulations.

Reviewer's Comments
Although many studies included patients of both genders, the efficacy findings were not analyzed separately for this demographic. As substantial numbers of males and females were enrolled in the various clinical studies, it is unlikely that a clinically significant difference in efficacy or dosing requirements would have gone unnoticed. None of the published studies performed efficacy analyses based on the American Society of Anesthesiologists physical status (ASA-PS) scores of the patients, although this information was generally captured. Most studies enrolled relatively healthy patients with ASA-PS of 1-3. Lastly, the patients' racial identification was rarely reported; efficacy was not analyzed based on this parameter.

Based on neostigmine's mechanism of action and its widespread use on patients of both genders and various racial backgrounds, there is no evidence to suggest that its efficacy would be affected by either of these demographics.

6.1.3 Subject Disposition

The Applicant did not perform an analysis of efficacy based on subject disposition.

Reviewer's Comments
The studies reported in the literature generally involved single-dose administration of neostigmine to the enrolled subjects; therefore, nearly all subjects completed the study. Those subjects not included in the intent-to-treat populations were generally patients in whom study drug was not administered for reasons such as premature termination of the surgical procedure or spontaneous recovery from the NMBA to the point where use of a reversal agent was not indicated. Based on these considerations, it is not likely that subject disposition had a clinically relevant impact on the evaluation of efficacy or safety.

6.1.4 Analysis of Primary Endpoint(s)

The Division's Basis for Recommendation of the Primary and Secondary Endpoints
In general, the goal in reversing a neuromuscular blocking agent (NMBA) is to expedite and assure the return of neuromuscular function to the extent that a patient is capable of maintaining a patent airway and an adequate level of ventilation so that mechanical ventilation can be discontinued and the trachea extubated. In the clinical practice of anesthesia, a number of assessments may be made to evaluate a patient's ability to carry out both of these functions. These assessments include:

- Mechanical responses of muscles to electrical stimulation of the motor nerves supplying them
- Grip strength, which requires a level of consciousness that permits the patient to follow commands
- Sustained head lift, for 5 or more seconds, which requires a level of consciousness that either allows the patient to follow commands or is associated with a return of the gag reflex
- Spontaneous ventilation parameters, such as
    - Negative inspiratory force > -20 cm H_2O
    - Tidal volume > 5 mL/kg
    - Vital capacity > 10 mL/kg
    - Respiratory rate < 30 breaths/min
    - Appropriate oxygen saturation and end-tidal CO_2 levels

Often, the decision as to whether a patient is adequately recovered from the NMBA is based on a combination of these assessments; however, the standard of care includes the use of a peripheral nerve stimulator (PNS) to apply electric stimuli and permit an assessment of motor response.

The peripheral nerve stimulator has been used in clinical research as part of the development program for NMBAs, specifically, to characterize their pharmacodynamics as part of NDAs and to support the efficacy findings and dosing requirements. In addition, and more apropos to this NDA, the device was used to generate pharmacodynamic and dosing and administration data for Enlon (edrophonium) and Enlon-Plus (edrophonium and atropine), which are approved for the same indications sought for neostigmine. The device was also more recently used to generate the primary endpoint data in the pivotal studies of sugammadex, a reversal agent for rocuronium and vecuronium. Although, sugammadex has not been approved as of the writing of this review, the Division publicly acknowledged the efficacy of the product, based on the PNS-generated data, during the Advisory Committee meeting held on March 11, 2008.

In the literature submitted with this NDA, efficacy was generally assessed by evaluating the responses of the abductor pollicis longus to varying types of electrical stimulation

applied to the radial nerve; the method commonly used in the clinical setting. In this regard, there is no evidence-based support that distinguishes a particular type of electrical stimulus as the most predictive of full recovery of neuromuscular function or that identifies a specific response to electrical stimulation as indicative that normal function has been fully restored. The types of electrical stimulation patterns typically used in clinical practice and clinical research are briefly described below. This serves as a preface to the analyses of the data reported in the literature that assess the efficacy of neostigmine in reversing drug-induced neuromuscular blockade, which will serve as the basis for determining when, after the discontinuation of an NMBA, and at what dose, neostigmine should be administered.

The following patterns of electrical stimulation are used to evoke mechanical responses for monitoring the level of neuromuscular blockade:

1. Single twitch – A single supramaximal impulse is delivered, and the twitch response is assessed. A supramaximal impulse is a current 20% to 25% greater than that which achieves a maximal mechanical response in the absence of an NMBA. This method of monitoring requires a comparator response, which is generally the response observed prior to the administration of an NMBA. The response over time may be monitored by intermittently or continuously applying the stimuli. For continuous monitoring, the stimuli are typically administered at a frequency of 0.1 Hz (once every 10 seconds).
2. Train-of-Four (TOF) ratio – Four electrical impulses of equal amplitude and duration (between 0.1 and 0.5 msec) are applied at 2 Hz (i.e., 0.5 sec intervals); the ratio of the twitch response to the forth impulse to that of the first impulse defines the TOF ratio. Prior to administration of an NMBA, all four twitch responses are (ideally) identical and the TOF ratio is 1.0. With increasing non-depolarizing blockade, the ratio decreases (fades) and the TOF ratio is < 1.0; with recovery, the TOF ratio increases until it returns to 1.0.
3. Double burst suppression – Two short tetanic stimuli separated by an interval long enough to allow muscle relaxation are applied and the ratio of the second response to the first is determined.
4. Tetanic stimulation – Electrical impulses are applied at rapid rates for specific durations. Typically, a 50 Hz frequency of impulses is applied for 5 seconds; although 1-second applications of stimuli applied at 50 to 200 Hz have been used by investigators. In the absence of neuromuscular blockade, a sustained muscle contraction occurs and does not weaken over the course of the stimulation. In the presence of incomplete neuromuscular blockade, the response fades.
5. Post-tetanic stimulation – A tetanic stimulation at 50 Hz for five seconds is applied followed 3 sec later by single twitch stimulation at 1 Hz. The number of evoked post tetanic twitches detected is called the post tetanic count (PTC). This method is useful when there is no response to single twitch, TOF or tetanic stimulations. A PTC of ≥ 8 indicates the imminent return of TOF responses.

There are limitations to each of these methods; some of which are more pronounced in the clinical practice setting than in the research setting. The use of the single twitch is limited in that the magnitude of the response cannot be interpreted without a comparator, typically the response prior to administration of an NMBA. Without a recording device, it is difficult to monitor and compare individual twitch heights over time; however, this method has been used in the pivotal clinical studies of NMBAs to characterize their pharmacodynamics. Furthermore, in the literature, it has been reported that, during nondepolarizing block, the response to single twitch stimulation is not reduced until at least 75% to 80% of the acetylcholine receptors at the neuromuscular junction are occupied by the NMBA. Therefore, this method of monitoring is not useful for discerning receptor blockade of less than 70%.

The TOF method does not require a "pre-NMBA" twitch response value for comparison as the responses needed to determine the ratio are obtained de novo with each set of four stimuli. Furthermore, TOF stimulation is less painful than tetanic stimulation for the patient regaining consciousness and generally does not affect subsequent assessments of the level of blockade to the extent that tetanic stimulation can. However, it is recommended that the TOF stimuli should not be applied too frequently, i.e., at ≤ 10 second intervals, to avoid the possibility of post-tetanic facilitation affecting the assessment. TOF is the more commonly used stimulation pattern in the practice of anesthesia.

The data reported in the literature during the mid-1970's suggested that a TOF ratio of 0.7 ($TOF_{0.7}$) was associated with clinically acceptable values for vital capacity, inspiratory force, and peak expiratory flow rates making this value often used as the standard cut-off point for adequate reversal of an NMBA. Specifically, Ali and Kitz (1) determined that a mean TOF ratio of 0.7 was associated with the several signs of clinical recovery of neuromuscular function:

- Ability to open eyes widely
- Ability to protrude the tongue
- Ability to cough
- Ability to maintain a raised head for at least 5 seconds
- Vital capacity exceeding 15 to 20 mL/kg

These parameters were thought to be adequate endpoints for determining whether a patient was capable of resuming adequate spontaneous ventilation and maintaining a patent airway. However, Eriksson and colleagues (2,3) showed, by administering vecuronium to unanesthetized volunteers, that the ventilatory response to hypoxemia was depressed if the TOF ratio was reduced to 0.7 and that it returned to normal when the TOF ratio increased to 0.9. In addition, Eriksson and colleagues (4) found that pharyngeal dysfunction and aspiration (defined as laryngeal penetration by secretions) occur with partial paralysis by vecuronium when the TOF ration is less than 90% as measured at the adductor pollicis following ulnar nerve stimulation.

The adequacy of $TOF_{0.7}$ was further challenged by the findings of Eikermann et al. (5) who evaluated repeated spirometric maneuvers performed at 5-minute intervals in awake volunteers before, during, and after partial paralysis evoked by rocuronium. They found that even at $TOF_{0.8}$, fade of pulmonary function, i.e., decline in a parameter with repeated testing, was observed for forced vital capacity (FVC), forced inspiratory volume at 1 second (FIV_1), peak expiratory force (PEF), and peak inspiratory force (PIF). A clinically relevant (≥ 10%) fade was associated with a 10% FVC reduction from baseline with all the measurements, while the FVC reduction was still present in 23% of measurements without a relevant FVC fade. Fade of pulmonary function disappeared with recovery from neuromuscular blockade to $TOF_{1.0}$.

Eikermann et al. (6) also assessed the incidence of upper airway obstruction (UAO), i.e., the ratio of maximal expiratory flow and maximal inspiratory flow at 50% of vital capacity [MEF_{50}/MIF_{50}] > 1, by repetitive spirometric assessments in patients before induction (but with sedation), immediately after tracheal extubation with $TOF_{0.9}$, and 30 minutes following extubation. They found that the incidence of UAO increased significantly from 63% before induction to 85% after extubation, and subsequently decreased 30 minutes later to baseline levels, 65%. The mean maximal expiratory flow and maximal inspiratory flow at 50% of vital capacity ratio after tracheal extubation was significantly increased from baseline and decreased 30 minutes later to values observed at baseline. They noted that an FVC fade of ≥ 10% was observed in 2 (2%) patients after extubation at $TOF_{0.9}$. They concluded that recovery to $TOF_{0.9}$ predicts with high probability an absence of neuromuscular blocking agent-induced UAO, but that outliers, i.e., persistent effects of neuromuscular blockade on upper airway integrity despite recovery of the TOF ratio, may occur.

An additional study by Eikermann et al. (7) conducted a study to assess whether impaired neuromuscular transmission predisposes individuals to inspiratory upper airway collapse. To do so, they assessed supraglottic airway diameter and volume by respiratory-gated magnetic resonance imaging, upper airway dilator muscle function (measuring genioglossus force and EMG activity), and changes in lung volume, respiratory timing, and peripheral muscle function before, during, and after partial neuromuscular blockade in healthy, awake volunteers. Partial neuromuscular blockade ($TOF_{0.5}$ and $TOF_{0.8}$) was associated with:

- a decrease of inspiratory retropalatal and retroglossal upper airway volume
- an attenuation of the normal increase in anteroposterior upper airway diameter during forced inspiration
- a decrease in genioglossus activity during maximum voluntary tongue protrusion
- no effects on upper airway size during expiration, lung volume, and respiratory timing

The authors concluded that impaired neuromuscular transmission, even to a degree insufficient to evoke respiratory symptoms, markedly impairs upper airway dimensions and function. They suggested that this could be due to an impairment of the balance

between upper airway dilating forces and negative intraluminal pressure generated during inspiration by respiratory muscles.

Based on the information above, the Division has determined that the use of TOF monitoring is appropriate for assessing the efficacy of neostigmine as it was the predominant means by which efficacy was assessed in the literature; there is some validation of its utility for determining whether a patient's neuromuscular function has been adequately restored to allow sufficient ventilation and maintenance of a patent airway without mechanical assistance; and it is commonly used in the clinical setting making it readily available for evaluating the degree of reversal that has occurred following the administration of neostigmine to individual patients. Furthermore, the information above indicates that a TOF ratio of 0.9 ($TOF_{0.9}$) or greater may be a more clinically relevant end-point for defining adequate recovery of neuromuscular transmission than $TOF_{0.7}$.

The Applicant's Analysis of the Primary Endpoint

Based on the information above and discussions at the Pre-IND meeting, studies using a primary endpoint of $TOF_{0.9}$ would be weighed more heavily than studies using $TOF_{<0.9}$, although the latter studies could be considered supportive.

The Applicant conducted a thorough review of the literature using PubMed to conduct their search but limited that search to reports of randomized, controlled trials. In addition, they provided documentation of their efforts to retrieve original protocols and data from the authors of the articles which met their search criteria. Unfortunately, they were not able to retrieve any of the source information; however, the extent and consistency of the literature supporting the efficacy of neostigmine compensates for the lack of this information.

The Applicant identified randomized, prospective studies that met the following criteria as the adequate and well-controlled studies to support the NDA:

1. Employed a control group (spontaneous recovery or placebo),
2. Statistically analyzed the effects of neostigmine versus the control group
3. Used an endpoint of time to a TOF ratio of 0.7 to 0.9 as determined by objective monitoring (i.e., acceleromyography, electromyography, or mechanomyography)

They found that five studies (one placebo-controlled and four spontaneous recovery-controlled) utilized $TOF_{0.9}$ and considered these as "pivotal" studies to support efficacy. An additional 13 studies that employed $TOF_{0.7}$ or $TOF_{0.8}$ were identified and used to provide supportive evidence of efficacy. Additional prospective, randomized studies employing a spontaneous recovery control group that used clinical endpoints other than these measures were also considered supportive and included in the NDA submission.

The literature submitted by the Applicant is summarized and evaluated for efficacy in two ways: first, to assess whether neostigmine is efficacious at reversing NMBA-induced paralysis and second, to determine when following NMBA discontinuation and at what dose neostigmine should be administered to effectively reverse the neuromuscular blockade.

The Applicant reports that the five prospective, randomized, controlled trials with a primary efficacy endpoint of $TOF_{0.9}$ showed significantly reduced recovery or reversal times for neostigmine compared to placebo or spontaneous recovery. They noted that actual recovery times in these studies varied due to clinical variables such as anesthetic agents used, neuromuscular blocking agent used, and depth of block at the time of neostigmine administration; however, the effects of neostigmine were considered by them, and the authors, to be clinically meaningful.

The five studies also showed beneficial effects of neostigmine within a range of administered doses. Although there was some evidence for a dose-response relationship, the Applicant described the dose effects as relatively modest and concluded that the efficacy of neostigmine was best supported by this body of literature in the range 30-70 mcg/kg. They propose that having a range of recommended neostigmine doses known to be effective may serve to provide anesthesiologists with a degree of latitude to individualize a patient's dose of neostigmine based on factors such as whether the intent of treatment is simply to ensure complete reversal of the NMBA at the time the patient is released to recovery or to reduce recovery time and facilitate extubation of the patient.

Table 1 below provides a summary of the information found in the five pivotal studies identified by the Applicant, which are discussed further in the Reviewer's Comments that follow.

Table 1. Summary of pivotal efficacy trials (Table 1 on p. 8 of Appendix 2 of section 2.7.3 of NDA)

Author/Year (Reference)	Total # Patient	NMBA and Dose	Neostigmine Administration	Neostigmine Dose	# Patients /Group	Recovery or Reversal Time (minutes)	
						Reversal to $TOF_{0.9}$ *Median (range)*	**Reversal to $TOF_{1.0}$** *Median (range)*
Fuchs-Buder et al. 2010 (8)	120 adult ASA I-III undergoing elective surgery under general anesthesia	Atracurium 0.5 mg/kg + 0.1 mg/kg as needed	At $TOF_{0.4}$ recovery	0 (saline)	15	13 (7 - 27)	19 (11 - 30)
				10	15	6 (3 - 12)****	11 (7 - 15)****
				20	15	6 (4 - 9)****	9 (6 - 13)****
				30 µg/kg	15	4 (3 - 6)****	6 (4 - 11)****
			At $TOF_{0.6}$ recovery	0 (saline)	15	10 (5 - 16)	15 (8 - 20)
				10	15	4 (2 - 9)****	6 (4 - 16)****
				20	15	3 (2 - 7)****	6 (4 - 14)****
				30 µg/kg	15	4 (2 - 6)****	5 (3 - 7)****
						Recovery to $TOF_{0.9}$	**Recovery to $TOF_{0.8}$**
Lederer et al. 2010 (9)	60 adults M&F ASA I & II undergoing elective surgery under general anesthesia	Rocuronium 0.4 mg/kg	5 minutes after NMBA	None (control)	20	39.0 ± 8.7	36.2 ±8.5
				30	20	22.6 ± 5.9***	20.2 ± 5.0***
				50 µg/kg + glycopyrrolate	20	19.4 ± 5.1***	17.8 ± 4.8***

*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 compared to spontaneous control

Author/Year (Reference)	Total # Patients	NMBA and dose	Neostigmine Administration	Neostigmine Dose	# Patients /Group	Recovery or Reversal Time (minutes)	
						Reversal to $TOF_{0.9}$ *Mean (SD) [median]*	**Reversal to $TOF_{0.7}$** *Mean (SD) [median]*
Adamus et al. 2006 (10)	120 adults M&F ASA I & II undergoing elective surgery under general anesthesia	Cisatracurium 0.10 mg/kg	T1 @ 25% recovery	None (control)	15	49.2 (8.0) [49]	15.9 (1.8) [16.3]
				40 µg/kg + atropine	15	11.5* (2.8) [12]	4.4* (0.9) [4.7]
		Cisatracurium 0.15 mg/kg		None (control)	15	52.5 (7.0) [54]	15.5 (1.7) [15.5]
				40 µg/kg + atropine	15	11.7* (2.7) [12]	4.5* (0.8) [4.7]
		Rocuronium 0.60 mg/kg	T1 @ 25% recovery	None (control)	15	43.1 (13.1) [41]	16.1 (3.7) [15.7]
				40 µg/kg + atropine	15	9.8* (2.0) [10]	4.3* (0.8) [4.3]
		Rocuronium 0.90 mg/kg		None (control)	15	56.7 (12.9) [56]	16.1 (4.0) [16.3]
				40 µg/kg + atropine	15	10.0* (2.7) [10]	4.7* (0.7) [4.6]

*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 compared to spontaneous control

Author/Year (Reference)	Total # Patients	NMBA and dose	Neostigmine Administration	Neostigmine Dose	# Patients /Group	Recovery or Reversal Time (minutes) [mean ± SD]	
						Recovery to $TOF_{0.9}$	**Recovery to $TOF_{0.7}$**
Bevan et al. 1999 (11)	80 adults F ASA I & II undergoing gynecologic surgery	Rocuronium 0.45 mg/kg	5 minutes post-NMB T1 @ 1% recovery T1 @ 10% recovery T1 @ 25% recovery	None (control)	8	54.3 ± 12.3	45.7 ± 11.5
				70	8	42.1 ± 17.3	27.6 ± 9.2**
				70	8	35.3 ± 14.5	26.5 ± 9.2**
				70	8	27.0 ± 8.5**	23.9 ± 7.9**
				70 µg/kg + glycopyrrolate	8	28.2 ± 10.8**	26.3 ± 9.4**
		Vecuronium 0.075 mg/kg	5 minutes post-NMB T1 @ 1% recovery T1 @ 10% recovery T1 @ 25% recovery	None (control)	8	66.2 ± 22.3	52.5 ± 15.6
				70	8	34.7 ± 12.0**	27.2 ± 8.2**
				70	8	32.9 ± 3.9**	26.5 ± 6.2**
				70	8	36.6 ± 12.0**	33.5 ± 11.4*
				70 µg/kg + glycopyrrolate	8	37.6 ± 9.9*	36.2 ± 8.0*
	80 children 2-12 years undergoing dental treatment	Rocuronium 0.45 mg/kg	5 minutes post-NMB T1 @ 1% recovery T1 @ 10% recovery T1 @ 25% recovery	None (control)	8	34.7 ± 10.0	28.8 ± 7.8
				70	8	17.1 ± 4.9**	14.1 ± 3.8*
				70	8	19.3 ± 6.6**	16.5 ± 5.7*
				70	8	20.0 ± 4.2**	18.4 ± 3.7*
				70 µg/kg + glycopyrrolate	8	24.4 ± 8.2	23.0 ± 8.3
		Vecuronium 0.075 mg/kg	5 minutes post-NMB T1 @ 1% recovery T1 @ 10% recovery T1 @ 25% recovery	None (control)	8	44.2 ± 12.3	36.4 ± 9.0
				70	8	28.6 ± 10.4*	20.2 ± 5.5**
				70	8	25.1 ± 6.9**	20.7 ± 5.0**
				70	8	29.2 ± 8.2*	25.9 ± 6.3
				70 µg/kg + glycopyrrolate	8	23.4 ± 3.5*	21.3 ± 3.1**

*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 compared to spontaneous control

Author/Year (Reference)	Total # Patients	NMBA and dose	Neostigmine Administration	Neostigmine Dose	# Patients /Group	Recovery or Reversal Time (minutes)	
						Reversal to $TOF_{0.9}$ *Mean (SEM)*	**Reversal to $TOF_{0.7}$** *Mean (SEM)*
Baurain et al. 1994 (12)	24 adults ASA I & II	Mivacurium 0.2 mg/kg + infusion	T1 @ 25% recovery	None(control) 40 µg/kg + atropine	12 12	13 (0.5) 10*** (0.9)	10 (0.6) 5*** (0.3)

*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 compared to spontaneous control

Reviewer's Comments
Each of these "pivotal" studies is individually described in greater detail and commented upon in section 9.1 of this review. The efficacy endpoint of $TOF_{0.9}$ was considered by the Division, as indicated by the Applicant, to be the most appropriate primary endpoint for assessing the dose requirements of neostigmine and the timing of its administration. The studies selected by the Applicant serve this purpose but with some limitations, most notably there is no one dose that has been identified as optimal for administration at any specific time point during spontaneous recovery. The data suggest that a range of doses will work for any particular level of spontaneous recovery, but lower doses will not hasten recovery as much as higher doses.

Table 2 below summarizes several key aspects of the studies.

Table 2. Summary of efficacy study dosing information

Study	NMBA Reversed	Timing of Administration	Neostigmine Dose (mcg/kg)	Comparator	Number of Subjects Treated with Neostigmine
Fuchs-Buder	Atracurium	$TOF_{0.4}$ or $TOF_{0.6}$	10, 20, or 30	Saline	90
Lederer	Rocuronium	5 min after NMBA	50	Spontaneous Recovery	40
Adamus	Cisatracurium and Rocuronium	T1 = 25%	40	Spontaneous Recovery	60
Bevan	Vecuronium and Rocuronium	5 min after NMBA or at T1 = 1, 10, or 25%	70	Spontaneous Recovery	68
Baurain	Mivacurium	T1 = 25% (~ $TOF_{0.1}$)	40	Spontaneous Recovery	12

These studies demonstrated that neostigmine can effectively hasten the reversal of five of the more commonly used NMBAs. The findings from the studies suggest that timing of administration is an important factor in determining the appropriate dose. With six different weight-based dose values, the highest of which is seven times greater than the lowest, administered at six different points during spontaneous recovery, it is not possible to identify a single dosing and administration method that will likely work equally well for most NMBAs in most patients. In the clinical setting where research-grade, twitch-monitoring equipment is not generally available, determination of the appropriate dose is made all the more difficult, as is assessing the extent of recovery following neostigmine administration. Therefore, as the Applicant suggests, there is merit to recommending a range of weight-based doses that can be used with the caveat

that patients should be carefully monitored, clinically, to evaluate the adequacy of recovery and the possible need for supplemental doses of neostigmine. Considering the doses evaluated in these studies, a range of 30 mcg/kg to 70 mcg/kg is recommended. While there was evidence of efficacy for the two lowest doses, i.e., 10 mcg/kg and 20 mcg/kg, the inability to precisely determine the timing of $TOF_{0.4}$ and $TOF_{0.6}$ in clinical practice and the additional efficacy (albeit small) observed with the 30 mcg/kg dose that had no apparent increase in risk associated with it, favor recommending a minimum weight-based dose of 30 mcg/kg.

6.1.5 Analysis of Secondary Endpoints(s)

The Applicant provided no analysis of secondary endpoints.

Reviewer's Comments
An analysis of secondary endpoints was not indicated in this application as these endpoints were either not included in the trial designs or were not as clinically relevant as the primary endpoint, e.g. $TOF_{0.7}$ or $TOF_{0.8}$ as secondary endpoints when the primary endpoint was $TOF_{0.9}$.

The Applicant did identify a number of other trials reported in the literature that were supportive of the efficacy of neostigmine in that they demonstrated an accelerated recovery from neuromuscular blockade when neostigmine was administered compared to spontaneous recovery, a placebo control, or a dose control. These trials did not use the $TOF_{0.9}$ as a primary endpoint and were therefore less useful in identifying an appropriate dosing regimen, but they did demonstrate a number of other NMBAs that could be reversed with neostigmine and provided some evidence of which weight-based doses would be expected to provide some clinical benefit. The following two tables list those studies and the key efficacy information as was provided in section 6.1.4 above. Table 3 includes trials with a primary efficacy endpoint is $TOF_{<0.9}$; Table 4 includes trials in which TOF assessed over various periods of time were the primary endpoints. More detailed information for and comments on some of these studies are provided in section 9.1 of this review. These tables reinforce the findings from the "pivotal" studies that indicate:

1. A range of doses can effectively hasten recovery.
2. Neostigmine is effective for both pediatric and adult patients who are generally healthy, i.e., ASA-PS 1 and 2, and for all non-depolarizing NMBAs studied.
3. The timing and dose of neostigmine both impact the extent to which recovery is hastened.
4. Recovery from shorter acting NMBAs is less affected by neostigmine.
5. Doses greater than 70 mcg/kg have not been evaluated.

Table 3. Supportive efficacy studies involving TOF ratios < 0.9 (Table 23 on pp. 58-63 in section 5.3.5.3 of the NDA)

Author/Year Country	Total # Patients	NMBA	Neostigmine Administration	Neostigmine Dose	# Patients /Group	Recovery or Reversal Time (minutes)	
Barrio et al. 2007 Spain	60 adult M&F ASA I & II	Rocuronium 0.6 mg/kg	T1 @ 25% recovery @ 25% recovery @ 5% recovery	0 (saline) 30 µg/kg 30 µg/kg + atropine	10 10 10	**Recovery to $TOF_{0.8}$** 62 ± 18.9 (n=9) 37.2 ± 8* 39.6 ± 7*	
		Cisatracurium 0.1 mg/kg	T1 @ 25% recovery @ 25% recovery @ 5% recovery	0 (saline) 30 µg/kg 30 µg/kg + atropine	10 10 10	66.96 ±15.9 (n=9) 53.9 ± 6* 53.4 ± 11*	
Lessard et al. 1997 Canada	100 adult M&F ASA I & II	Mivacurium bolus 0.2 mg/kg + infusion to maintain T1 depression @ 90-95%	At end of NMB infusion, i.e. @ T1 5-10% of control	0 (saline) 10 20 40 µg/kg + glycopyrrolate	24 25 22 23	**Reversal to $TOF_{0.7}$** 17.0 ± 5.1 14.6 ± 4.2 11.4 ± 3.0***§ 11.4 ± 3.5***§	§ 20 & 40 µg/kg statistically Δ from 10 µg/kg
Devcic et al. 1995 United States	30 adult ASA I & II	Mivacurium 0.2mg/kg	T1 @ 1-8% recovery	0 (saline) 70 µg/kg + atropine Edrophonium	10 10 10	**Reversal to:** $TOF_{0.25}$: 10.1 ± 0.6 $TOF_{0.5}$: 13.3 ± 0.6 $TOF_{0.7}$: 15.8 ± 0.9 $TOF_{0.25}$: 4.3 ± 0.5* $TOF_{0.5}$: 7.5 ± 1* $TOF_{0.7}$: 12.5 ± 3.1 See paper for results	

Author/Year Country	Total # Patients	NMBA	Neostigmine Administration	Neostigmine Dose		# Patients /Group	Recovery or Reversal Time (minutes)	
							Reversal to $TOF_{0.75}$ *Mean (SD)*	
Magorian et al. 1990 United States	40 adult ASA I & II	Vecuronium 0.1 mg/kg	**Dose 1**: 15 minutes after NMBA and no twitch response **Dose 2**: at 10% T1 recovery	**Dose 1** Placebo	**Dose 2** Placebo	10	122.6 (39.4)	
				Placebo	70µg/kg	10	60.4* (21.8)	
				70µg/kg	Placebo	10	79.5* (24.7)	
				70µg/kg + glycopyrronium	70µg/kg + glycopyrronium	10	71.5* (32.5)	
							Recovery to $TOF_{0.8}$ *Median [range]*	**Recovery to $TOF_{0.7}$** *Median [range]*
Hayes et al. 2000 UK	30 adults M&F	Rapacuronium 1.5 mg/kg SD	T1 @ 25% recovery	None (control)		15	33.4 [20.0-79.0]	30.4 [18.3-73.1]
				70 µg/kg		15	21.2*** [13.9-33.7]	20.1*** [13.5-33.4]

Author/Year Country	Total # Patients	NMBA	Neostigmine Administration	Neostigmine Dose	# Patients /Group	Recovery or Reversal Time (minutes)	
						Recovery to $TOF_{0.8}$ *Mean (SD)*	
McCourt et al. 1999a UK	80 adults (+40 adults in Part 2) M&F	Rocuronium 0.5 mg/kg + additional as needed. Continuous isoflorane		None (control)	10	44.0 (15.5)	§p<0.01 compared with reversal @ T1=25% with neostigmine doses 35 or 50 µg/kg
			T1 @ 10% recovery	20	10	18.6***§ (3.8)	
			@ 10% recovery	35	10	10.3 ***(4.3)	
			@ 10% recovery	50	10	10.5 *** (6.2)	
			T1 @ 25% recovery	Control group value	10	33.0 (8.9)	
			@ 25% recovery	20	10	10.2*** (3.3)	
			@ 25% recovery	35	10	7.0*** (4.8)	
		Discontinued isoflorane	@ 25% recovery	50 µg/kg + glycopyrronium	10	6.4*** (1.9)	
			@ 25% recovery	50 µg/kg + atropine	40	5.7*** (2.3)	
						Recovery to $TOF_{0.8}$	Recovery to $TOF_{0.7}$
Purdy et al. 1999 Canada	117 adults M&F ASA I - III	Rapacuronium 1.5 mg/kg	2 minutes post NMBA	None (control)	13	42.7 ± 11.5	37.9 ± 10.0
				50	11	23.1 ± 7.1*	19.2 ± 6.4*
				70	12	22.7 ± 7.8*	17.2 ± 5.4*
			7 minutes post NMBA	50	12	19.2 ± 3.9*	16.5 ± 3.2*
				70 µg/kg + glycopyrrolate	12	23.2 ± 8.4	18.1 ± 7.3*
		Rapacuronium 2.5 mg/kg	2 minutes post NMBA	None (control)	11	59.6 ± 10.5	54.3 ± 13.0
				50	12	30.5 ± 7.8*	25.8 ± 6.6*
				70	12	37.7 ± 10.0*	31.6 ± 9.1*
			7 minutes post NMBA	50	11	37.6 ± 15.7*	31.9 ± 11.5*
				70 µg/kg + glycopyrrolate	11	35.1 ± 12.9*	28.0 ± 10.2*

Author/Year Country	Total # Patients	NMBA	Neostigmine Administration	Neostigmine Dose	# Patients /Group	Recovery or Reversal Time (minutes)	
						Reversal to $TOF_{0.8}$ *Mean (SD)*	Reversal to $TOF_{0.7}$ *Mean (SD)*
McCourt et al. 1999b UK and Austria	90 adults 2 centers	Rapacuronium 1.5 mg/kg + 3 doses 1.5 mg/kg at T_{25}	T1 @ 25% recovery	None (control) 50 µg/kg + glycopyrrolate	11 14	72.4 (16.5) 9.9* (4.5)	58.0 (12.4) 5.8* (2.0)
		Rapacuronium 1.5 mg/kg + infusion after T_5 to maintain 90% block		None (control) 50 µg/kg + glycopyrrolate	9 10	66.1 (26.9) 8.6* (6.1)	53.0 (18.4) 4.2* (2.1)
		Rapacuronium 1.5 mg/kg + Rocuronium 2 doses 0.15 mg/kg at T_{25}		None (control) 50 µg/kg + glycopyrrolate	14 12	36.7 (15.8) 5.7* (2.5)	28.7 (13.9) 3.6* (1.0)
						Reversal to $TOF_{0.7}$	Recovery to $TOF_{0.7}$
Bartunek et al. 1997 Austria	48 adults M&F ASA I & II	Mivacurium 0.2 mg/kg	T1 @ 5% recovery @ 5% recovery @ 5% recovery	None (control) 40 Edrophonium	10 9 10	15.9 ±2.9 10.0 ± 1.9 7.7 ± 2.2*	30.0 ± 6.1 26.9 ± 5.1 22.9 ± 3.3
			T1 @ 25% recovery @ 25% recovery @ 25% recovery	Control group value 40 µg/kg Edrophonium 1 mg/kg	10 10 9	10.7 ± 2.2 5.1 ± 2.0* 5.3 ± 1.5*	NA 23.5 ± 4.4 23.7 ± 7.5

Author/Year Country	Total # Patients	NMBA	Neostigmine Administration	Neostigmine Dose	# Patients /Group	Recovery or Reversal Time (minutes)	
Van den Broek et al. 1994 The Netherlands	60 adults M&F ASA I - III	Rocuronium 0.6 mg/kg	2 minutes after NMBA T1 @ 25% recovery	None (control) 40 40 µg/kg + atropine	20 20 20	**Recovery to $TOF_{0.7}$** *Mean (SD) [CI 95%]* 53.2 (14.5) [46.5-59.9] 29.3* (9.5) [24.9-33.7] 31.8* (5.6) [29.2-34.4]	
Caldwell et al. 1986 UK	59 adults	Vecuronium 0.1 mg/kg	5 minutes after T1 = 0 5 minutes after T1 = 0	None (control) 40 µg/kg + atropine Edrophonium	10 10 10	**Reversal to $TOF_{0.7}$** 66.7 ± 3.3 43.5 ± 5.1** 59.8 ± 5.6*	
		Atracurium 0.5 mg/kg	5 minutes after T1 = 0 5 minutes after T1 = 0	None (control) 40 µg/kg + atropine Edrophonium	10 10 10	66.4 ± 2.2 44.1 ± 2.9** 49.2 ± 3.8*	

Author/Year Country	Total # Patients	NMBA	Neostigmine Administration	Neostigmine Dose	# Patients /Group	Recovery or Reversal Time (minutes)	
Jones et al. 1987 UK	50 adults M&F ASA I & II	Vecuronium 0.1 mg/kg	T1 @ 10% recovery @ 10% recovery	None (control) 2.5 mg + atropine 2.5 + 2.5 mg + atropine	10 10 10	**Reversal to $TOF_{0.7}$** 24.2 (11.4) 9.2** (5.3) 5.6** (3.7)	
			T1 @ 50% recovery @ 50% recovery	None (control) 2.5 mg + atropine 2.5 + 2.5 mg + atropine	10 10 10	6.9 (3.2) 2.1** (1.0) 1.5** (0.53)	
Kao and Le 1996 United States	30 adults ASA I & II	Mivacurium 0.15 mg/kg + infusion as needed to maintain T1 @ 2-3%	T1 @ 2-3% recovery	None (control)	10	**Recovery to:** *Mean (SD)* **$TOF_{0.5}$**: 11.75 (3.74) **$TOF_{0.7}$**: 13.78 (4.39) **$TOF_{0.9}$**: 17.86 (6.44)	
				70 µg/kg + atropine	10	**$TOF_{0.5}$**: 14.47 (8.73) **$TOF_{0.7}$**: 21.25 (11.06) **$TOF_{0.9}$**: 31.37 (12.11)	
			T1 @ 2-3% recovery	Edrophonium + atropine	10	See paper for results	

*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 compared to spontaneous control

Table 4. Supportive efficacy studies involving TOF ratios over time (Table 24 on pp. 64-67 in section 5.3.5.3 of the NDA)

Author/Year Country	Total # patients	NMBA	Neostigmine Administration	Neostigmine Dose	# Patients /group	Reversal TOF Ratios over Time	
Naguib and Riad 2000 Saudi Arabia or United States	144 adults ASA I & II	Atracurium 0.5 mg/kg + 0.1 mg/kg as required	T1 @ 10% recovery	None (control) 5 10 20 50 µg/kg + atropine Edrophonium	8 8 8 8 8 32		**TOFR @ 10 minutes** *Mean (95% CI)* 0.19 (0.1-0.3) 0.35 (0.18-0.52) 0.55* (0.38-0.71) 0.60* (0.52-0.68) 0.82* (0.74-0.90) See paper for results
		Cisatracurium 0.1 mg/kg + 0.02 mg/kg as required	T1 @ 10% recovery	None (control) 5 10 20 50 µg/kg + atropine Edrophonium	8 8 8 8 8 32		0.18 (0.09-0.26) 0.33* (0.25-0.41) 0.46* (0.29-0.63) 0.68* (0.59-00.75) 0.82* (0.74-0.90) See paper for results

Author/Year Country	Total # patients	NMBA	Neostigmine Administration	Neostigmine Dose	# Patients /group	Reversal TOF Ratios over Time	
						TOF(%) @ 5 minutes *Mean (95% CI)*	TOF(%) @ 10minutes *Mean (95% CI)*
Abdulatif et al. 1996 Egypt	50 adults ASA I & II	Rocuronium 0.6 mg/kg bolus	T1 @ 10% recovery	None (control)	10	51 (0.0-11.0)	18.7 (0.73-29.9)
				5	10	11.5 (0.75-18.4)	29.1 (22.8-35.7)
				10	10	25.6* (21.3-31.2)	47.2* (39.1-56.4)
				20	10	37.9* (28.1-47.6)	61.7* (51.1-71.0)
				50 µg/kg + Atropine	10	61.8* (50.8-71.1)	77.6* (67.3-83.6)
	40 children ASA I & II		T1 @ 10% recovery	None (control)	10	24.3 (19.9-28.6)	48.0 (39.0-57.9)
				5	10	39.1 (17.1-61.1)	73.0* (54.8-91.9)
				10	10	61.7* (50.5-72.9)	88.5* (81.7-95.2)
				20	10	84.6* (73.6-95.6)	97.7* (94.9-99.0)
				50 µg/kg + Atropine	10	92.5* (85.8-99.0)	98.7* (96.1-99.9)

Author/Year Country	Total # patients	NMBA	Neostigmine Administration	Neostigmine Dose	# Patients /group	Reversal TOF Ratios over Time	
						TOF(%) @ 5minutes	TOF(%) @10 minutes
Bevan et al. 1996 Canada	54 adults ASA I & II	Mivacurium bolus 0.2 mg/kg + infusion to maintain 90-95% block	T1 @ 10% recovery	None (control)	6	14.3 ± 3.9	29.5 ± 12.7
				5	6	22.3 ± 13.5	54.7* ± 9.5
				10	6	21.8 ± 5.1	40.5 ± 12.8
				20	6	45.7*** ± 5.9	80.8*** ± 9.7
				50 µg/kg + Atropine	6	42.8* ± 14.9	78.0*** ± 13.9
			T1 @ 10% recovery	Edrophonium	24	See paper for results	See paper for results
	54 children ASA I & II		T1 @ 10% recovery	None (control)	6	52.5 ± 4.9	83.7 ± 5.2
				5	6	45.2 ± 12.2	79.3 ± 6.9
				10	6	62.0 ± 18.6	92.8 ± 8.1
				20	6	72.2 ± 15.5	92.2 ± 6.3
				50 µg/kg + Atropine	6	69.8 ± 20.3	97.0** ± 2.7
			T1 @ 10% recovery	Edrophonium	24	See paper for results	See paper for results

Author/Year Country	Total # patients	NMBA	Neostigmine Administration	Neostigmine Dose	# Patients /group	Reversal TOF Ratios over Time	
							TOFR @ 10minutes
Naguib et al. 1993b United Arab Emirates	80 adults ASA I & II	Mivacurium 0.15 mg/kg	T1 @ 10% recovery	None (control) 5 10 20 50 µg/kg + Atropine	16 8 8 8 8		*Mean (CI 95%)* 0.48 (0.42-0.53) 0.61 (0.47-0.74) 0.68* (0.56-0.79) 0.84* (0.75-0.93) 0.78*(0.66-0.89)
			T1 @ 10% recovery	Edrophonium	32		See paper for results

*p<0.05, **p<0.01, ***p<0.001

6.1.6 Other Endpoints

No other endpoints were analyzed by the Applicant.

Reviewer's Comments
No endpoints that provided clinically relevant information about the efficacy of neostigmine were identified in the literature search conducted as part of this review.

6.1.7 Subpopulations

Pediatric Population

The Applicant identified five trials reported in the literature that they considered being adequate and well controlled. In each study, neostigmine significantly hastened the recovery from the NMBA compared to spontaneous recovery.

From the data in these studies, summarized in the table below, the Applicant concluded that:

1. A neostigmine dose of 70 µg/kg effectively reduces recovery time to $TOF_{0.9}$ from rocuronium- or vecuronium-induced NMB when administered at all levels of residual blockade; and
2. Neostigmine doses as low as 5 µg/kg may be effective in reducing recovery time to $TOF_{0.7}$ or higher from deep and moderate residual blockade.

The Applicant searched for trials reporting efficacy across pediatric age groups. Two reports in the literature provided such information:

1. Motsch et al. (13) grouped patients into two age groups, 1-4 years and 5-10 years. They found that reversal times from rocuronium to T1 = 75% or 90% of baseline were significantly longer in the younger group (by 1-2 minutes), but the times to $TOF_{0.7}$ were not significantly different.
2. Kirkegaard-Nielsen et al. (14) studied neostigmine and edrophonium reversal in five age groups of pediatric patients:
    a. 0-2 months
    b. 3-11 months
    c. 2-5 years
    d. 6-10 years
    e. 11-15 years

    They administered 50 mcg/kg of neostigmine to 8 subjects in each age group when T1 recovered to 10% of its baseline value; 1 mg/kg of edrophonium was administered to another 8 subjects in each age group at the same time point. They found that by 15 minutes after study drug, the TOF ratio was greater for neostigmine-treated patients than edrophonium-treated patients and that recovery was age dependent: patients less than 1 year of age had the shortest mean recovery times to $TOF_{0.7}$ (approximately 3.5 minutes), which differed significantly compared to the oldest patient group (approximately 8 minutes).

Lastly, the Applicant searched the literature for trials comparing efficacy in pediatric patients to that in adult patients. They found three such trials:

1. Abdulatif et al. (15) examined the dose-response relationships for neostigmine antagonism of 90% rocuronium-induced neuromuscular block in 8 children (2-10 yrs.) and 10 adults (18-60 yrs.). The time to 10% recovery of T1 was shorter in children than in adults (25 min vs. 39 min). Both spontaneous and neostigmine-assisted recoveries were more rapid in children than in adults. Adequate

recovery, i.e., $TOF_{0.8}$, occurred in children at 4, 5, and 8 min after neostigmine 50, 20 and 10 mcg/kg, respectively; whereas adequate recovery was not produced in adults by any dose of neostigmine within 10 min. The effective doses of neostigmine required to achieve $TOF_{0.8}$ after 10 min in children and adults were determined to be 7 mcg/kg and 57 mcg/kg, respectively.

2. Bevan et al. (16) evaluated recovery from spontaneous and neostigmine-induced recovery from mivacurium in 54 children (mean age 5 yrs.) and 54 adults (mean age 40 yrs.). Placebo or a 5, 10, 20, or 50 mcg/kg dose of neostigmine was administered when T1 recovered to 10% of baseline. They found that spontaneous recovery from mivacurium proceeded more rapidly in children than in adults. At 10 min, T1 had recovered to 97 in children compared with 69 in adults and TOF had recovered to 84% in children but only 30% in adults. In children, 10 min after neostigmine administration, recovery of T1 and TOF was enhanced only by the three larger doses of neostigmine; in adults, recovery was accelerated by neostigmine.
3. Bevan et al. (11) also investigated the influence of the timing of neostigmine administration on recovery from rocuronium or vecuronium neuromuscular blockade. They compared the T1 and TOF recovery of 80 adults (mean age 40 yrs.) and 80 children (mean age ~54 months) who were randomized to spontaneous recovery or reversal with 70 mcg/kg neostigmine given 5 min after relaxant, or first twitch (T1) recovery of 1%, 10%, or 25%. The mean spontaneous recovery times to $TOF_{0.7}$ after rocuronium and vecuronium administration in adults were 46 and 53 minutes, respectively, but significantly less in children: 29 and 35 minutes respectively. Neostigmine accelerated recovery in all reversal groups by approximately 40%. Recovery from rocuronium and vecuronium blockade after neostigmine administration was more rapid in children than in adults. Return of neuromuscular function after reversal was not influenced by the timing of neostigmine administration.

Based on the information above, the Applicant proposes the following language for product labeling regarding pediatric use of neostigmine:

8.4. Pediatric Use

Recovery of neuromuscular activity occurs more rapidly with smaller doses of (b) (4) in infants and children than in adults. (b) (4) However, infants and small children may be at greater risk of complications from incomplete reversal of neuromuscular blockade due to decreased respiratory reserve. The dose of (b) (4) required to reverse neuromuscular blockade in children varies between 30-70 µg/kg, the same dose range shown to be effective in adults. (b) (4)

(b) (4)

Reviewer's Comments
The neostigmine dosing, timing of administration, and TOF ratio endpoints for each of the studies is summarized in Table 5 below.

Table 5. Doses of neostigmine (mcg/kg) in pediatric trials of neostigmine vs. spontaneous recovery (based on Table 20 on p. 47 of the ISE)

NMBA	Residual Block @ Neostigmine Administration				TOF Ratio	Reference [# neostigmine exposures]
	Profound T1 = 0	Deep 0<T1≤10%	Moderate 10<T1≤25%	Light T1>25%		
Rocuronium						
	70	70	70		0.9, 0.7	Bevan et al. (11)
			40		0.7	Motsch et al. (13)
		5 10 20 50			0.73 0.89 0.98 0.99	Abdulatif et al. (15)
Vecuronium						
	70	70	70	70	0.9	Bevan et al. (11)
	70	70		70	0.7	
Mivacurium						
		50			0.97	Bevan et al. (16)

As can be seen in the table above, the 70 mcg/kg dose was the most commonly evaluated in the 156 patients that constitute this efficacy database. Similar to the adult studies, there is so much variability in the trial designs that is not possible to recommend a single weight-based neostigmine dose that will be effective in all or most clinical settings. The study results do indicate that neostigmine can be effective at all levels of residual blockade, from profound to light, and that 70 mcg/kg dosing appears to be consistently effective, without reports of delayed recovery that were occasionally observed in adult patients.

Regarding age-related variation in recovery, the findings of the two studies appear to be conflicting; however, most of the differences that were observed by Kirkegaard-Nielsen et al. occurred in patients less than 1 year of age, a group not evaluated by Motsch et

al. The findings of the three trials comparing adult to pediatric responses were consistent: pediatric patients recover faster whether spontaneously or with neostigmine, and neostigmine exhibits a dose effect for both populations, though more so for adults.

Based on the literature, it appears:

1. Sufficient numbers of pediatric patients > 1 year of age have been evaluated for efficacy and dosing requirements to adequately inform the label.
2. Neostigmine is effective over the range of pediatric age groups and a variety of NMBAs.
3. Doses as high as 70 mcg/kg have been demonstrated to be effective, but higher doses have not been evaluated.
4. Doses as low as 10 mcg/kg have been demonstrated to produce $TOF_{>0.8}$ within a clinically relevant time frame, i.e., 10 minutes.

Although relatively few neonates and infants have been evaluated for efficacy, the available data strongly suggest:

1. Their recovery from NMBAs is faster than their older pediatric counterparts and adults.
2. Their neostigmine dosing requirements are probably less than these other patient groups.
3. They tolerate a 70 mcg/kg dose of neostigmine as well as the other patient groups.

Therefore, there does not appear to be a need for further study of any segment of the pediatric patient population

The Applicant makes a valid point when suggesting that the higher doses be recommended in the labeling so as to error on the side of achieving greater recovery in a shorter period of time in a population may not be readily able to indicate they are experiencing problems with maintaining a patent airway or adequately ventilating. Although prolonged blockade was not observed in the pediatric trials involving the 70 mcg/kg dose of neostigmine, the possibility of such an outcome has not been rigorously evaluated and cannot be ruled out. This introduces some risk to recommending treatment with 70 mcg/kg for all pediatric patients at all levels of spontaneous recovery. Therefore, recommending adult dosing, i.e., 30-70 mcg/kg, for the entire pediatric age group is a reasonable approach, provided it is accompanied by the caveats of carefully monitoring recovery and of being alert for the possibility of delayed recovery due to a relatively high dose of neostigmine rather than an inadequate dose.

Based on the amount of evidence for efficacy and the concerns for safety in the pediatric population, the following edits are recommended to the Applicant-proposed labeling for Pediatric Use:

8.4. Pediatric Use

Recovery of neuromuscular activity occurs more rapidly with smaller doses of (b) (4) in infants and children than in adults. (b) (4) However, infants and small children may be at greater risk of complications from incomplete reversal of neuromuscular blockade due to decreased respiratory reserve (b) (4) (b) (4) .

(b) (4) the dose of (b) (4) required (b) (4) to reverse neuromuscular blockade in children varies between (b) (4) 30-70 mcg/kg, the same dose range shown to be effective in adults, (b) (4) (b) (4)

Geriatric Patients

The Applicant identified four clinical trials reported in the literature specifically evaluating neostigmine efficacy in elderly patients. The findings for each are summarized below:

1. McCarthy et al. (17) conducted a double-blinded, dose-controlled study of 36 adult (aged 18-50 years) and 36 elderly (aged more than 70 years) ASA-PS 1 and 2 patients for whom neostigmine was used to antagonize NMB induced by vecuronium. Doses of 5, 15, 25, 35, or 45 µg/kg of neostigmine were administered after T1 had recovered to 10% of control. They found that the dose-response curves from 5 minutes to 10 minutes were parallel for adult and elderly patients; however, the curve for the elderly was shifted significantly to the right (i.e., slower reversal time) of the curve for the adults at all time points. The estimated doses of neostigmine required to achieve $TOF_{0.7}$ within 5–10 minutes was significantly greater in the elderly at each time point. While the reason for this difference was not discernable, the data indicated that greater doses (approximately 30-60%) of neostigmine are required in the elderly than in younger adults to reverse deep vecuronium-induced blockade within 10 minutes.
2. Marsh et al. (18) assessed the recovery of pancuronium-induced neuromuscular blockade in 13 elderly (70-91 years) and 13 adult (17-33 years) patients following neostigmine that was administered. Neostigmine doses of 2.5 mg (for subjects weighing < 50 kg), 3.0 mg (for subjects weighing 50-70 kg), or 3.5 mg (for subjects weighing > 70 kg) were administered 30 minutes after the last dose of pancuronium. The investigators noted that there was considerable variation in the degree of neuromuscular blockade at the time neostigmine was

administered. The mean time to reach $TOF_{0.6}$ was 5 (range from 2-17) minutes in the young adult patients and 11 (range from 1-29 minutes) in the elderly patients. The differences between the groups were not significant.

3. Young et al. (19) evaluated the differences between 18 young (mean age 35 years) and 14 elderly (mean age 68 years) patients with respect to the duration of antagonism of metocurine-induced neuromuscular blockade by neostigmine and pyridostigmine. The mean ages for the ten young and seven elderly neostigmine-treated patients were 42 years and 72 years, respectively. The 70 mcg/kg of neostigmine or 0.14 mg/kg of pyridostigmine were administered during the metocurine infusion after T1 had been stable at 10% of baseline for at least 30 minutes. The investigators then assessed the start of response, maximum response, and duration of maximum response for both age groups and both treatments. For the neostigmine-treated patients, they found no significant difference between the elderly and the younger adult patients in the neostigmine times to onset and maximum response; however, the mean duration of maximum response to neostigmine was significantly prolonged in the elderly: 32 versus 11 minutes.
4. Koscielniak-Nielsen (20) showed that neostigmine-assisted recovery from doxacurium-induced neuromuscular blockade was not significantly different between 24 elderly (aged 70-85 years) and young 24 young adult (aged 18-40 years) patients who were all ASA-PS 1 or 2. The study compared the dose-response of 5, 10, 20, or 40 µg/kg of neostigmine administered after T1 had recovered to 25% of control. Neostigmine dose-response curves were obtained using the amplitudes of T1 and TOF measured 10 minutes after the antagonist was administered. The investigators found that the mean time to 25% recovery of T1 after 30 µg/kg of doxacurium was 80 min in the young versus 133 min in the elderly. Neostigmine-assisted recovery was not significantly different in both groups. The estimated doses of neostigmine to obtain $TOF_{0.7}$ after 10 min were 54 µg/kg in the young and 42 µg/kg in the elderly.

The Applicant did not analyze the data further; their proposed labeling for this age subgroup is as follows:

8.5. Geriatric Use

(b) (4) the duration of action of neostigmine is prolonged in the elderly. However, elderly (b) (4) also experience slower spontaneous recovery from neuromuscular blocking agents. (b) (4)

Reviewer's Comments

There is, as the Applicant notes, very little information about neostigmine's efficacy in the elderly. The findings of the studies that have been published are, to varying degrees, confounded and have produced disparate results. While the information available is insufficient to support labeling the product differently for dosing in the

geriatric population, some additional information should be provided in the labeling, specifically the following edits:

8.5. Geriatric Use

(b) (4) the duration of action of neostigmine is prolonged in the elderly. However, elderly (b) (4) also experience slower spontaneous recovery from neuromuscular blocking agents. (b) (4)

Renally and Hepatically Impaired Patients

The Applicant did not identify any studies in the literature evaluating the changes in efficacy for neostigmine that may occur in patients with renal or hepatic impairment. They therefore, recommend the following language for the label:

8.6. Renal Impairment

(b) (4)

8.7. Hepatic Impairment

No adjustments to dosing appear to be warranted in patients with hepatic insufficiency.

Reviewer's Comments

It is important to consider the effects of renal and hepatic impairment on both neostigmine and the NMBA that was used. If neostigmine, which is cleared by the kidneys, was used to reverse a renally cleared NMBA, there should be no need, theory, to adjust the neostigmine dose or observe the patient for a longer period than when the products are administered to a patient with normal renal function. The change in renal function would affect both drugs similarly, unless different mechanisms of clearance are involved, e.g., diffusion and active transport. As little is known about the mechanisms of renal clearance for the various NMBAs and neostigmine, it is recommended that patients be observed for signs of returning neuromuscular blockade for a period that would permit full spontaneous recovery from the NMBA given the patient's level of renal function. Such a determination could be predicated on the NMBA dosing intervals observed during the surgical procedure; if available, this information could be used to accurately predict duration of action for the NMBA in any patient.

However, if a patient has hepatic impairment and receives an NMBA cleared in part or completely by the liver, there is the possibility that the effects of the NMBA may outlast those of the neostigmine and additional doses of neostigmine may be required. For these patients, extending the period of time for observation following neostigmine administration is warranted. The same would apply for NMBAs that have active metabolites, which would further compound the issue.

Based on these concerns, the following edits are recommended to these sections of the label:

8.6. Renal Impairment

(b) (4) to assure the effects of the neuromuscular blocking agent do not persist beyond those of neostigmine. In this regard, the interval for redosing the neuromuscular blocking agent during the surgical procedure, (b) (4), may be useful in determining whether, and to what extent, post-operative monitoring needs to be extended.

8.7. Hepatic Impairment

No adjustments to dosing appear to be warranted in patients with hepatic insufficiency. However, patients should be carefully monitored if hepatically cleared neuromuscular blocking agents were used during their surgical procedure as their duration of action may be prolonged by hepatic insufficiency whereas neostigmine, which undergoes renal elimination, will not likely to be affected. This could result in the effects of the neuromuscular blocking agent outlasting those of neostigmine. This same situation may arise if the neuromuscular blocking agent has active metabolites. In this regard, the interval for redosing the neuromuscular blocking agent during the surgical procedure, if available, may be useful in determining whether, and to what extent, post-operative monitoring needs to be extended.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Applicant notes that the literature they have been able to identify for evaluation of neostigmine's pharmacologic activity and efficacy to reverse neuromuscular block (NMB), with only a few exceptions, represented relatively healthy subjects presenting for elective surgical procedures. In this population, neostigmine was shown to be efficacious in shortening the time for reversal of neuromuscular block, compared to spontaneous reversal for both males and females, across an age range from infant through the elderly, and with a variety of NMBAs. They state that although it is not possible to compare NMB reversal times between specific published studies due to variables such as depth of block and time to determination of efficacy, it is clear that the conclusion of neostigmine efficacy is consistent across the literature evaluated.

Based on their review of the literature, they concluded that the dose range found to be useful in shortening the time to reversal of neuromuscular blockade in the pivotal studies using the more conservative efficacy endpoint of $TOF_{0.9}$ was 30-70 mcg/kg, which was also shown to be an effective dose range in all the supportive studies that used less stringent endpoints (e.g., $TOF_{<0.9}$). They believe this consistency is important because anesthesiologists vary in their approaches to neuromuscular blockade reversal and the TOF ratio they target as adequate for any given patient. They do caution that patients who might be expected to react to neostigmine differently from otherwise healthy subjects (e.g., patients with myasthenia gravis or pre-existing states of cholinergic crisis due to organophosphate poisoning, patient who are taking medication that could influence neuromuscular block), were not evaluated in the studies.

In consideration of dosing recommendations, the Applicant has divided the literature findings based on the duration of action of the NMBA reversed, i.e., long, intermediate and short) and then subdivided the findings based on the degree of blockade at the time neostigmine was administered, i.e., profound, deep, moderate, or light. They note that the length of time the NMBA drug persists at the site of action determines the duration of neuromuscular blockade and the extent to which neostigmine may affect recovery time. The elimination half-life of an NMBA does not always correlate with duration of action as the termination of action sometimes depends on redistribution instead of elimination of the parent compound and its metabolites. Long-duration NMBAs have long (1-2 hours) elimination half-lives and depend on liver and/or kidney function, i.e., metabolism, for termination of action. Intermediate-duration drugs have either an intermediate elimination half-life (e.g., atracurium, cisatracurium), or they may have a long elimination half-life (1-2 hours), but their termination of effect is primarily due to redistribution (e.g., vecuronium, rocuronium). Short-duration drugs have short elimination half-lives (e.g., mivacurium). At the time of the NDA submission, five NMBAs have active NDAs: pancuronium, atracurium, vecuronium, rocuronium, and cisatracurium. Of these, they considered pancuronium to have a long duration of action based on its 60-120 minute time to spontaneous recovery of T1 to 25%. The others

were considered to be of intermediate duration based on their 30-45 minute times to spontaneous recovery of T1 to 25%.

Long-Acting NMBAs
The Applicant states that no adequate and well-controlled studies of neostigmine reversal of pancuronium-induced (or pipecuronium-induced) block were found in their literature review.

Intermediate-Acting NMBAs
Table 6. below summarizes the Applicant's findings in the literature for the results from the adequate and well-controlled studies using intermediate-duration NMBAs, by degree of blockade at neostigmine administration.
Based on these findings they concluded that for intermediate-duration NMBAs:

- Neostigmine doses of 30-70 µg/kg effectively reduce recovery time to $TOF_{0.7}$ or higher from profound residual blockade;
- Neostigmine doses of 20-70 µg/kg effectively reduce recovery time to $TOF_{0.7}$ or higher from deep and moderate residual blockade; and
- Neostigmine doses as low as 10 µg/kg effectively reduce recovery time to $TOF_{0.7}$ or higher from light residual blockade.

Table 6. Neostigmine dosing information for intermediate-duration NMBAs (Table 15 on p. 39 of ISE)

NMBA**	Residual Block @ Neostigmine Administration				Reference	TOF Ratio
	Profound T1 = 0	Deep 0<T1≤10%	Moderate 10<T1≤25%	Light T1>25%		
Rocuronium						
		30	30		Barrio et al. (21)*	0.8
	30, 50				Lederer et al. (9)	0.9, 0.8
			40		Adamus et al. (10)	0.9, 0.7
		70	70		Bevan et al. (11)	0.9
	70	70	70			0.7
		20, 35, 50	20, 35, 50		McCourt et al. (22)	0.8
	40		40		Van den Broek et al. (23)	0.7
		50			Abdulatif et al. (15)	0.78
Vecuronium						
	70		70		Magorian et al. (24)*	0.75
	70	70, 70	70		Bevan et al. (11)	0.9, 0.7
	40				Caldwell et al. (25)	0.7
		38.8†, 67.4†		35.7†, 80.5†	Jones et al. (26)	0.7
Atracurium						
				10, 20, 30	Fuchs-Buder et al. (8)*	0.9, 1.0
	40				Caldwell et al. (25)	0.7
		50			Naguib and Riad (27)	0.82
Cisatracurium						
		30	30		Barrio et al. (21)*	0.8
			40		Adamus et al. (10)	0.9, 0.7
		50			Naguib and Riad (27)	0.82

* Placebo-controlled studies (all other studies spontaneous-recovery controlled)

** Doses of NMBAs were within current recommended dosages listed in the Prescribing Information
† Calculated: 2.5 mg or 5.0 mg dose divided by the mean weight reported for each group

Short-Acting NMBAs

Table 7 below summarizes the Applicant's findings in the literature for the results from the adequate and well-controlled studies using short-duration NMBAs, by degree of blockade at neostigmine administration.

Based on these findings they concluded that for intermediate-duration NMBAs:

- Neostigmine doses of 50-70 µg/kg effectively reduce recovery time to $TOF_{0.7}$ or higher from profound rapacuronium-induced residual blockade;
- Neostigmine doses of 20-50 µg/kg can effectively reduce recovery time to $TOF_{0.7}$ or higher from deep residual blockade, however, neostigmine has occasionally failed to reverse mivacurium-induced deep residual block; and
- Neostigmine doses of 40-70 µg/kg effectively reduce recovery time to $TOF_{0.7}$ or higher from moderate residual blockade.
- There are no results for neostigmine reversal of rapacuronium- or mivacurium-induced light residual blockade.

Table 7. Neostigmine dosing for short-duration NMBAs (Table 16 on p. 41 of ISE)

Residual Block @ Neostigmine	Residual Block @ Neostigmine Administration				Reference	TOF Ratio
		Deep 0<T1≤10%	Moderate 10<T1≤25%	Light T1>25%		
Rapacuronium						
			20, 40		Lessard et al. (28)*	0.7
				7	Hayes et al. (29)	0.8, 0.7
		50, 70†			Purdy et al. (30)	0.8, 0.7
				5, 0	McCourt et al. (22)	0.8, 0.7
Mivacurium						
			(70)		Devcic et al. (31)*	(0.25, 0.5)
				4	Baurain et al. (12)	0.9, 0.7
			(40)††	4	Bartunek et al. (32)	0.7
			(70)††		Kao and Le (33)	0.5, 0.7, 0.9
			20		Bevan et al. (16)	0.81
			50			0.78
			20		Naguib et al. (34)	0.84
			50			0.78

* Placebo-controlled studies. All other studies spontaneous-recovery controlled.
** Doses of NMBAs were within current Prescribing Information.
† Ninety-two of 117 patients were at 100% block when neostigmine was administered
†† Neostigmine dose not significantly different from spontaneous recovery

Based on the information above, the Applicant concluded that the published data adequately support the use of neostigmine in the dose range of 30-70 µg/kg for the reversal of short- and intermediate-duration NMBAs and that insufficient information is available to document the effectiveness of neostigmine in reversing long-acting NMBAs. The dose of neostigmine needs to be predicated, in part, on the level of spontaneous recovery that has occurred at the time it is to be administered.

Reviewer's Comments

The Applicant was charged at the preNDA meeting with trying to identify a single (weight-based) dose of neostigmine that would reliably reverse NMBAs when administered at a specified point during spontaneous recovery. Based on their review of the literature, and that of this reviewer, it is not possible to achieve this goal with the data currently available. Therefore, the recommendation of a dosing range, which is supported by data from the literature and accompanied to the extent possible with information on how to determine the most appropriate dose for patient, is a reasonable alternative.

A review of the more recent literature finds growing support that the TOF ratios that correlate most strongly to a degree of reversal that would allow a patient to maintain and protect a patent airway and adequately ventilate without assistance appear to be those ≥ 90%. Although most of the older literature has used a TOF ratio of 70% as the standard for assessing adequate reversal, more recent clinical studies have used ratios of 80% and 90%, as the Applicant has identified. This reviewer has identified 11 articles that described clinical trials in which recovery was assessed to these higher TOF ratios. In Table 8 below, the findings for those studies are summarized.

Table 8. Summary of neostigmine dosing information that resulted in TOF ratios > 70%

Source	NMBA Reversed	Dose of Neostigmine (mcg/kg)	Timing of Neostigmine Administration	Maximum TOF Reported (%)	Time to TOF assessment or Maximum TOF (min)	Population
Abdulatif (15)	rocuronium	Spont. recovery	--	48	TOF ratio assessed at 10 min after T_1 = 10%	pediatric
		5	T_1 = 10%	73		
		10		89		
		20		98		
		50		99		
		Spont. recovery	--	19		adults
		5	T_1 = 10%	29		
		10		47		
		20		62		
		50		78		
Baurain (35)	rocuronium	40	T_1 = 25%	90	TOF ratio assessed at 15 min after T_1 = 25%	adults
	vecuronium			88		
	atracurium			92		
	pancuronium			76		
Baurain (36)	vecuronium	20	T_1 = 10%	76	TOF ratio assessed at 15 min after neostigmine	adults
			T_1 = 25%	85		
			T_1 = 50%	92		
		40	T_1 = 10%	86		
			T_1 = 25%	86		
			T_1 = 50%	94		
		80	T_1 = 10%	80		
			T_1 = 25%	88		
			T_1 = 50%	86		

Source	NMBA Reversed	Dose of Neostigmine (mcg/kg)	Timing of Neostigmine Administration	Maximum TOF Reported (%)	Time to TOF assessment or Maximum TOF (min)	Population
Bevan (11)	rocuronium	70	T_1 = 1%	90	< 20	pediatric
			T_1 = 10%		< 20	
			T_1 = 25%		< 25	
			T_1 = 1%		< 30	adults
			T_1 = 10%		< 30	
			T_1 = 25%		< 40	adults
	vecuronium	70	T_1 = 1%	90	< 30	pediatric
			T_1 = 10%		< 30	
			T_1 = 25%		< 30	
			T_1 = 1%		< 40	adults
			T_1 = 10%		< 40	
			T_1 = 25%		< 40	
Caldwell (37)	vecuronium	40	TOF = 29%	86	10	adults
Goldhill (38)	atracurium	Spont. recovery	--	90	45	adults
		15	T_1 = 6%		16	
		35	T_1 = 12%		10	
		55	T_1 = 15%		10	
		75	T_1 = 9%		10	
Lederer (9)	rocuronium	Spont. recovery	--	90	39	adults
		30	5 min. after rocuronium		23	
		50			19	

Source	NMBA Reversed	Dose of Neostigmine (mcg/kg)	Timing of Neostigmine Administration	Maximum TOF Reported (%)	Time to TOF assessment or Maximum TOF (min)	Population
McCourt (39)	rapacuronium boluses	Spont. recovery	--	80	72	
		50	T_1 = 25%		10	adults
	rapacuronium infusion	Spont. recovery	--		66	
		50	T_1 = 25%		9	adults
	rocuronium	Spont. recovery	--		37	
		50	T_1 = 25%		6	adults
Meistelman (40)	vecuronium	30	T_1 = 1%	80	12	adults
			T_1 = 10%	100	8	adults
			T_1 = 25%	100	5	adults
Sacan (41)	rocuronium	70	T_1 = 12%	90	17	adults
Schaller (42)	rocuronium	Placebo	--	90	19	adults
		5	TOF = 50%		9	
		8	TOF = 50%		5	
		15	TOF = 50%		4	
		25	TOF = 50%	90	3	
		40	TOF = 50%		2	

The data in the table indicate that lower doses of neostigmine are adequate to reverse NMBAs with shorter half-lives, e.g., rocuronium. They also indicate that lower doses of neostigmine are adequate when more substantial levels of spontaneous recovery have occurred. Lastly, there are limited data regarding the recovery of pancuronium to a level of TOF recovery greater than 70%. This may be attributed, in part, to it being an older drug that would have been evaluated under the "old" gold standard for measuring reversal, which used a TOF ratio of 70%. However, the data, of Baurain and colleagues, seem to indicate that pancuronium behaves differently compared to vecuronium, rocuronium, and atracurium. The reduced TOF maxima for pancuronium suggests that it may bind more strongly to the acetylcholine receptors in the neuromuscular junction than the other MNBAs, and therefore, the additional acetylcholine that is available for the lower dose of neostigmine (40 mcg/kg administered at T_1 = 25%) may have only a limited effect on pancuronium's reversal.

Based on the information in the table, several guidelines for dosing can be recommended:

1. Peripheral nerve stimulation devices capable of delivering a TOF stimulus are essential to effectively using neostigmine.
2. There must be a twitch response to the first stimulus in the TOF of at least 10% of its baseline level, i.e., the response prior to NMBA administration.
3. A 30 mcg/kg to 70 mcg/kg dose of neostigmine will generally achieve a TOF ratio of 90 within 10 to 20 minutes of administration. The greater the extent of spontaneous recovery at the time of neostigmine administration; the lower the dose of neostigmine is needed to produce $TOF_{0.9}$. If there is a need for more rapid recovery, a higher dose of neostigmine should be administered.
    a. The 30 mcg/kg dose is generally effective for reversal of NMBAs with shorter half-lives, e.g., rocuronium, or when the first twitch response is substantially greater than 10% of baseline or when a second twitch is present.
    b. The 70 mcg/kg dose is generally effective for NMBAs with longer half-lives, e.g., vecuronium and pancuronium, or when the first twitch response is relatively weak, i.e., not substantially greater than 10% of baseline.
4. Precise assessments of twitch responses may not be possible in the clinical setting. In those situations, using a dose of neostigmine closer to 70 mcg/kg may be preferable, if the patient's condition is likely to tolerate it.
5. TOF monitoring should continue to be used to evaluate the extent of recovery of neuromuscular function and the possible need for an additional dose of neostigmine.
6. TOF monitoring alone should not be relied upon to determine the adequacy of reversal of neuromuscular blockade as related to a patient's ability to adequately ventilate and maintain a patent airway following tracheal extubation.
7. Patients should continue to be monitored for adequacy of reversal from NMBAs for a period of time that would assure full recovery based on the patient's medical condition and the pharmacokinetics of neostigmine and the NMBA used.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Regarding persistence of efficacy, the Applicant noted that some investigators reported that they did not observe "recurization," i.e., signs or symptoms of recurring neuromuscular blockade; however, systematic assessments using nerve stimulation were not made.

They postulate that with neostigmine's half-life estimated to be between 77 and 113 minutes, its effects should outlast those of the NMBAs currently used in clinical practice, with the possible exception of pancuronium, which has a half-life estimated to be between 89 and 161 minutes.

They recommend that regardless of the NMBA used, patients should be carefully observed following administration of neostigmine due to:

- Limitations in interpreting TOF responses in the clinical setting, with the potential for overestimating the extent of reversal
- Interactions of other drug products that can affect the intensity or duration of neuromuscular blockade, e.g., volatile anesthetic agents and some antibiotics
- Variations in metabolism of the NMBA and neostigmine that can occur due to a patient's underlying medical condition and concomitant medications.

Regarding tolerance to the effects of neostigmine, the Applicant states that its acute use in the perioperative, and occasionally, the intensive care unit, settings limits the likelihood of this occurrence. They note that it is possible that treatments for certain neurological conditions, e.g. myasthenia gravis, may alter the acetylcholine/acetylcholinesterase balance at the neuromuscular synapse; however, the need to adjust the dose of both the NMBA and neostigmine should be apparent with appropriate monitoring of neuromuscular functioning, and such monitoring should allow the dose of neostigmine to be titrated to the desired effect.

Reviewer's Comments

The observations and arguments put forth by the Applicant regarding both persistence of efficacy and tolerance of effects are valid. A review of the literature found that the vast majority of articles did not comment on whether the effects of neostigmine failed to outlast the effects of the NMBA; in those articles that addressed the issue, the phenomenon of "recurization" was not observed, as indicated by the Applicant. The review of the literature did not find any reports describing a need to adjust the dose of neostigmine for the purpose of reversing the effects of an NMBA when a patient was treated with an anticholinesterase for an underlying medical condition. Similarly, the failed to find any report of changes in the pharmacodynamics of neostigmine associated with the chronic use an anticholinesterase.

The Applicant's recommendations for careful monitoring of patients is sound, and the incorporation of this advice in the product's labeling is appropriate.

6.1.10 Additional Efficacy Issues/Analyses

The Applicant has identified several studies where their findings suggest that if neostigmine is given when neuromuscular recovery is nearly complete, that it can actually prolong neuromuscular blockade.

1. Payne et al. (43) showed that after an initial 2.5 mg dose of neostigmine administered after neuromotor blockade with tubocurarine, dimethyl tubocurarine, or gallamine in the presence and absence of halothane anesthesia, there was reversal of tetanic fade and an increase in tetanic twitch height. However, when a second 2.5 mg dose of neostigmine was administered 2-5 minutes after the initial dose, tetanic fade reoccurred and tetanic twitch height was reduced in the presence of halothane; the same was true in the absence of halothane, but to a lesser extent.
2. Caldwell (37) showed a decrease in TOF in 8 out of 30 patients who received a 40 µg/kg dose of neostigmine 2-4 hours after a single dose of vecuronium 0.1 mg/kg. These patients had minimal block at the time neostigmine was administered, TOF ratios of ≥ 0.9, after which TOF ratios decreased by as much as 0.2. This phenomenon was not observed when patients had a greater degree of residual paralysis or when reduced doses (20 µg/kg) of neostigmine were administered. Caldwell concluded that high but not low doses of neostigmine given at a shallow level of neuromuscular blockade may produce neuromuscular weakness.
3. Kao and Le (33) assessed whether anticholinesterases inhibit the activity of plasma cholinesterases and thereby prolong rather than shorted the recovery time for mivacurium, which is hydrolyzed by plasma cholinesterase. They found that, compared to spontaneous recovery, 70 mcg/kg of neostigmine administered when T1 was > 3% of baseline levels produced a faster recovery to T1 values of 25%, 50%, and 75% of baseline, but recovery to T1 = 95% of baseline was delayed. This finding was not observed in a group of subjects administered 1 mg/kg of edrophonium at the same point of spontaneous recovery, i.e., all subjects in this group had faster recovery times to all four T1 endpoints compared to the spontaneous recovery group.

Reviewer's Comments

The findings of Payne et al. suggest that there is an upper limit to the dose of neostigmine that will reduce the recovery time from neuromuscular blockade, at least for the NMBAs that were evaluated in their trial. This limit would correspond to a 70 mcg/kg dose of neostigmine based on the 5 mg dose they administered and assuming the patients weighed 70 kg.

The findings of Caldwell suggest that there may be an upper limit to when neostigmine can be administered, in the course of spontaneous recovery, and still have a positive effect.

The findings of Kao and Le echo those of Payne et al. However, whether their suggestion that the reason for the prolonged recovery from mivacurium is due to an effect of neostigmine on plasma cholinesterase activity is difficult to assess. It is not consistent with the findings of Baurain et al. (12); although they evaluated a 40 mcg/kg dose of neostigmine, versus the 70 mcg/kg dose evaluated by Kao and Le. Their hypothesis would also have to include that the effects on plasma cholinesterase is unique to neostigmine, as it was not observed with edrophonium. It is possible that the effect is related to the 70 mcg/kg dosing and that such a high dose has the potential for the same consequences regardless of the NMBA used.

In summary, the findings of these studies further support a recommendation for limiting the weight-based dosing of neostigmine to ≤ 70 mcg/kg and incorporating language in the labeling that patients need to be carefully monitored if neostigmine is administered later in recovery or at 70 mcg/kg. Studies of its administration up to $TOF_{0.6}$ did not report these findings making this a possible cutoff point for more intensive monitoring; however, it is not possible to discern how well the protocols would have captured such a finding or whether the investigators would have reported such a finding in their published results

7 Review of Safety

Safety Summary

Neostigmine has been in clinical use for many decades following its synthesis by Aeschlimann and Reinert in 1931. In 1939, neostigmine was approved by FDA, under the trade name of Prostigmin, for the prevention and treatment of post-operative, non-obstructive, abdominal distention, i.e., adynamic ileus. In the 1950's, the use of neostigmine became routine for reversing neuromuscular blockade. As part of the "Liverpool anaesthetic technique," a 5 mg dose was administered at the end of surgery in an effort to avoid incomplete recovery from neuromuscular blocking agents.(44) The safety of neostigmine throughout this long history of use in the clinical setting has been documented in the literature in the form of adverse event reporting for controlled clinical studies and case reports. The literature, combined with an analysis of the information contained in the FDA's Adverse Event Reporting System (AERS), which was performed by both the Applicant and the Division of Pharmacovigilance II, formed the basis for characterizing the risk profile associated with the proposed use of neostigmine.

The adverse events related to the use of neostigmine were found to be primarily related to its actions as an inhibitor of the enzyme, acetylcholinesterase (AChE). Shortly after its intravenous administration, neostigmine reaches the synaptic cleft of the neuromuscular junction where it binds to and inhibits AChE. The inhibition of AChE results in increased levels of acetylcholine (ACh), which competes with nondepolarizing neuromuscular blocking agents, thereby reversing their effect. However, the activity of neostigmine is not limited to AChE at the nicotinic receptors of the neuromuscular junction; as a result of its administration, increased levels of ACh occur at nicotinic receptors outside the neuromuscular junction and muscarinic receptors as well.

Nicotinic receptors are located in both the peripheral and central nervous system. Because neostigmine has a quaternary ammonium group, it is unable to penetrate the blood-brain barrier; therefore, its effects are exerted primarily at the peripheral nervous system via the autonomic ganglia and adrenal medulla. However, the muscarinic side-effects of anticholinesterases tend to predominate. These include nausea and vomiting, bradycardia and prolongation of the QT interval of the electrocardiograph (ECG), bronchoconstriction, stimulation of salivary glands, miosis, and increased intestinal tone.(44) All of these have been observed with neostigmine.

Indeed, the muscarinic side effects described above were the most frequently reported in the literature and in the AERS database. These effects can be mitigated with coadministration of an anticholinergic agent; typically, atropine or glycopyrrolate are used for this purpose in the practice of anesthesia. The efficacy, safety and dosing of these anticholinergic agents is not the subject of this review; however, it should be noted that glycopyrrolate (ANDA 090963) is approved for this indication, and atropine

has been approved for this purpose as part of a combination product, Enlon-Plus (NDA 19678), which contains edrophonium and atropine.

In addition to those adverse events that can be attributed to neostigmine's mechanism of action, a number of other adverse events were reported in the literature and to the FDA's adverse event reporting system (AERS). The literature included several reports of clinical trials involving neostigmine; some of these included placebo or spontaneous recovery as controls. Safety assessments from these studies provided the best sources of information that could be used to discern adverse events that were most likely due to neostigmine versus those due to any of the large number of other medications administered in the perioperative period or to the surgical procedure itself. Other adverse events gleaned from the literature, in the form of case reports and safety findings from other types of clinical trials, and from the analyses, by the Applicant and FDA, of the reports in the AERS database provided additional safety information that was treated in a manner similar to adverse events reported in the post-marketing period of FDA-approved drug products.

The Applicant has proposed the following text for the safety related sections of the neostigmine label:

4. **CONTRAINDICATIONS**

(b) (4) is contraindicated in patients with known hypersensitivity to (b) (4) (b) (4) (b) (4) with peritonitis or mechanical obstruction of the intestinal or urinary tract.

5. **WARNINGS AND PRECAUTIONS**

(b) (4)

Large doses of (b) (4) administered when neuromuscular blockade is minimal can produce neuromuscular dysfunction. The dose of (b) (4) should be reduced if recovery from neuromuscular blockade is nearly complete.

It is important to differentiate between myasthenic crisis and cholinergic crisis caused by overdosage of (b) (4) Both conditions result in extreme muscle weakness but require radically different treatment. [*see Overdosage (10)*]

6. **ADVERSE REACTIONS**

Adverse reactions to (b) (4) are (b) (4) attributable to exaggerated pharmacological effects. (b) (4)

Quantitative adverse event data are available from (b) (4) (b) (4) The following (b) (4) with an overall frequency of 1% or (b) (4)

Cardiovascular Disorders: Bradycardia, hypotension, tachycardia/heart rate increase
Gastrointestinal Disorders: Nausea, vomiting, postprocedural nausea, dry mouth
General Disorders and Administration Site Conditions: Procedural pain, incision site complication, pharyngolaryngeal pain, procedural complication
Nervous System Disorders: Dizziness, headache, postoperative shivering, prolonged neuromuscular blockade
Psychiatric Disorders: Insomnia
Respiratory, Thoracic and Mediastinal Disorders: Dyspnea, desaturation <90%
Skin and Subcutaneous Tissue Disorders: Pruritus

(b) (4)

Allergic Disorders: Allergic reactions, anaphylaxis
Nervous System Disorders: Fasciculation, convulsions, loss of consciousness, drowsiness, dysarthria, miosis, visual changes
Cardiovascular Disorders: Cardiac arrhythmias (A-V block, nodal rhythm), nonspecific EKG changes, cardiac arrest, syncope, hypotension
Respiratory, Thoracic and Mediastinal Disorders: Increased oral, pharyngeal and bronchial secretions, respiratory depression, respiratory arrest, bronchospasm
Skin and Subcutaneous Tissue Disorders: Rash, urticaria
Gastrointestinal Disorders: Flatulence, increased peristalsis, bowel cramps, diarrhea
Renal and Urinary Disorders: Urinary frequency
Musculoskeletal and Connective Tissue Disorders: Muscle cramps and spasms, arthralgia
Miscellaneous: Diaphoresis, flushing, (b) (4)

7. **DRUG INTERACTIONS**

(b) (4)

Based on the review of the safety data, the risks of neostigmine have been well characterized, are mostly consistent with the drug's mechanism of action, and can be readily monitored and treated in the perioperative setting. The Applicant's labeling accurately and adequately describes the product's safety profile although minor changes, described in the sections that follow, are recommended. Differences between the Applicant's and FDA's analyses of the AERS data and the associated findings are also discussed below; however, these differences do not impact the benefit-risk analysis or the proposed product labeling.

7.1 Methods

The safety of neostigmine, when used to reverse the effects of neuromuscular blocking agents (NMBA), was assessed by reviewing the literature for case reports and safety findings from clinical studies and by analyzing the adverse event reports that were available in the Agency's Adverse Events Reporting System (AERS) database. The Applicant provided the literature which captured safety information; both the Applicant and the review team from the Division of Pharmacovigilance II in the Office of Surveillance and Epidemiology performed an analysis of the AERS data; the review team also conducted their own search for and analysis of safety information reported in the published literature.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The literature provided by the Applicant that assessed the safety of neostigmine included:

- 5 prospective, controlled trials offering quantitative presentation of adverse events (200 patients treated with neostigmine)
- 10 additional studies offering qualitative safety information (624 patients treated with neostigmine; 5 studies (348 patients) also discussed in efficacy section)
- Safety information on neostigmine from controlled trials presented during FDA Advisory Committee meeting for sugammadex (167 patients treated with neostigmine; it is unclear if this population overlaps with published studies on sugammadex)
- 2 meta-analyses and a systematic review on gastrointestinal adverse events (a total of 2,570 patients treated with neostigmine or allowed to spontaneously recover)
- 1 randomized, controlled trial on the effects of neostigmine on heart rate (41 patients treated with neostigmine)
- 27 case reports (35 patients treated with neostigmine)
- 3 studies offering additional pediatric safety information (61 patients treated with neostigmine).

The two tables below, Table 9 and Table 10, list the studies the Applicant utilized for the safety evaluation for adult and pediatric patients. Other studies in the literature for these two patient groups were identified by this reviewer and are listed in the two subsequent tables, Table 11 and Table 12.

Reviewer's Comments

The safety data gathered from the literature identified in Tables 9-12 is derived from 3,194 adult and 249 pediatric patients who were exposed to neostigmine. Although it is not possible to determine whether any patients participated in more than one of the studies, or how many were included in both of the meta-analyses, the number of exposures should be adequate to identify any life-threatening, severe, or moderately severe reactions that occur with the administration of neostigmine in both the pediatric and adult populations. Furthermore, the data derived from the five controlled clinical trials also allows a quantification of adverse events, compared to placebo treatment, for 200 neostigmine-treated adult patients, including adverse events that would be considered mild in severity. The literature-based safety data, therefore, are expected to be adequate for performing a benefit:risk analysis and for labeling the safety issues related to the use of the product.

Table 9. Applicant-identified clinical studies for evaluating the safety of neostigmine for adult patients

Citation	Number of Patients Exposed	Primary Safety Outcome Measured	Dose of neostigmine (mg) or (mg/kg)	Dose of Atropine or Glycopyrrolate (mg or µg/kg)	Agent(s) Reversed
Schaller et al. (42)	51	Adverse events recorded until patient was discharged from recovery room	0.005, 0.008, 0.015, 0.025, or 0.04 mg/kg	Glycopyrrolate 1 µg per 5 µg neostigmine	rocuronium
Lemmens et al. (45)	77	Follow up period for assessing adverse events not stated	0.07 mg/kg	Glycopyrrolate 14 µg/kg	vecuronium
Khuenl-Brady et al. (46)	94	Adverse events up to 7 days post-dose recorded	0.05 mg/kg to a maximum of 5 mg	glycopyrrolate 10 µg/kg	vecuronium
Flockton et al. (47)	76	Adverse events up to 7 days post-dose recorded	Neostigmine 0.05 mg/kg	glycopyrrolate 10 µg/kg	rocuronium or cisatracurium
Jones et al. (48)	77	Adverse events up to 7 days post-dose recorded	0.07 mg/kg up to 5 mg	Glycopyrrolate 14 µg/kg (total dose ≤ 1.0 mg)	rocuronium
Lessard et al. (28)	70	Monitoring of ECG, pulse oximetry and non-invasive MAP	0.010 – 0.04 mg/kg	glycopyrrolate 0.25, 0.5, or 1 mg	mivacurium
McCourt et al. (22)	110	Incidence of emetic symptoms	0.02 – 0.05 mg/kg	Glycopyrrolate 10 µg/kg or atropine 20 µg/kg	rocuronium
Fuchs-Buder et al. (49)	24	Incidence of bradycardia	0.02 mg/kg	atropine 10µg/kg	vecuronium

Citation	Number of Patients Exposed	Primary Safety Outcome Measured	Dose of neostigmine (mg) or (mg/kg)	Dose of Atropine or Glycopyrrolate (mg or µg/kg)	Agent(s) Reversed
Hayes et al. (29)	15	Monitoring of ECG, pulse oximetry and non-invasive MAP	0.05 mg/kg	Not reported	rapacuronium
Purdy et al. (30)	93	Postanesthetic AEs and SAEs	0.05 – 0.07 mg/kg	glycopyrrolate 0.01 mg/kg	rapacuronium
Larijani et al. (50)	119	Heart rate and incidence of bronchospasm	0.05 mg/kg	glycopyrrolate 10 mcg/kg	rapacuronium
Tribuddharat et al. (51)	46	Role of different doses of atropine on cardiovascular effects	2.5 mg	atropine 0.9 or 1.2 mg	vecuronium
Sacan et al. (41)	20	Adverse events recorded during the operation and upon discharge from the postanesthesia care unit	0.07 mg/kg	glycopyrrolate 14 µg/kg	rocuronium
Owens et al. (52)	43 (> 64 years)	ECG monitored following administration of antagonist continuously for 90 minutes, except during transport	0.07 mg/kg	Atropine 0.036 mg/kg, up to 2 mg	Not specified
Backman et al. (53)	41	effect of neostigmine on heart rate in patients with normally innervated hearts and in patients who had undergone recent or remote cardiac transplantation	0.0025 mg/kg repeated to a max of 0.075 mg/kg or 0.01 mg/kg doses repeated to a max of 0.05 mg/kg	Atropine 1.2 mg	Not specified

Citation	Number of Patients Exposed	Primary Safety Outcome Measured	Dose of neostigmine (mg) or (mg/kg)	Dose of Atropine or Glycopyrrolate (mg or µg/kg)	Agent(s) Reversed
Fuchs-Buder et al. (8)	90	No safety assessment plan described	0.01, 0.02 or 0.03 mg/kg	Atropine 15 µg/kg	atracurium
Lederer et al. (9)	40	No safety assessment plan described	0.03 mg/kg or 0.05 mg/kg	Glycopyrrolate 7 µg/kg, or for the higher neostigmine dose: glycopyrrolate 10 µg/kg	rocuronium
Adamus et al. (10)	60	No safety assessment plan described	0.04 mg/kg	Atropine 15 µg/kg	cisatracurium or rocuronium
Bevan et al. (11)	80	Monitoring of ECG, pulse oximetry and non-invasive MAP	0.07 mg/kg	glycopyrrolate 0.01 mg/kg	rocuronium or vecuronium
Baurain et al. (12)	12	No safety assessment plan described	0.04 mg/kg	Atropine 15 µg/kg	mivacurium
Barrio et al. (21)	40	No safety assessment plan described	0.03 mg/kg	with or without atropine 10 µg/kg	Rocuronium or cisatracurium
Devcic et al. (31)	10	No safety assessment plan described	0.07 mg/kg	Atropine 20 µg/kg	Mivacurium
Magorian et al. (24)	30	No safety assessment plan described	0.07 mg/kg	glycopyrrolate 15 µg/kg	Vecuronium
McCourt et al. (39)	36	Monitoring of ECG, pulse oximetry and non-invasive MAP	0.05 mg/kg	glycopyrrolate 10 µg/kg	rapacuronium with and without rocuronium

Citation	Number of Patients Exposed	Primary Safety Outcome Measured	Dose of neostigmine (mg) or (mg/kg)	Dose of Atropine or Glycopyrrolate (mg or µg/kg)	Agent(s) Reversed
Bartunek et al. (32)	19	No safety assessment plan described	0.04 mg/kg	Atropine 15 µg/kg	Mivacurium
Van den Broek et al. (23)	40	Investigate the effects of neostigmine and atropine on heart rate	0.04 mg/kg	with and without atropine 7 µg/kg	Rocuronium
Caldwell et al. (25)	19	No safety assessment plan described	0.07 mg/kg	Atropine 1.2 mg	Vecuronium or Atracurium
Jones et al. (26)	40	No safety assessment plan described	2.5 or 5 mg	Atropine 1.2 mg	Vecuronium
Kao and Le (33)	10	No safety assessment plan described	0.07 mg/kg	Atropine 20 µg/kg	Mivacurium
Naguib and Riad (27)	64	No safety assessment plan described	0.005, 0.01, 0.02 or 0.05 mg/kg	Atropine 0.3-1.5 mg as needed	Atracurium or Cisatracurium
Abdulatif et al. (15)	40	No safety assessment plan described	5, 10, 20, 50 µg/kg	Atropine 5-20 µg/kg as needed	Rocuronium
Bevan et al. (16)	24	No safety assessment plan described	0.005, 0.01, 0.02 or 0.05 mg/kg	Atropine 2, 4, 8, or 20 µg/kg	Mivacurium
Naguib et al. (34)	32	No safety assessment plan described	0.005, 0.01, 0.02 or 0.05 mg/kg	Atropine 0.3-1.5 mg	Mivacurium

Citation	Number of Patients Exposed	Primary Safety Outcome Measured	Dose of neostigmine (mg) or (mg/kg)	Dose of Atropine or Glycopyrrolate (mg or µg/kg)	Agent(s) Reversed
Harper et al. (54)	57	Monitoring of vital signs, ECG, capnography and pulse oximetry	0.02 – 0.08 mg/kg	atropine 0.4mg/1mg neostigmine	atracurium
Kirkegaard-Nielsen et al. (55)	46	No safety assessment plan described	0.036 mg/kg	Atropine 14 µg/kg	Vecuronium
Kirkegaard-Nielsen et al. (56)	83	No safety assessment plan described	0.07 mg/kg	Atropine 2, 4, 8, or 20 µg/kg	Atracurium
Rupp et al. (57)	41	No safety assessment plan described	0.04 mg/kg	glycopyrrolate 10 µg/kg	Atracurium, Pancuronium, or Vecuronium
Payne et al. (43)	26	No safety assessment plan described	2.5, 5, or 7.5 mg	Atropine 1.2 mg	Tubocurarine, dimethyl-tubocurarne, gallamine, or none
Caldwell et al. (37)	60	Monitoring of ECG and non-invasive MAP	0.02 – 0.04 mg/kg	glycopyrrolate 4 or 8 µg/kg	vecuronium
McCarthy et al. (17)	60	No safety assessment plan described	0.005, 0.015, 0.025, 0.035, or 0.045 mg/kg	Glycopyrrolate (dose not specified)	Vecuronium
Marsh et al. (18)	26	No safety assessment plan described	2.5, 3.0 or 3.5 mg	atropine 1.2 mg	Pancuronium
Young et al. (19)	32	No safety assessment plan described	0.07 mg/kg	Atropine 20 µg/kg	Metocurine

Citation	Number of Patients Exposed	Primary Safety Outcome Measured	Dose of neostigmine (mg) or (mg/kg)	Dose of Atropine or Glycopyrrolate (mg or µg/kg)	Agent(s) Reversed
Koscielniak-Nielsen et al. (20)	148	No safety assessment plan described	0.005, 0.01, 0.02, or 0.04 mg/kg followed by second neostigmine dose to total 0.06 mg/kg	Atropine 0.6-1.2 mg	Doxacurium

Table 10. Applicant-identified clinical studies for evaluating the safety of neostigmine in pediatric patients

Citation	Number of Patients Exposed	Primary Safety Outcome Measured	Dose of neostigmine (mg) or (mg/kg)	Dose of Atropine or Glycopyrrolate (mg or µg/kg)	Agent(s) Reversed
Watcha et al. (58)	38	Whether antagonism with neostigmine or edrophonium was associated with postoperative emesis	0.07 mg/kg	Glycopyrrolate 10 µg/kg	mivacurium
Salem et al. (59)	20	Hemodynamic response to atropine-neostigmine antagonism of neuromuscular block	0.05 mg/kg	atropine 20 µg/kg	tubocurarine
Gonzalez et al. (60)	3	Reports on three cases of neostigmine use in the treatment of constipation in critically ill children	11 µg/kg per hour for 12 hours; or 5 µg/kg per hour for 18 hours; or 11 µg/kg per hour for 30 hours	none	none
Bevan et al. (11)	80	Monitoring of ECG, pulse oximetry and non-invasive MAP	0.07 mg/kg	glycopyrrolate 0.01 mg/kg;	rocuronium or vecuronium

Citation	Number of Patients Exposed	Primary Safety Outcome Measured	Dose of neostigmine (mg) or (mg/kg)	Dose of Atropine or Glycopyrrolate (mg or µg/kg)	Agent(s) Reversed
Motsch et al. (13)	8	No safety assessment plan described	0.04 mg/kg	Atropine 7 µg/kg	Rocuronium
Kirkegaard-Nielsen et al. (14)	40	No safety assessment plan described	0.05 mg/kg	Atropine 10 µg/kg	Atracurium
Gwinnutt et al. (61)	18	Monitoring of ECG, pulse oximetry and non-invasive MAP	0.05 – 0.10 mg/kg	atropine 20 µg/kg	atracurium
Bevan et al. (16)	24	No safety assessment plan described	0.005, 0.01, 0.02 or 0.05 mg/kg	Atropine 2, 4, 8, or 20 µg/kg	Mivacurium

Table 11. Additional clinical studies evaluating the safety of neostigmine in adults

Citation	Number of Patients Exposed	Primary Safety Outcome Measured	Dose of neostigmine (mg) or (mg/kg)	Dose of Atropine or Glycopyrrolate (mg or µg/kg)	Agent(s) Reversed
Ostheimer et al. (62)	305	Safety assessment between atropine and glycopyrrolate	2.5 mg	Atropine 1.0 mg or glycopyrrolate 0.5 mg	d-tubocurarine or pancuronium
Mirakhur et al. (63)	40	Safety assessment between atropine and glycopyrrolate	2.5 mg	Atropine 1.2 mg or glycopyrrolate 0.5 mg	tubocurarine or pancuronium
Brock-Utne et al. (64)	20	Lower esophageal tone	2.5 mg 5.0 mg	glycopyrrolate 0.6 mg	Suxameth-onium

Citation	Number of Patients Exposed	Primary Safety Outcome Measured	Dose of neostigmine (mg) or (mg/kg)	Dose of Atropine or Glycopyrrolate (mg or µg/kg)	Agent(s) Reversed
Salem et al. (65)	115	Postoperative heart rate and oral secretions	5 mg	Atropine 1.2 or 1.8 mg or; glycopyrrolate 0.6 mg or 0.9 mg	pancuronium
King et al. (66)	19	Incidence of postoperative nausea and vomiting	2.5 mg	atropine 1.2 mg	tubocurarine
Goldhill et al. (67)	51	Incidence of dysrhythmias, abnormal heart rate and BP	0.01 – 0.08 mg/kg	glycopyrrolate 0.2 mg	pancuronium
Johnson et al. (68)	26	ECG, and arterial pressure	0.01 – 0.04 mg/kg	Atropine 0.4 mg/1.0 mg neostigmine	vecuronium
Nagiub et al. (69)	70	Change in heart rate via ECG	0.04 – 0.06 mg/kg	atropine 0.014-0.04 mg/kg	pancuronium
Wetterslev et al. (70)	55	Change in heart rate via ECG	0.035 mg/kg	Atropine 8 µg/kg or glycopyrrolate 7 µg/kg	gallamine
Sursesh et al. (71)	32	Dose response to cardiovascular changes	0.015 – 0.075 mg/kg	glycopyrrolate 3-15 µg/kg	atracurium
Boeke et al. (72)	40	Incidence of postoperative nausea and vomiting	1.5 mg	atropine 0.5 mg	vecuronium
Dhonneur et al. (73)	80	Effect of renal failure on reversal from neuromuscular block	0.04 mg/kg	atropine 20 µg/kg	vecuronium

Citation	Number of Patients Exposed	Primary Safety Outcome Measured	Dose of neostigmine (mg) or (mg/kg)	Dose of Atropine or Glycopyrrolate (mg or µg/kg)	Agent(s) Reversed
Hovorka et al. (74)	80	Incidence of postoperative nausea and vomiting	2.0 mg	glycopyrrolate 0.4 mg	mivacurium
Joshi et al. (75)	40	Incidence of postoperative nausea and vomiting	2.5 mg	glycopyrrolate 0.5 mg	mivacurium or rocuronium

Table 12. Additional clinical study evaluating the safety of neostigmine in pediatric patients

Citation	Number of Patients Exposed	Primary Safety Outcome Measured	Dose of neostigmine (mg) or (mg/kg)	Dose of Atropine or Glycopyrrolate (mg or µg/kg)	Agent Reversed
Debaene et al. (76)	18	Monitoring of ECG, pulse oximetry and non-invasive MAP	0.03 mg/kg	atropine 10 µg/kg	vecuronium

7.1.2 Categorization of Adverse Events

The Applicant grouped and categorized adverse events by system organ class (SOC) and preferred terms. As the events were reported in the literature and the original data could not be retrieved, the Applicant categorized the events as described in the publications to the best of their ability.

Reviewer's Comments
The categorization of adverse events gleaned from the literature is limited by the descriptions and terms used by the authors in reporting the events. The Applicant was consistent in their classification of the adverse events by SOC and preferred terms. They were also appropriate in their classifications, i.e., there was no evidence that the Applicant attempted to understate an adverse event in the selection of the preferred terms.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Applicant pooled data across studies to the extent possible and attempted to estimate and compare incidence of adverse events. The results from the analyses must be viewed with some caution due to the number of confounding factors affecting safety both within and among the studies, e.g., other anesthetic agents used, risks from the surgical procedures, patient demographics, concomitant medical conditions and medications, and coadministration of anticholinergic agents with the neostigmine.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The studies identified by the Applicant for the evaluation of safety are listed in Table 9 and Table 10. These studies reflect exposure to neostigmine in up to 3,637 adult and 61 pediatric patients. They were not able to determine whether any patients were included in more than one study, particularly, in the reports of meta-analyses and reports of the safety findings relative to sugammadex at the FDA advisory committee meeting.

The Applicant noted the following regarding the safety data reported in the literature:

1. The patients were not highly selected.
2. Most patients were undergoing elective surgery.
3. The majority of the patients in clinical trials were adults (age range 18-74); however, children aged 2-14 years old were also studied.
4. The age range for safety data derived from case reports was 13 months to 82 years.
5. Both genders were equally represented.
6. The majority of the patients were ASA 1-3.
7. Many papers did not identify the racial or ethnic groups of the patients; those that did list racial groups indicated that the subjects were predominantly Caucasian.

Reviewer's Comments
Although the safety database does not contain the amount of demographic information generally captured with clinical trials for which the full study reports are provided to the Agency, there is adequate information available to characterize the overall risks of neostigmine associated with the proposed indication and the populations in whom the product will be used.

7.2.2 Explorations for Dose Response

The Applicant did not conduct an exploration for dose responses of adverse events. Although such an exploration may be possible, the data to do so are limited and confounded by a number of factors, most notably, the use of varying doses of anticholinergic agents to mitigate or prevent excessive acetylcholine related adverse events and the concurrent use of anesthetic agents each with its own adverse event profile.

Reviewer's Comments
Based on the mechanism of action for neostigmine, it would be reasonable to anticipate an increase in the incidence and the severity of acetylcholine-related adverse events with an increase in neostigmine dose, and it would not be unreasonable to adjust the dose of the co-administered anticholinergic agent in parallel with the neostigmine dose to minimize the risk of these adverse events.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing of neostigmine was performed by the Applicant or included in the literature search.

7.2.4 Routine Clinical Testing

Clinical laboratory testing to evaluate the effects, if any, of neostigmine on serum electrolytes and glucose, renal and hepatic function, hematology and coagulation parameters, acid-base parameters and urine composition were not reported in the literature. The literature does not contain reports of commonly observed abnormalities in any of these assessments despite widespread use of neostigmine for the proposed indication for over half a century. The Applicant noted that three studies involving sugammadex reported safety information from analysis of blood or urine samples; these are described in Section 7.4.2.

Reviewer's Comments
The limited amount of data available regarding the impact of neostigmine on parameters assessed by clinical laboratory methods is adequate due to the acute use of the product and its long history of use for the proposed indication. Any effect neostigmine may have on these parameters is likely to be clinically irrelevant as those effects likely to have a substantial impact on patients' health would likely have been discerned and well characterized in the literature, similar to the way the hemodynamic effects of neostigmine have already been reported.

7.2.5 Metabolic, Clearance, and Interaction Workup

As noted in the Clinical Pharmacology review by Drs. Naraharisetti and Xu, nonclinical information provided in the submission indicated that neostigmine is eliminated in the urine unchanged and undergoes hepatic metabolism in the liver microsomes. 3-

hydroxyphenytrimethyl ammonium (PTMA) is the primary metabolite, which then becomes glucuronide conjugated PTMA. The pharmacokinetics of neostigmine in patients with hepatic impairment has not been studied.

Cronnelly et al. (77) determined the pharmacokinetics of neostigmine in patients with normal renal function (n = 8), undergoing renal transplantation (n = 6) or status post bilateral nephrectomy (n = 4). Neostigmine, 70 mcg/kg, and atropine, 30 mcg/kg, were given by infusion over a 2-minute period. Plasma concentration data versus time plots fitted a two-compartment pharmacokinetic model. Elimination half-lives for normal, transplant, and anephric patients were 80 ± 49, 105± 64, and 181 ± 54 min (mean ± SD), respectively. Clearances for normal, transplant and anephric patients were 17 ± 5, 19 ± 6 and 8 ± 3 mL/min/kg (mean ± SD), respectively. The clearance in patients with impaired renal function was lower compared to patients with normal renal function.

The pharmacokinetic interaction between neostigmine and other drugs has not been reported in the literature.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Pyridostigmine and edrophonium are the other anticholinesterases approved for reversal of nondepolarizing neuromuscular blocking agents. The labels for these products contain descriptions of adverse events similar to those reported for neostigmine.

The Adverse Reactions section of the Regonol label (pyridostigmine; NDA 017398) contains the following wording:

> The side effects of pyridostigmine bromide are most commonly related to overdosage and generally are of two varieties, muscarinic and nicotinic. Among those in the former group are nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis, and diaphoresis. Nicotinic side effects are comprised chiefly of muscle cramps, fasciculation, and weakness. Muscarinic side effects can usually be counteracted by atropine. As with any compound containing the bromide radical, a skin rash may be seen in an occasional patient. Such reactions usually subside promptly upon discontinuance of the medication. Thrombophlebitis has been reported subsequent to intravenous administration.

The Adverse Reactions section of the Enlon label (edrophonium; NDA 017398) contains the following wording:

> Careful observation should be made for severe cholinergic reactions in the hyperreactive individual. The myasthenic patient in crisis who is being tested with ENLON should be observed for bradycardia or cardiac standstill and cholinergic reactions if an overdose is given.
>
> The following reactions common to anticholinesterase agents may occur, although not all of these reactions have been reported with the administration of ENLON, probably because of its short duration of action and limited indications:
>
> | | |
> |---|---|
> | **Eye:** | Increased lacrimation, pupillary constriction, spasm of accommodation, diplopia, conjunctival hyperemia. |
> | **CNS:** | Convulsions, dysarthria, dysphonia, dysphagia. |
> | **Respiratory:** | Increased tracheobronchial secretions, laryngospasm, bronchiolar constriction, paralysis of muscles of respiration, central respiratory paralysis. |
> | **Cardiac:** | Arrhythmias (especially bradycardia), fall in cardiac output leading to hypotension. |
> | **G.I.:** | Increased salivary, gastric and intestinal secretion, nausea, vomiting, increased peristalsis, diarrhea, abdominal cramps. |
> | **Skeletal Muscle:** | Weakness, fasiculations. |
> | **Miscellaneous:** | Increased urinary frequency and incontinence, diaphoresis. |

Reviewer's Comments

As indicated in section 7.3 below, the adverse events associated with neostigmine are similar to those associated with both Regonol and Enlon.

7.3 Major Safety Results

7.3.1 Deaths

The Applicant found no reports of deaths attributable to neostigmine in the studies in which neostigmine was given intravenously to reverse neuromuscular blockade. They did find a report by Briggs et al. (78) on the death of a girl who was diagnosed with megacolon at 6 months of age and treated with 3.75 mg to 7.5 mg of neostigmine daily. The dose was increased to 15 mg daily at 7 years age. At age 9 years old, she presented with constipation and required disimpaction. One hour later, she was unable to move her legs and experienced shortness of breath that progressed to apnea and death. Neostigmine overdose was suspected and was confirmed via determination of serum cholinesterase levels.

A review of the literature, conducted by this reviewer, revealed three reports of acute cardiac arrest leading to death in anesthetized patients following intravenous administration of neostigmine. The etiologies of these deaths were attributed to the rapid administration of neostigmine or inappropriate timing of administration of atropine leading to bradycardia and cardiac arrest. These reports are summarized in Table 13 below.

Table 13. Neostigmine related deaths associated with general anesthesia

Author [Year] Reference	Age/ Gender	Neostig-mine Dose (mg)	Pre-Operative Diagnosis	Atropine Dose (mg)	Relevant Clinical Observations
Clutton-Brock (79)	62 years Female	2.0 mg	Common bile duct obstruction	0.65 mg	Intra-operative cardiac "irregularities" were reported
Hill (80)	7 months Gender not reported	0.25 mg	Congenital atresia of the bile duct	0.22 mg	Autopsy findings were normal exception for the bile duct
Macintosh (81)	38 years Male	2.5 mg	Acute surgical abdomen	0.65 mg	Autopsy findings included cardiac hypertrophy and generalized peritonitis

Reviewer's Comments
The anesthesia-associated deaths appear to have been due to the expected cardiac effects of neostigmine as opposed to some unknown action of the product. These

events emphasize the need for careful monitoring and the timely use of an anticholinergic agent (b) (4)

7.3.2 Nonfatal Serious Adverse Events

The Applicant did not report on nonfatal serious adverse events. In the review of the literature, potentially life-threatening adverse events were reported; however, the articles generally did not specify whether these events met the regulatory criteria for being serious adverse events. These events included anaphylaxis and cardiac arrhythmias. The arrhythmias were consistent with the known effects of neostigmine at the muscarinic receptors. In the 120-day safety update, the Applicant identified a published case report by Tufek et al. (82) of cardiac arrest that occurred in an 18-month old male following surgery for congenital glaucoma. The patient received 0.015 mg/kg of atropine followed by 40 mcg/kg of neostigmine. The report states that immediate bradycardia occurred, followed by cardiac arrest. The child recovered, without sequelae, after 15 minutes of chest compressions and multiple doses of adrenaline (100 mcg every 3 minutes). More details regarding this case are provided in Section 7.7 below.

Reviewer's Comments
These events, similar to the reports of deaths described in section 7.3.1, emphasize the need for careful monitoring and timely administration of an appropriate dose of an anticholinergic agent when neostigmine is to be administered perioperatively.

7.3.3 Dropouts and/or Discontinuations

The Applicant did not report on or conduct an analysis of the dropouts and discontinuations in the reported studies. In the review of the literature, it was noted that both of these events were rarely reported. This is an expected finding consistent with the acute use of neostigmine in the surgical setting and the short duration of follow-up, which was generally limited to the time in the operating room and post-anesthesia care unit following surgery. There were reports in some of the studies about subjects being withdrawn due to issues related to the surgical procedure (e.g., procedure was aborted), lack of need for reversal at the end of surgery (i.e., spontaneous recovery precluded use of the study drug) and treatment with the wrong study drug.

7.3.4 Significant Adverse Events

As with serious adverse events, the Applicant did not analyze adverse events on the basis of their severity. Based on the review of the literature, specific adverse events were rarely graded on severity. When they were graded, most often the adverse events were considered as a whole and described as “mild or moderate.”

7.3.5 Submission Specific Primary Safety Concerns

Although not commented on by the Applicant, none of the adverse events reported in the literature raised special safety concerns due either to their unanticipated occurrence or the frequency with which they were reported.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The Applicant notes that, in most of the older literature, the potential contribution of neostigmine to the adverse events observed at the end of surgical procedures was not evaluated. They further note that a number of medications are administered in the perioperative period, both prior to and after neostigmine, that have adverse events associated with them making it difficult to discern what role, if any, neostigmine had to do with them. The Applicant has therefore relied upon information contained in studies involving the use of neostigmine with sugammadex, a reversal agent for nondepolarizing neuromuscular blocking agents. These studies were discussed publicly at an FDA Advisory Committee (AC) meeting in 2008, and the Applicant drew their information from the briefing package for that meeting. In that document, two Phase 3, active-comparator trials in neuromuscular blockade reversal were described including the adverse event information for neostigmine (dosed at 50-70 mcg/kg) administered to 167 treated patients. Altogether, 149 subjects (89%) of those patients experienced adverse events associated with use of neostigmine. As noted by the Applicant, causality assessments were not included in the AC briefing document presentation of adverse events; however, most of the observed events are common surgical and post-operative findings. Table 14 below lists these adverse events.

Table 14. Common adverse events (frequency ≥ 2%) by preferred terms (based on Table 2 on pp. 14-15 of ISS)

SOC	Preferred Term	No. Adverse Events (%)
Injury, poisoning and procedural complications	**Total**	**113 (67.7)**
	Procedural pain	85 (50.9)
	Incision site pain	14 (8.4)
	Procedural nausea	13 (7.8)
	Procedural hypertension	9 (5.4)
	Procedural complication	14 (8.4)
	Procedural hypotension	11 (6.6)
	Procedural vomiting	5 (3.0)
	Airway complication of anesthesia	4 (2.4)
	Post procedural complication	4 (2.4)
	Neuromuscular block prolonged	4 (2.4)
Gastrointestinal disorders	**Total**	**89 (53.3)**
	Nausea	61 (36.5)
	Vomiting	22 (13.2)

SOC	Preferred Term	No. Adverse Events (%)
Gastrointestinal disorders	Flatulence	4 (2.4)
	Constipation	11 (6.6)
	Retching	8 (4.8)
	Abdominal pain	6 (3.6)
	Dry mouth	14 (8.4)
	Oral pain	6 (3.6)
	Dyspepsia	5 (3.0)
General disorders and administration site conditions	**Total**	**35 (21.0)**
	Pain	14 (8.4)
	Chills	7 (4.2)
	Pyrexia	8 (4.8)
Nervous system disorders	**Total**	**34 (20.4)**
	Headache	13 (7.8)
	Dizziness	11 (6.6)
Investigations	**Total**	**18 (10.8)**
	Blood creatine phosphokinase increased	3 (1.8)
Psychiatric disorders	**Total**	**27 (16.2)**
	Insomnia	9 (5.4)
	Anxiety	8 (4.8)
	Sleep disorder	4 (2.4)
Respiratory, thoracic and mediastinal disorders	**Total**	**23 (13.8)**
	Pharyngolaryngeal pain	17 (10.2)
Musculoskeletal and connective tissue disorders	**Total**	**20 (12.0)**
	Back pain	7 (4.2)
	Muscular weakness	5 (3.0)
	Myalgia	6 (3.6)
Skin and subcutaneous tissue disorders	**Total**	**13 (7.8)**
	Pruritus	6 (3.6)
	Erythema	4 (2.4)
Renal and urinary disorders	**Total**	**9 (5.4)**
Blood and lymphatic system disorders	**Total**	**9 (5.4)**
Metabolism and nutrition disorders	**Total**	**7 (4.2)**
Infections and infestations	**Total**	**7 (4.2)**
Cardiac disorders	**Total**	**5 (3.0)**

A number of publications describing pharmacologic responses to neostigmine for reversal of non-polarizing neuromuscular blockade included discussions of safety

findings. Five of these included quantitative presentations of the adverse events associated with neostigmine that were incorporated into a table, which is copied below (Table 15). Some of these publications involve studies comparing neostigmine to sugammadex. It is not possible to determine the extent of overlap for the data in the Table 14 above and Table 15 below.

Table 15. Summary of adverse events reported in the literature (Table 3 on pp. 16-17 of ISS)

Adverse Event	Schaller et al. 2010 (42)		Jones et al. 2008[A] (48)	Lemmens et al. 2010[A] (45)	Khuenl-Brady et al. 2010[B] (46)	Flockton et al. 2008[C] (47)	TOTAL
	Neostigmine n=42	Placebo n=9	Neostigmine n=38	Neostigmine n=36	Neostigmine n=45	Neostigmine n=39	Neostigmine n=200
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Procedural pain			29 (76.3)	24 (66.7)		16 (41.0)	53 (26.5)
Nausea			19 (50)	12 (33.3)	2 (4.4)	10 (25.6)	43 (21.5)
Incision site complication			8 (21.1)	8 (22.2)			16 (8.0)
Vomiting			7 (18.4)	4 (11.1)		4 (10.3)	15 (7.5)
Dizziness			5 (13.2)	4 (11.1)		4 (10.3)	13 (6.5)
Bradycardia	12 (27)	0 (0)					12 (6.0)
Headache			4 (10.5)	2 (5.6)		6 (15.4)	12 (6.0)
Pharyngolaryngeal pain			4 (10.5)	7 (19.4)			11 (5.5)
Postoperative shivering	11 (25)	0 (0)					11 (5.5)
Procedural complication			6 (15.8)		4 (8.9)		10 (5.0)
Insomnia			4 (10.5)			5 (12.8)	9 (4.5)
Postprocedural nausea			5 (13.2)	2 (5.6)			7 (3.5)
Pruritus			4 (10.5)	2 (5.6)			6 (3.0)
Dry mouth					4 (8.9)		4 (2.0)
Desaturation <90%	3 (7)	0 (0)					3 (1.5)
Hypotension	3 (7)	4 (44)					3 (1.5)

Adverse Event	Schaller et al. 2010 (42)		Jones et al. 2008[A] (48)	Lemmens et al. 2010[A] (45)	Khuenl-Brady et al. 2010[B] (46)	Flockton et al. 2008[C] (47)	TOTAL
	Neostigmine n=42	Placebo n=9	Neostigmine n=38	Neostigmine n=36	Neostigmine n=45	Neostigmine n=39	Neostigmine n=200
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Tachycardia/Heart rate increase	2 (5)	0 (0)			1 (2.2)		3 (1.5)
Neuromuscular block prolonged					2 (4.4)		2 (1.0)
Acute lung failure	1 (2)	0 (0)					1 (0.5)
Anesthetic complications (cough/movement)	1 (2)	0 (0)					1 (0.5)
Beta-N-acetyl-D-glucosaminidase increase						1 (2.6)	1 (0.5)
Erythema					1 (2.2)		1 (0.5)
Gamma-glutamyl-transferase increase					1 2.2)		1 (0.5)
Hypertension	1 (2)	0 (0)					1 (0.5)
Hypokalemia	1 (2)	1 (11)					1 (0.5)
Hypocalcemia	1 (2)	1 (11)					1 (0.5)
Procedural					1 (2.2)		1 (0.5)

Adverse Event	Schaller et al. 2010 (42)		Jones et al. 2008[A] (48)	Lemmens et al. 2010[A] (45)	Khuenl-Brady et al. 2010[B] (46)	Flockton et al. 2008[C] (47)	TOTAL
	Neostigmine n=42	Placebo n=9	Neostigmine n=38	Neostigmine n=36	Neostigmine n=45	Neostigmine n=39	Neostigmine n=200
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
hypertension							
Sleep disorder					1 (2.2)		1 (0.5)
Supraventricular extrasystoles					1 (2.2)		1 (0.5)
Tremor						1 (2.6)	1 (0.5)
Ventricular extrasystoles					1 (2.2)		1 (0.5)
Hypoglycemia	0 (0)	1 (11)					0 (0)
Paresthesia *nervus ulnaris*	0 (0)	1 (11)					0 (0)
Postoperative nausea & vomiting	0 (0)	2 (22)					0 (0)

[A] Adverse events occurring in at least 10% of the patients in either the sugammadex or neostigmine treatment group
[B] Adverse events considered by the investigator as possibly, probably or definitely related to study drug
[C] Adverse events occurring in at least 10% of patients in either the sugammadex or neostigmine treatment group and/or considered drug-related

Reviewer's Comments
The most common adverse events associated with neostigmine were cardiovascular effects, which appeared to be effectively prevented with the co-administration of atropine and glycopyrrolate. These cardiovascular effects are discussed in greater detail below.

Post-operative nausea and vomiting were also commonly reported; however, as the Applicant notes, controlled clinical studies and meta-analyses have produced mixed conclusions about whether neostigmine is associated with an increased risk of these gastrointestinal side effects. The data are discussed in greater detail below.

Other adverse events that have been reported, for the controlled studies above, in ≥ 5% of patients included: procedural pain, incision site complication, procedural hypertension, dizziness, headache, constipation, dry mouth, pain, insomnia, pharyngolaryngeal pain, postoperative shivering, and procedural complication.

One adverse event that deserves special attention is weakness or "neuromuscular block prolonged" following neostigmine administration. It is not possible to tell from the reports of the studies whether these events reflected an inadequate dose of neostigmine, which appears more likely based on the timing of administration, or muscle weakness due solely to the neostigmine, which has been reported when larger doses of neostigmine were administered following substantial spontaneous recovery.

7.4.2 Laboratory Findings

The Applicant identified three studies in the literature, all involving sugammadex, which reported safety information from analysis of blood or urine samples. Each of these is described below.

Khuenl-Brady et al. (46) assessed blood samples for abnormalities in routine biochemistry parameters and urine samples for microalbumin, β-2 microglobulin, and N-acetyl glucosaminidase. They reported no drug-related abnormalities in any hematological or biochemical variables tested following a 50 mcg/kg dose of neostigmine.

Flockton et al. (47) analyzed blood samples for hematocrit, hemoglobin, blood counts, electrolytes, liver enzymes, creatinine kinase, lactate dehydrogenase, total bilirubin, total protein albumin, total cholesterol and haptoglobin levels following a 50 mcg/kg dose of neostigmine. There were no drug-related abnormalities reported for any hematological or biochemical variables tested. They also performed urinalysis that included assessments of urine chemistry and urine sediment. These were remarkable

for on subject with increased urinary levels of NAG; however, these values were similar pre- and post-operatively.

Lastly, Jones et al. (48) reported that there were no clinically meaningful changes in laboratory evaluations, except for an increase in mean leukocyte and neutrophil counts observed at the 4-hour and 6-hour and post-anesthetic assessments; however, these changes were seen in the sugammadex group as well.

Other than the above, the literature does not contain any reports of commonly observed abnormalities in any routine clinical laboratory assessments despite widespread use of neostigmine for the proposed indication for over half a century.

Reviewer's Comments
Based on the limited information reported above, the decades of use of neostigmine to reverse neuromuscular blockade, and the acute use of the product, it appears that neostigmine does not alter renal or hepatic function, blood cell counts, or blood or urine chemistries in any clinically meaningful way.

7.4.3 Vital Signs

The Applicant stated that there were no mentions of important findings related to vital signs or physical findings in the majority of the studies reported in the literature. More recent studies involving sugammadex did report relevant information related to vitals signs and these noted that, for neostigmine, there were increases in mean heart rates from baseline values, but these changes were described as transient and not clinically significant. The data from three of these studies were cited and are described below.

In Flockton et al. (47), safety assessments included monitoring of physical examination and vital signs following administration of 50 mcg/kg of neostigmine, with glycopyrrolate 10 mcg/kg, to reverse cisatracurium. Systolic arterial pressures of ≥160 or ≤90 mmHg, diastolic pressures of ≥95 or ≤45 mmHg, and heart rates of ≥120 or ≤50 bpm were observed in 8 of the 39 patients given neostigmine. None of these events were considered clinically significant and were not, therefore, recorded as adverse events.

Lemmens et al. (45) evaluated vital signs following a 70 mcg/kg dose of neostigmine administered with 14 mcg/kg of glycopyrrolate. There was an increase in mean heart rate from baseline 2-10 minutes post-dose, but the heart rate returned to baseline by the time of the subsequent assessments.

Jones et al. (48) evaluated vital signs following a 70 mcg/kg dose of neostigmine administered with 14 mcg/kg of glycopyrrolate. They reported an increase in the mean

heart rate (< 15 beats per minute) compared to baseline, at 2, 5, and 10 minutes after administration of neostigmine and glycopyrrolate.

Reviewer's Comments
These data suggest that the combination of neostigmine and an anticholinergic agent do not always have predictable cardiac effects; however, the combinations help avoid substantial changes that can negatively affect patient outcomes.

7.4.4 Electrocardiograms (ECGs)

The Applicant neither summarized nor analyzed the limited ECG information provided in the literature. However, it is possible to generate a list of ECG-related adverse events based on safety findings reported in some of the published clinical studies. The following list was constructed by this reviewer and includes references for each adverse event:

1. Bradycardia [Ostheimer (62); Mirakhur (63); Goldhill (67); Nagiub (69); Suresh (71); Wetterslev (70); Caldwell (37); Lessard (28); Fuchs-Buder (49)]
2. A-V dissociation [Nagiub (69)]
3. Premature ventricular contraction [Ostheimer (62); Nagiub (69)]
4. First degree heart block [Nagiub (69); Wetterslev (70)]
5. Ventricular extrasystoles [Wetterslev (70)]
6. T-wave inversion [Mirakhur (63)]
7. Cardiac arrest [Clutton-Brock (79); Hill (80); Macintosh (83)]
8. Sinus arrhythmia [Mirakhur (63)]
9. Tachycardia [Mirakhur (63)]

Reviewer's Comments
As continuous electrocardiographic monitoring is the standard of care in both the operating room and post-anesthesia care unit, and neostigmine-induced rhythm changes are expected to occur within minutes of drug administration, it is likely that the adverse events reported accurately reflect the types of events that occur, if not the incidence for each.

7.4.5 Special Safety Studies/Clinical Trials

The Applicant conducted no clinical or nonclinical studies to support this NDA. There were no reports of special safety studies or clinical trials that were identified in the literature that are not covered elsewhere in this review.

7.4.6 Immunogenicity

The Applicant provided no information regarding the immunogenicity of neostigmine. None could be found in the literature search performed for this review. There appears to be no evidence suggesting neostigmine is immunogenic despite a history of extensive use of spanning more than five decades,

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The variations in the clinical studies reported in the literature, e.g., anesthetic agents used, surgical procedures performed, dose and type of anticholinergic agents co-administered, made a meaningful comparison of the doses of neostigmine and incidence of adverse events impossible. Therefore, the Applicant made no assessment of the dose dependency of the adverse events.

Reviewer's Comments
While not reported in the literature, it would be reasonable to anticipate that the cardiac effects of neostigmine are dose dependent unless the dose of the anticholinergic agent used in conjunction with it is similarly increased. In addition, it appears from the literature that doses of neostigmine substantially higher than required, based on the extent of spontaneous recovery, may lead to muscle weakness.

7.5.2 Time Dependency for Adverse Events

The Applicant made no assessment of the time dependency of the adverse events reported in the literature.

Reviewer's Comments
Based on the literature submitted, and consistent with the pharmacokinetics of neostigmine, it appears that most of the adverse events occurred from within seconds to a couple hours following administration. The cardiac effects appeared within the time required for neostigmine to circulate to the heart; nausea and vomiting tended to occur following extubation while the patients were in the post-anesthesia care units.

7.5.3 Drug-Demographic Interactions

The Applicant made no assessment of the potential for drug-demographic interactions other than the effects of age. The literature did not provide sufficient information for such an assessment or analysis to be performed.

7.5.4 Drug-Disease Interactions

The Applicant made no assessment of the potential for drug-disease interactions.

Reviewer's Comments
The literature did not provide sufficient information for such an assessment or analysis to be performed with the exception of renal failure, for which there are limited data.

One study compared patients with normal renal function to renal transplant patients and anephric patients. Neostigmine pharmacokinetics were not significantly different in patients with normal renal function from those having undergone renal transplantation; however, anephric patients had a significantly prolonged elimination half-life and decreased total serum clearance of neostigmine when compared to patients with normal renal function or those with recent renal transplantation.(77) A statement concerning these findings should be included in the labeling and has been incorporated into the labeling recommendations in Section 9.2 below.

7.5.5 Drug-Drug Interactions

The Applicant has divided drug-drug interactions into two categories: those that enhance neostigmine's safety or efficacy and those that have deleterious effects. They identified the muscarinic antagonists atropine or glycopyrrolate as having desirable interactions as they can prevent or mitigate bradycardia and reduced cardiac output.

The following drugs or drug classes were identified as having deleterious effects:

1. Succinylcholine: Concurrent use of neostigmine and succinylcholine has been reported to produce a prolonged and intense neuromuscular block. (84)
2. Halogenated anesthetics: Halogenated anesthetics drugs can act as a neuromuscular junction stabilizing agent producing synergistic effects with neuromuscular blocking agents (NMBAs). This effect can reduce the need for an NMBA or require an increased dose of neostigmine. The effect of at least one of these anesthetics, sevoflurane, has been shown to be concentration dependent. (85)
3. Aminoglycoside and tetracycline antibiotics: These antibiotics may have inhibitory action at postsynaptic receptors or affect the neuromuscular junction by calcium chelation, causing accentuated block and potentially necessitating neostigmine dose adjustments. (84,86)
4. Other products with effects similar to antibiotics: Calcium channel blockers, antiarrhythmics, lithium, cyclosporin and other concomitant medications. (84,87) It appears that these drugs either enhance the potency of NMBAs or act directly at the neuromuscular junction. (87) Furthermore, it appears that if neostigmine is

administered after some spontaneous recovery has already occurred there may be no adverse effect on recovery of neuromuscular function. (88)

Reviewer's Comments

In addition to the Applicant's findings, the literature includes another key interaction that needs to be considered in clinical practice and that should be included in product labeling. Specifically, neostigmine-induced recovery is attenuated in patients treated with magnesium sulfate ($MgSO_4$) due to the independent effects of $MgSO_4$ at the neuromuscular junction rather than a drug-induced decreased response to neostigmine.(49,89)

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

This product is indicated for acute use only. Therefore, carcinogenicity evaluations are not required.

7.6.2 Human Reproduction and Pregnancy Data

There are no human data regarding the effects of neostigmine on reproduction or pregnancy. As per the Division's PreIND meeting with the Applicant, reproductive toxicology studies will be conducted as a post-approval requirement.

7.6.3 Pediatrics and Assessment of Effects on Growth

The Applicant provided no information regarding the effects of neostigmine on the growth of pediatric patients. A review of the literature revealed no reports describing such effects.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The Applicant indicated only one report of a fatal overdose could be found in the literature, which was related to chronic oral neostigmine use for megacolon (see section 7.3.1). They did not comment otherwise on the subject of overdose. They noted that neostigmine has not been reported to be associated with any abuse, withdrawal or rebound issues.

Reviewer's Comments
Based on its mechanism of action, it would not be expected that neostigmine produces an effect that would lead to drug seeking behaviors. The acute nature of its use, in the perioperative setting, precludes the types of exposure that would lead to changes in acetylcholinergic receptor numbers or baseline levels of acetylcholine, which could lead to either withdrawal or rebound effects.

Overdosing of neostigmine is possible. Depending on the use, and the amounts, of muscarinic anticholinergic drugs coadministered, the result of a neostigmine overdose could include increased incidence or exaggerated degrees of nausea and vomiting, bradycardia and QT interval prolongation, bronchoconstriction, salivary gland stimulation, miosis, and increased intestinal tone. In addition, an excessive dose of neostigmine may also lead to a depolarizing block, similar to succinylcholine, due to excess acetylcholine (Ach) in the neuromuscular synapses. Elevated level of Ach may not only overcome the residual neuromuscular blocking agent but may produce repeated stimulation of the nicotinic receptors resulting in the development of action potentials that can lead to asynchronous excitation and fasciculation of the muscle.

7.7 Additional Submissions / Safety Issues

The Applicant submitted a 120-day safety update on November 30, 2012. In the update, they identified five articles, out of approximately 60 published since January 2011, that they considered relevant for the reporting of adverse events associated with the use of neostigmine. These publications included three prospective clinical studies and two case reports. Each article is summarized below; however, the key findings include the following:

1. Islam et al. (90) conducted a randomized, dose-controlled study and determined that a 15 mcg/kg dose of atropine is preferred to a 10 mcg/kg and 20 mcg/kg dose for limiting the effects of neostigmine on heart rate.
2. Sauer et al. (91) conducted a randomized, placebo-controlled study and found that a 20 mcg/kg dose of neostigmine was effective in antagonizing rocuronium-induced blockade, i.e., producing a TOF ratio of 1 prior to extubation. However, they also noted the presence of minimal neuromuscular blockade which was associated with an increased risk of developing hypoxemia ($SaO_2 \leq 93\%$).
3. Geldner et al. (92) conducted a randomized, active-controlled study comparing neostigmine to sugammadex. They found that a 50 mcg/kg dose of neostigmine administered with a 10 mcg/kg dose of atropine to reverse neuromuscular blockade from rocuronium produced a mean recovery time to a TOF ratio of 0.9 of 8.4 min. They noted the two products had similar adverse event profiles but that neostigmine was associated with more clinically relevant episodes of bradycardia (13% of subjects).
4. Tufek et al. (93) reported the case of an 18-month old male who experienced cardiac arrest following neostigmine administration despite atropine administration immediately following the neostigmine dose. The child was resuscitated without sequelae.
5. Jain et al. (94) reported two cases of inadvertent, intra-arterial injection of neostigmine. Neither case was associated with a vascular-related adverse event.

Reviewer Comments:
Islam et al. (90) conducted a prospective, comparative study in which they evaluated the effects on heart rate of different doses of atropine administered with neostigmine at the end of surgery. Subjects included 60 adult patients (ages 20-60 years old), in relatively good health (ASA 1 or 2), underwent general anesthesia for elective orthopedic, gynecological, ENT or other general surgery. The patients were assigned to receive one of three doses of atropine (10, 15, or 20 mcg/kg) mixed with neostigmine 50 mcg/kg to reverse neuromuscular blockade. There were no significant demographic differences or differences in mean baseline heart rate between the three groups of patients. Following treatment with atropine and neostigmine, the change in heart rate

was significantly less in the 10 mcg/kg treatment group compared to higher atropine dose groups at 1 minute after reversal, but this difference did not persist through 2 minutes later. However, more patients in the lowest atropine dose group experienced increased tracheobronchial secretions and laryngospasm compared to the higher atropine dose groups. For this reason, the authors concluded that atropine 10 mcg/kg affects heart rate less than higher doses of atropine but does not sufficiently mitigate the increased respiratory secretions associated with neostigmine. Because, atropine 20 mcg/kg has the potential to cause complications in hemodynamically unstable patients, they concluded that an atropine dose of 15 mcg/kg is the preferred dose to minimize heart rate changes and adverse events.

Sauer et al. (91) reported the results of a randomized, prospective, placebo-controlled trial that was designed to measure the incidence of critical respiratory events in patients with minimal residual neuromuscular blockade. In this study, 114 adult patients (ages 18-80 years old; ASA 1-3) undergoing orthopedic surgery were enrolled. Subjects were randomized to receive either a saline placebo or 20 mcg/kg of neostigmine to reverse rocuronium-induced blockade. Following surgery, patients in the neostigmine group were extubated when the train-of-four ratio (TOF) was 1.0, whereas patients in the placebo group were extubated at TOF<1.0 provided there was no fade detected to both the TOF and double-burst stimuli. Patients were assessed for signs and symptoms of muscle weakness, hypoxemia and other critical respiratory events including:

1. Post-operative respiratory insufficiency requiring intervention
2. Hypoxemia with $SaO_2 \leq 93\%$
3. Non-specific respiratory problems such as airway obstruction, tachypnea, or sustained coughing

Patients in the placebo groups were significantly older than those in the neostigmine group; otherwise, the two groups were comparable. No patients required re-intubation or artificial ventilation, and non-specific respiratory problems were not observed. The incidence of hypoxemia was significantly greater in the placebo group (p=0.021). Mild to moderate hypoxemia (SaO_2 of 90% - 93%) occurred significantly more often in the placebo group, but the incidence of severe hypoxemia (SaO_2 of < 90%) did not differ between the groups. After 2 h, 40 patients (35%) experienced hypoxemia when breathing room air for 10 min; however, there was no significant difference between the two treatment groups. None of the patients experienced post-operative pneumonia or had an increased length of stay in hospital.

Among the signs and symptoms of muscle weakness, the incidence of swallowing difficulties was significantly higher in the placebo group compared with the neostigmine group (8 versus 1).

The authors concluded that the presence of minimal neuromuscular blockade was associated with an increased risk of developing hypoxemia, but that 20 mcg/kg of

neostigmine was effective in antagonizing rocuronium-induced blockade. The authors acknowledged that the difference in age between the groups might have contributed to the increased incidence of critical respiratory events in the placebo group, but they state that a post-hoc association analysis revealed no direct relationship between age and hypoxemia.

Geldner et al. (92) reported the results of a randomized, active-controlled, multicenter trial that compared the reversal of rocuronium-induced neuromuscular blockade by neostigmine and sugammadex. A total of 140 adult patients (age 35-67 years old;; ASA 1-3) who were undergoing general anesthesia for scheduled laparoscopic cholecystectomy or appendectomy were randomized to receive either sugammadex (4 mg/kg) alone or neostigmine (50 mcg/kg) and atropine (10 mcg/kg) after rocuronium-induced muscular blockade. Sugammadex was given at a post-tetanic count of 1-2 (deep muscular blockade), with neostigmine given at the reappearance of the second twitch (T2) of a train-of-four (TOF) stimulation (moderate blockade). Safety was evaluated by assessments of vital signs, physical examinations, and adverse events with adverse event assessments made by a treatment-blinded safety assessor.

The efficacy findings for neostigmine included the geometric mean (95% CI) times to recovery of the TOF ratio to 0.9, which was 8.4 (7.2–9.8) min. For patients with available recovery times, 20% (13⁄65) in the neostigmine group recovered (i.e., TOF ≥ 0.9) within 5 minutes; 94% (61⁄65) of neostigmine patients had recovered to that extent by 20 minutes.

The safety population consisted of 66 patients receiving sugammadex and 67 patients receiving neostigmine with both groups having comparable baseline characteristics. The adverse events profiles for the two groups were similar with the exception of anesthetic complication – cardiac (specifically, bradycardia) which occurred more often in neostigmine-treated patients (9 subjects; 13%) than in sugammadex-treated patients (1 subject; 2%). The adverse events that occurred in more than 10% of subjects for either treatment group are listed in Table 16 below.

Table 16. Adverse Events (Table 3 on p. 995 of the publication)

Adverse Event	Sugammadex (n = 66)	Neostigmine (n = 67)
Any adverse event	65 (98%)	65 (97%)
Procedural pain	60 (91%)	60 (90%)
Nausea	16 (24%)	12 (18%)
Anaesthetic complication cardiac (all were instances of bradycardia)	1 (2%)	9 (13%)
Vomiting	8 (12%)	7 (10%)
C-reactive protein increased	8 (12%)	6 (9%)

Serious adverse events occurred in 10 patients: 4 in the sugammadex group and 6 in the neostigmine group. However, only one serious adverse event was considered to be possibly related to the study drug, a case of postoperative upper abdominal pain after neostigmine.

Residual neuromuscular blockade was not observed in any patients, and no patients experienced a recurrence of neuromuscular blockade based on neuromuscular monitoring. The authors note that there was a suggestion of clinical evidence of recurrence of neuromuscular blockade, i.e., moderate dyspnea, which occurred in one patient beginning 30 min after sugammadex administration and lasting for 45 min.

The authors reported that there was no difference in blood pressure between the two treatment groups, although heart rate was generally lower in the neostigmine group. Abnormally low heart rates that were considered to be clinically relevant occurred in 5 patients in the neostigmine group. The number of cases of post-operative nausea and vomiting was similar in the two study groups, although the small number of cases overall made it difficult to draw conclusions. The authors concluded that there were more adverse events that were considered to be related to the study drug among the neostigmine group; the most common was bradycardia, a well-recognized potential side effect.

The adverse event data from this study have been incorporated into the labeling for adverse reactions derived from clinical studies.

Tufek et al. (93) reported the case of an 18-month old male who experienced cardiac arrest following neostigmine administration. The child had no previous cardiovascular history or laboratory abnormalities; at the time of the incident he underwent surgery for congenital glaucoma. Anesthesia was induced using propofol 30 mg, lidocaine 15 mg, and fentanyl 20 mcg. Rocuronium bromide 7.5 mg was administered to facilitate intubation. After recovery of spontaneous ventilation, atropine 15 mcg/kg was administered, followed by neostigmine 40 mcg/kg. The authors reported that bradycardia, without any other cardiac arrhythmia, was observed immediately after the neostigmine was administered, which was followed by asystolic arrest.

Chest compressions were initiated and epinephrine was administered - 100 mcg every 3 minutes. The patient was successfully resuscitated after 15 minutes. No other adverse sequelae were described. The authors commented that this was an unexpected adverse event for these typical doses of atropine and neostigmine in pediatric patients. They hypothesized that because infants do not have mature vagal systems, they may also have less stable ventricular electrical systems, which might have made this child susceptible to cardiac arrest.

Jain et al. (94) reported two cases of accidental, intra-arterial injection of neostigmine. In the first case, an 18-year old female undergoing craniotomy and tumor excision received 2.5 mg of neostigmine and 0.5 mg of glycopyrrolate via a 3-way with 10-cm extension line attached to a left dorsalis pedis arterial cannula. There were no apparent vascular adverse events at the time, and the authors noted that the TOF ratio increased from 0.4 to less than 0.9 in less than 10 minutes. In the second case, a 58-year old female undergoing aneurysm clipping received an intra-arterial injection of 3.5 mg of neostigmine with 1.4 mg of atropine. The site of the intra-arterial cannula was not specified for this patient, but based on the subsequent discussion in the article, appears to have been in the left dorsalis pedis artery. There were no apparent vascular adverse events at the time, and the authors noted that the TOF ratio increased from 0.4 to less than 0.9 in 15 minutes.

The authors reported that, in both patients, the adequacy of circulation of the left foot was monitored postoperatively using pulse oximetry, intermittent palpation of the left dorsalis pedis artery, and a tissue ischemia score. No immediate or delayed vascular complications were observed in either patient, and Doppler studies of the involved vessel revealed good blood flow with no evidence of vasospasm or IA thrombus formation.

Based on the adverse event information contained in Table 15 and Table 16 above, Table 17 below should be used in the label to reflect the quantitative data available from published trials and provide a listing of adverse reactions with an overall frequency of 1% or greater for the 267 patients who received neostigmine in the six controlled studies. The Applicant has included only the information found in (b) (4) in their proposed labeling; the only addition to that table, which is derived from the work of (b) (4) The adverse events are listed in order of decreasing frequency. The reactions are those expected based on the pharmacological action of neostigmine and those which may be due in part to other products administered during an anesthetic or to the surgical procedure itself, e.g., nausea, vomiting shivering, pharyngeal pain, and postoperative pain.

Table 17. Adverse reactions associated with neostigmine methylsulfate occurring with a frequency of ≥ 1% as reported for controlled clinical trials

System Organ Class	Adverse Reaction
Cardiovascular	bradycardia
	hypotension
	tachycardia/heart rate increase
Gastrointestinal	nausea
	vomiting
	postprocedural nausea
	dry mouth

System Organ Class	Adverse Reaction
General and Administration Site Reactions	procedural pain
	incision site complication
	pharyngolaryngeal pain
	procedural complication
	C-reactive protein increased
Nervous System	dizziness
	headache
	postoperative shivering
	prolonged neuromuscular blockade
Psychiatric	insomnia
Respiratory, Thoracic and Mediastinal	dyspnea
	oxygen desaturation <90%
Skin and Subcutaneous Tissue	pruritus

8 Postmarket Experience

Applicant Reported Findings

The Applicant conducted a search of the Agency's Adverse Event Reporting System (AERS) database for adverse events associated with the use of neostigmine methylsulfate. Other salt forms of neostigmine were excluded from the search. The query output was further limited to the intravenous route of administration with known or possible use of neostigmine for neuromuscular blockade reversal. Cases were included in the analysis if neostigmine was identified as a suspect medication, i.e., cases with neostigmine listed as a concomitant medication were excluded. The date range of the query was unrestricted through September 30, 2011, the most recent AERS quarterly update available at time of their query execution.

Their query identified 118 cases, 107 of which were categorized as serious, including 11 fatal outcomes. A total of 412 adverse events were recorded from all cases, with a majority, 397, derived from serious cases. Fatal cases had a total of 64 associated adverse events. The analysis was confounded in that many cases had medications other than neostigmine also identified as suspect; therefore, the Applicant focused their analysis on cases in which neostigmine was the sole suspect medication.

Other than drug ineffectiveness and post procedural complications, cardiac events were of the highest frequency. In particular, cardiac arrest (14 events), bradycardia (14 events), and tachycardia (10 events) were most frequently reported, although relatively few of these reports were from cases in which neostigmine was the sole suspect medication. Other events included coma (11 events) and hypotension (10 events). The majority of reports were from the adult population; 6 cases were from the pediatric population, specifically, ages 2-6 years old. Also of note, were a single case of Stevens-Johnson Syndrome (SJS) and 5 cases of toxic epidermal necrolysis (TEN). The cases of coma, SJS and TEN are discussed in further detail in the Reviewer's Comments below.

Because narratives are not provided in the publically available AERS database, the Applicant relied upon the reported Indication Preferred Term to determine whether neostigmine was administered for reversal of neuromuscular blockade, neuromuscular blockade, anesthesia reversal, and muscle relaxant therapy.

The administered doses, when provided, were often within the 1-5 mg range both for cases in which neostigmine was the sole suspect medication and in cases where other medications were suspect as well. The Applicant noted that this dose range is consistent with the neostigmine doses used in the majority of the supportive clinical literature (30-70 mcg/kg in adult patients), and suggests that the AERS data reflect safety findings associated with standard and appropriate use of the drug. They further note that doses of neostigmine administered to the 6 pediatric patients ranged between

0.5-1.5 mg, suggesting that overdosage did not contribute to any adverse events in this population.

It was noted by the Applicant that many of the reported adverse events were more likely related to a patient's underlying disease, the surgical procedure, or concomitant anesthetic medications than to neostigmine. Also evident from their tabulation of adverse events was that many could be anticipated with use of neostigmine based on exaggerated pharmacologic activity, including bradycardia with the potential for arrhythmias, bronchospasm, dyspnea, abdominal symptoms consistent with increased intestinal peristalsis, and muscle cramps. In addition, it was noted that four reports included the preferred term "Drug Interaction" with the interacting drugs identified as donepezil, fentanyl, glycopyrrolate, procardia, succinylcholine, amiodarone, propofol, clonazepam, desflurane, duloxetine, hydromorphone, lamotrigine, lithium, midazolam, ondansetron, quetiapine, rocuronium, topiramate, ketorolac tromethamine, and mivacron.

Based on their AERS analysis, the Applicant concluded there is no evidence to suggest any particular unsuspected events of interest not already reported in the neostigmine pharmacology literature. They further reason that given the 8 decades of neostigmine use combined with the long history of use of edrophonium and pyridostigmine, these anticholinergic agents have likely been administered to millions of surgical patients for reversal of neuromuscular blockade, and the adverse events identified in the AERS database suggest the drugs generally well-tolerated with only occasional adverse clinical outcomes.

The tables that follow were constructed by the Applicant based on their analysis of the AERS database. These include adverse event summaries reported by system organ class and preferred term (Table 18); adverse event counts based on gender (Table 19) and age (Table 20); and adverse event counts based on neostigmine dose (Table 21). A separate table of adverse event counts based on system organ class and preferred terms was also constructed for the pediatric data; it too is included below (Table 22).

Table 18. Summary of all (adult and pediatric) neostigmine adverse events reported in the AERS database through September 30, 2011 (Table 7 on pp. 40-46 of the ISS)

System Organ Class/Preferred Term	Number of Events: All Cases	Number of Events: Neostigmine Sole Suspect Medication
Blood and lymphatic system disorders		
Agranulocytosis	1	
Anaemia	1	
Coagulopathy	4	
Leukopenia	1	
Lymphocytic infiltration	1	

System Organ Class/Preferred Term	Number of Events: All Cases	Number of Events: Neostigmine Sole Suspect Medication
Lymphocytosis	1	
Lymphopenia	1	
Plasmacytosis	1	
Cardiac disorders		
Arrhythmia	1	1
Arrhythmia supraventricular	1	1
Atrioventricular block	1	
Atrioventricular block complete	2	
Atrioventricular block second degree	4	
Bradycardia	14	5
Cardiac arrest	14	7
Cardiac failure	2	1
Cardiogenic shock	1	
Cardio-respiratory arrest	5	4
Cyanosis	2	
Electromechanical dissociation	1	1
Long QT syndrome	1	
Nodal rhythm	1	
Sinus arrest	1	
Supraventricular tachycardia	1	
Tachycardia	10	1
Torsade de pointes	1	
Ventricular tachycardia	2	
Eye disorders		
Eye movement disorder	1	
Gaze palsy	1	
Lacrimal disorder	1	1
Gastrointestinal disorders		
Abdominal compartment syndrome	1	
Abdominal distension	6	1
Abdominal pain	1	
Ascites	1	
Constipation	1	
Diarrhoea	2	1
Gastrointestinal haemorrhage	1	
Gastrointestinal necrosis	1	

System Organ Class/Preferred Term	Number of Events: All Cases	Number of Events: Neostigmine Sole Suspect Medication
Ileus	1	
Intestinal perforation	1	
Mesenteric occlusion	1	
Gastrointestinal disorders (continued)		
Mouth haemorrhage	1	
Nausea	2	
Oral soft tissue disorder	1	
Peritonitis	2	
Tongue coated	1	
Vomiting	1	
General disorders and administration site conditions		
Asthenia	5	4
Disease progression	1	
Drug effect decreased	3	3
Drug effect increased	2	
Drug ineffective	18	15
Drug interaction	4	
Drug resistance	1	
Infusion related reaction	1	1
Injection site extravasation	1	
Injection site inflammation	1	
Injection site swelling	1	
Irritability	2	2
Mucosal erosion	1	
Mucous membrane disorder	1	
Multi-organ failure	1	
Oedema peripheral	1	
Pain	2	
Potentiating drug interaction	1	
Product deposit	1	
Product quality issue	3	1
Pyrexia	4	
Therapeutic product ineffective	2	2
Hepatobiliary disorders		
Acute hepatic failure	5	

System Organ Class/Preferred Term	Number of Events: All Cases	Number of Events: Neostigmine Sole Suspect Medication
Hepatomegaly	3	
Liver disorder	1	
Immune system disorders		
Anaphylactic reaction	2	
Anaphylactic shock	1	
Anaphylactoid reaction	1	
Drug hypersensitivity	1	
Infections and infestations		
Pneumonia	1	
Sepsis	1	
Staphylococcal scalded skin syndrome	1	
Injury, poisoning and procedural		
Anaesthetic complication	4	1
Cardiac function disturbance postoperative	1	1
Delayed recovery from anaesthesia	1	
Drug administration error	2	2
Gastrointestinal anastomotic leak	1	1
Medication error	2	
Neuromuscular block prolonged	4	1
Post procedural complication	12	3
Post procedural haematoma	1	
Weaning failure	2	2
Investigations		
Activated partial thromboplastin time prolonged	1	
Blood cholinesterase abnormal	1	
Blood immunoglobulin E	1	
Blood immunoglobulin E increased	1	
Blood lactic acid increased	1	
Blood potassium increased	1	
Blood pressure decreased	3	2
Blood pressure diastolic decreased	2	
Blood pressure increased	2	2
Body temperature decreased	1	
Body temperature increased	1	
Breath sounds abnormal	1	
Chest X-ray abnormal	1	

System Organ Class/Preferred Term	Number of Events: All Cases	Number of Events: Neostigmine Sole Suspect Medication
Electrocardiogram PR prolongation	1	
Electrocardiogram QT prolonged	3	
Eosinophil count	2	
Investigations (continued)		
Grip strength decreased	2	2
Heart rate decreased	3	1
Heart rate increased	4	4
Liver function test abnormal	1	
Lymphocyte count decreased	1	
Neurological examination abnormal	1	
Oxygen saturation decreased	8	2
Pulse absent	1	1
Sputum abnormal	1	
Volume blood decreased	1	
Musculoskeletal and connective tissue		
Muscle twitching	2	2
Pain in extremity	1	
Nervous system disorders		
Anticholinergic syndrome	1	
Aphasia	2	
Cerebral infarction	1	1
Coma	11	4
Disturbance in attention	2	
Dizziness	1	
Hypoaesthesia	2	
Hypotonia	1	
Intracranial hypotension	1	
Neuromuscular blockade	1	
Paralysis	1	1
Paralysis flaccid	1	
Sedation	2	2
Serotonin syndrome	2	
Somnolence	5	
Unresponsive to stimuli	2	
Psychiatric disorders		
Conversion disorder	5	

System Organ Class/Preferred Term	Number of Events: All Cases	Number of Events: Neostigmine Sole Suspect Medication
Listless	1	1
Restlessness	1	1
Renal and urinary disorders		
Bladder spasm	1	
Haematuria	6	
Oliguria	5	
Proteinuria	1	
Renal disorder	1	
Renal failure	1	
Renal failure acute	4	
Respiratory, thoracic and mediastinal		
Acute pulmonary oedema	1	
Acute respiratory distress syndrome	1	1
Acute respiratory failure	1	
Apnoea	2	
Aspiration	1	
Bronchial haemorrhage	1	
Bronchospasm	5	3
Dyspnoea	7	6
Hypoventilation	2	2
Hypoxia	1	
Laryngeal oedema	2	
Laryngospasm	1	
Non-cardiogenic pulmonary oedema	2	2
Pulmonary embolism	1	
Pulmonary haemorrhage	1	
Pulmonary oedema	1	1
Respiratory acidosis	1	
Respiratory arrest	1	
Respiratory distress	3	2
Respiratory failure	1	
Sputum discoloured	1	
Stridor	6	
Respiratory, thoracic and mediastinal disorders		
Tachypnoea	5	

System Organ Class/Preferred Term	Number of Events: All Cases	Number of Events: Neostigmine Sole Suspect Medication
Vocal cord polyp	1	
Wheezing	1	
Skin and subcutaneous tissue disorders		
Angioedema	1	
Blister	2	
Drug eruption	1	
Erythema	1	
Erythema multiforme	1	
Pruritus	2	
Skin discolouration	1	
Skin exfoliation	1	
Stevens-Johnson syndrome	1	
Swelling face	2	
Toxic epidermal necrolysis	5	
Urticaria	1	
Social circumstances		
Pharmaceutical product complaint	2	2
Surgical and medical procedures		
Cystostomy	1	
Vascular disorders		
Circulatory collapse	2	
Flushing	4	
Haemorrhage	1	
Hypertension	3	
Hypotension	10	1
Shock	1	1
TOTAL EVENTS:	**412**	**110**

Table 19. Adverse event counts by gender (Table 8 on p. 47 of ISS)

Gender	All Adverse Events (N)	Percentage of All Adverse Events	Adverse Events, Sole Suspect Neostigmine (N)	Percentage of Adverse Events, Sole Suspect Neostigmine
Female	241	58.50%	38	34.55%
Male	152	36.89%	63	57.27%
Unknown/Unspecified	19	4.61%	9	8.18%
Total	412	100.00%	110	100.00%

Table 20. Adverse event count by patient age (Table 9 on p. 47 of ISS)

Age (years)	All Adverse Events (N)	Percentage of All Adverse Events	Adverse Events, Sole Suspect Neostigmine (N)	Percentage of Adverse Events, Sole Suspect Neostigmine
2-6	24	5.83%	7	6.36%
18-65	298	72.33%	53	48.18%
>65	56	13.59%	32	29.09%
Unknown/Unspecified	34	8.25%	18	16.36%
Total	412	100.00%	110	100.00%

Table 21. Adverse event count by neostigmine dose (Table 10 on p. 48 of ISS)

Dose (mg)	All Adverse Events (N)	Percentage of All Adverse Events	Adverse Events, Sole Suspect Neostigmine (N)	Percentage of Adverse Events, Sole Suspect Neostigmine
<0.5	14	3.40%	6	5.45%
0.5	16	3.88%	0	0.00%
0.7	12	2.91%	0	0.00%
1	8	1.94%	5	4.55%
1.5	6	1.46%	5	4.55%
2	15	3.64%	15	13.64%
2.5	52	12.62%	9	8.18%
3	37	8.98%	27	24.55%
4	18	4.37%	8	7.27%
5	27	6.55%	9	8.18%
>5	7	1.70%	6	5.45%
Unknown	200	48.54%	20	18.18%
Total	412	100.00%	110	100.00%

Table 22. Summary of all neostigmine adverse events reported in the AERS database for pediatric patients through September 30, 2011 (Table 11 on p. 49 of the ISS)

System Organ Class/Preferred Term	Number of Events: Pediatric Cases (ages 2-6)
Cardiac disorders	
Arrhythmia supraventricular	1
Atrioventricular block	1
Cardiac arrest	3
Bradycardia	2
General disorders and administration site conditions	
Irritability	1
Injury, poisoning and procedural complications	
Anaesthetic complication	1
Investigations	
Blood immunoglobulin E increased	1
Eosinophil count	2
Blood immunoglobulin E	1
Electrocardiogram QT prolonged	1
Nervous system disorders	
Coma	1
Respiratory, thoracic and mediastinal disorders	
Bronchospasm	2
Non-cardiogenic pulmonary oedema	1
Skin and subcutaneous tissue disorders	
Pruritus	2
Swelling face	2
Vascular disorders	
Flushing	2

Division of Pharmacovigilance II Findings – AERS Database

The was by Martin Pollack and colleagues in the Division of Pharmacovigilance II (DPV-2) in the Office of Surveillance and Epidemiology conducted a review of the AERS database, as well as the literature, for adverse events related to the use of neostigmine for the proposed indication.

The AERS search was conducted on January 25, 2012, and covered the time period from January 1, 1969 to January 25, 2012. No limitations were imposed on the MedDRA search terms so that all events would be retrieved. The search identified 339 reports, 74 of which were determined to be duplicates. Of the remaining 265 cases, 48 were eliminated for various reasons, e.g., neostigmine had not been given, the event

occurred prior to neostigmine administration, illegible report. Neostigmine was used for reversal of neuromuscular blockade in 150 (69%) of the remaining cases, which formed the case series for their analysis. These 150 cases were associated with 268 adverse events, which are listed by preferred terms in the tables below. Table 23 provides counts for the adverse events that are listed in the label for the currently marketed (unapproved) product, and Table 24 provided counts for adverse events not listed in that label.

Table 23. Adverse event counts for events described in the current unapproved label

Labeled Adverse Events by Preferred Term	Adverse Event Count
SOC (All)	268
Cardiac SOC (All)	129
Cardio and/or respiratory arrest	27
Bradycardia or decreased heart rate	23
Tachycardia or heart rate increased	19
Arrhythmias (ventricular, atrial, NOS)	18
Hypotension or blood pressure decreased	14
Atrioventricular block	13
EKG abnormal	10
Myocardial infarction	2
Resp SOC (All)	74
Oxygen saturation decreased/hypoxia	15
Respiratory arrest, depression, distress or failure	13
Dyspnoea or apnoea	12
Bronchospasm or laryngospasm	7
Respiratory acidosis	4
Cyanosis	3
Hypercapnia	3
Increased bronchial secretion/laryngoedema	3
Stridor or wheezing	3
Cough	2
Hypoventilation	2
Respiration abnormal	2
Nervous SOC All	25
Sedation, somnolence or asthenia	10
Coma or LOC	7
Convulsion	3
GI SOC (All)	9
Nausea or vomiting	4
Abdominal pain/pain	2
Diarrhoea	2
Skin SOC (All)	9
Rash/erythema/urticaria	7

Labeled Adverse Events by Preferred Term	Adverse Event Count
Vascular SOC (All)	7
Shock/circulatory collapse	5
Flushing	2
Immune SOC (All)	5
Anaphylaxis/hypersensitivity	5
Musc SOC (All)	5
Muscle spasms/twitching	4
Eye SOC (All)	4
Miosis/visual changes	4

Table 24. Adverse event counts for events not described in the current unapproved label

SOC	Adverse Events (n ≥ 2)
Blood (12)	Lymphocyte abnormalities (2); hemoglobin changes (2); decreased protein parameters (2); coagulation abnormalities (2)
Cardiac (15)	Blood pressure increased (11)
Gastrointestinal (7)	GI hemorrhage (2)
General (61)	Drug ineffective (36); drug interaction (7); pyrexia (3); malignant hyperthermia (3); injection site complication (3); edema (3); multi-organ failure (2)
Hepatobiliary (14)	Hepatic failure or injury (3); hepatitis (3); bilirubin increased (2); cholestasis or cholelithiasis (2); increased LFT (2)
Infection (3)	Sepsis (2)
Injury and poisoning (35)	Post procedural complication (11); delayed recovery from anesthesia or prolonged NM block (9); medication error-related (6); anesthetic complication (4)
Metabolic (7)	Metabolic acidosis (3)
Musculoskeletal (8)	Rhabomyolysis-related (3)
Nervous (23)	Paralysis or hypotonia (7); unresponsive to stimuli or hypoaesthesia (5); serotonin syndrome (2); dyskinesia (2)
Psychiatric (10)	Anxiety related (6)
Renal (12)	Hematuria (3); oliguria (2); renal infarct or thrombosis (2)

SOC	Adverse Events (n ≥ 2)
Respiratory (18)	Pulmonary edema (5); breath sounds abnormal (2); bronchial or pulmonary hemorrhage (2)
Skin (7)	Blister or drug eruption (2)

The reviewers from DPV-2 noted numerous confounding factors in the AERS cases including concomitant medications, medical history (surgical or procedural complications occurring before neostigmine administration), and the lack of sufficient clinical information to assess neostigmine association. Therefore, they concluded that there was insufficient evidence to warrant inclusion of any of the adverse events in Table 24 in the product's label.

Division of Pharmacovigilance II Findings – Literature Search

On March 28, 2012, DPV-2 conducted their literature search using PubMed to identify English-language literature using "neostigmine" in the title and the word "adverse" as an unrestricted search term. Those case reports that had not been submitted to the NDA or to AERS formed the basis for this portion of their review. The search resulted in 52 reports with dates of publication ranging from 1948 through 2011; these included five cases in which the patient died, two of which involved the proposed indication for use. Most of the reports (n=23) concerned patients who received neostigmine to reverse the effects of a nondepolarizing neuromuscular blocking agent after surgery.

Regardless of the indication for use, the adverse events associated with neostigmine administration were either labeled events or consistent with labeled events. These included asystole, bradycardia, atrioventricular block, hypotension, excess salivation, and nausea, abdominal pain, anaphylaxis, and bronchospasm. Other reported adverse events included increased or decreased pharmacological effects attributed to renal failure (5 patients), hypokalemia, and concomitant use of medications (beta blockers (4), verapamil (1), methyldopa (1), or reduced or atypical cholinesterase activity (4). There was case of anaphylaxis (a labeled event) in which the role of neostigmine was supported by a skin prick test. One of the cardiovascular adverse event reports was of a fetus who experienced a drop in heart rate, with no other adverse event, following administration of neostigmine to the mother.

There were two deaths that were included in the review. The first was reported by Middleton et al. (95) and involved a patient who died from cardiovascular shock 23 hours after reversal of apnea with neostigmine during surgery for an abdominal gunshot wound. The authors attributed the apnea to neomycin rather then neuromuscular blockade and did not attribute the death to neostigmine. The second death was

reported by Buzello et al. (96)and involved a 57 year-old woman with dystrophia myotonica who died of bronchopneumonia, hypoxemia, hypercapnia, and recurrent bradyarrhythmia approximately 3 weeks after neostigmine had been given for reversal of pancuronium following a cholecystectomy.

The DPV-2 reviewers concluded that the neostigmine associated adverse events reported in the literature, both related to the proposed indication and otherwise, primarily involved labeled events and deaths due to various causes that appeared to be unrelated to neostigmine. The review of these adverse events, including the deaths, did not reveal any safety concerns not already addressed in the proposed label.

Reviewer's Comments

The conclusions drawn by DPV-2 are appropriate given the nature and the amount of information regarding the adverse events reported in the literature they evaluated. However, there are several adverse events that are listed in Table 18 (the Applicant's summary of all adverse events) as well as Table 23 and Table 24 (DPV-2 generated tables) that deserve further attention due to their serious nature. These include reports of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and coma.

Although the DPV-2 review did not specifically report incidents of SJS or TEN, they noted 2 reports of "blister or drug eruption" that could represent cases of these life-threatening reactions. The DPV-2 review did identify multiple incidents of coma. The individual reports for the incidents of coma identified by the Applicant, and all reports for SJS and TEN that could be identified by DPV-2 were obtained from the database and are considered below.

The Applicant cited 11 reports of coma compared to seven reports identified by DPV-2 after their screening process, although they too counted a total of 11 cases. The 11 cases included the following:

- Five cases of "hysterical post-operative coma" in which the patient had abnormal behaviors in the recovery room post-operatively. All of these reports likely described the save event based on the similarities in the case itself, i.e., the patient's age, gender, concomitant medications, and the wording in the reports. The behaviors exhibited included unresponsiveness to commands and unusual symptoms, e.g., flickering eyelids and fixed upward gaze. There was no mention in any of the reports that the patient had abnormal hemodynamics or weakness. All the reports stated the reaction resolved spontaneously; although in one of the reports, it mentions that the patient's airway was deliberately blocked with a face mask to elicit a purposeful movement (removal of the face mask), which he did within 60 seconds, and after which, he immediately opened his eyes and had normal cognitive function. Citalopram, a selective serotonin uptake inhibitor, was reported as a concomitant medication in each of the reports. It does not appear likely that neostigmine contributed to these adverse events.

- Two cases of patients who were given neostigmine at the end of surgery and extubated only to become weak, apneic, and unresponsive requiring reintubation. In one case, a 79 year old patient who had also been given epidural morphine, repeat doses of neostigmine and naloxone were administered with improvement followed by worsening of his level of consciousness for a 2-hour period after which he was alert, responsive, and able to be extubated. In the other case, an 85 year old patient who was on donepezil (a centrally acting acetylcholinesterase inhibitor), had an atypical pseudocholinesterase activity, and was administered curare at induction and pancuronium during the 2-hour surgical procedure, repeat doses of neostigmine were given but with incomplete recovery of strength. This patient was mechanically ventilated overnight and successfully extubated the next morning. In both of these cases, neostigmine did not directly cause the diminished levels of consciousness; rather incomplete recovery of motor function leading to apnea produced the unresponsive state.
- One case of "coma, anticholinergic syndrome" for which no detailed information was provided except that the 57 year old patient received 2.5 mg of neostigmine and 1.2 mg of atropine. Of note, atropine readily crosses the blood-brain barrier and is capable of inducing central anticholinergic syndrome with altered mental status including, on rare occasion, seizures, coma, and death. Neostigmine methylsulfate, in comparison, has a quaternary ammonium group that prevents its penetration through the blood-brain barrier. Therefore, it is more likely that atropine caused the adverse event for this patient.
- Two cases of coma that occurred in association with bradycardia/asystole and cardiac arrest. There was limited information on each. In one case, the patient was a 6 year old male who received 1.5 mg of neostigmine. The outcome for this event was listed only as "hospitalization" suggesting the child recovered. In the second case, the patient was a 67 year old man who had undergone a lung resection. Following reversal with neostigmine his heart rate slowed, he became unresponsive and ultimately asystolic. He fully recovered after 45 seconds of chest compressions, and single doses of atropine and epinephrine. For both cases, it appears that neostigmine caused bradycardia that led to cardiac arrest with resulting unresponsiveness/coma, i.e., neostigmine did not directly cause these cases coma.
- One case of bronchospasm followed by cardio-respiratory arrest, unresponsiveness/ coma and death in a 47 year old woman. There was no other descriptive information of the event; however, it appears to be similar in nature to the two cases described above in terms of the role likely played by neostigmine.

Although in each of the cases above, the patients were unresponsive to external stimuli, the reasons appear to be attributable to the effects of other drugs, i.e., citalopram and atropine; residual weakness limiting the patient's ability to respond to stimuli; or the result of cardiac arrest (perhaps induced by neostigmine) that resulted in cerebral anoxia and a resultant comatose state. It does not appear likely that, in any of these cases, neostigmine induced the comatose state by its direct effects on the brain.

The Applicant has not listed “coma” in the adverse events section of their proposed label. Given the nature of the adverse events reported in the AERS database, and the lack of any additional source information to justify its inclusion, it is recommended that the adverse reaction “coma” not be included in the product’s labeling.

For the reports of SJS and TEN, 84 listings were found in the adverse events reporting system’s database. Of these, there were 18 unique individual study report numbers, and within these, there were seven unique cases. In each instance, there were multiple suspect drugs, from 5 to 76 products, administered in the days preceding the adverse event, some of which have been previously identified as causing either SJS or TEN. In addition, for two of the reports, there was too little information to determine the basis on which the diagnosis was made or the qualifications of the individual making the diagnosis.

Although the Applicant recorded the finding of one incident of SJS and five incidents of TEN in their review of the AERS database, they made no comments about these events in their discussion of the AERS data and have not incorporated them in the proposed product labeling. Although neostigmine cannot be ruled out, with certainty, as the direct cause of SJS or TEN for the three cases that reported signs consistent with the diagnoses, the reports are too confounded by the number of concomitant medications, including some that have been clearly demonstrated to be associated with SJS/TEN, to justify including these reactions in the product’s label at this time.

The reports of coma, SJS and TEN were also reviewed by and discussed with Dr. Judith Racoosin, Deputy Director for Safety, who concurs with the recommendation not to describe these adverse reactions in labeling for the reasons listed above.

Lastly, the following wording is recommended for the Postmarketing Adverse Reactions section of the labeling:

Post Marketing Adverse Reaction Reports from Literature and Other Sources
The following adverse reactions have been identified during parenteral use of neostigmine methylsulfate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

System Organ Class	Adverse Reaction
Allergic Disorders	allergic reactions
	anaphylaxis
Nervous System Disorders	fasciculation
	convulsions
	loss of consciousness
	drowsiness

System Organ Class	Adverse Reaction
Nervous System Disorders	dysarthria
	miosis
	visual changes
Cardiovascular Disorders	cardiac arrhythmias (A-V block, nodal rhythm)
	nonspecific EKG changes
	cardiac arrest
	syncope
	hypotension
Respiratory, Thoracic and Mediastinal Disorders	increased oral, pharyngeal and bronchial secretions
	respiratory depression
	respiratory arrest
	bronchospasm
Skin and Subcutaneous Tissue Disorders	rash
	urticaria
Gastrointestinal Disorders	flatulence
	increased peristalsis
	bowel cramps
	diarrhea
Renal and Urinary Disorders	urinary frequency
Musculoskeletal and Connective Tissue Disorders	weakness
	muscle cramps
	spasms
	arthralgia
Miscellaneous	diaphoresis
	flushing

9 Appendices

9.1 Literature Review/References

Synopses of the published clinical studies that were used as a basis for a finding of efficacy are summarized below. The entire list of references utilized in this review is provided in section 9.4, which contains the bibliography.

In the synopses, the "Reported Results" section provides the results, as described by the authors, which are relevant to this application. Non-relevant findings, e.g., efficacy findings for sugammadex versus placebo or versus neostigmine, were deliberately excluded. The comments in the "Discussion" section are those of this reviewer and not those of the authors.

Abdularif et al. (1996)

Abdulatif M, Mowafi H, Al-Ghamdi A And El-Sanabary M: Dose–response relationships for neostigmine antagonism of rocuronium-induced neuromuscular block in children and adults. *British Journal of Anaesthesia* 1996; 77: 710–715

This article describes a randomized, prospective study examining the dose-response relationships for neostigmine antagonism of 90% rocuronium-induced neuromuscular block, i.e., the first twitch of the train-of-four (TOF) response (T_1) recovered to 10% of its control (T_0), in 40 children and 50 adults, during general anesthesia consisting of nitrous oxide and isoflurane. Five doses of neostigmine 0, 5, 10, 20 or 50 mcg/kg were evaluated.

Neither the original protocol nor the raw data from this study were submitted by the Applicant.

Population
Forty children and 50 adults were enrolled in the study.

Inclusion Criteria
- Undergoing low-risk elective surgical procedures
- ASA-PS 1 or 2
- Aged 2-10 years old or 18-60 years old

Exclusion Criteria
- cardiac, vascular, respiratory, hepatic, renal, neuromuscular disorders
- small joint arthritis
- medications known or suspected to affect normal neuromuscular transmission

Methods
Pediatric subjects were premedicated with midazolam 0.5 mg/kg orally, 20–30 min before surgery. Adult subjects were premedicated with diazepam 10–15 mg orally, approximately 90 min before surgery. In the operating room, the ECG was monitored continuously and arterial pressure was measured every 5 min. Anaesthesia was induced with propofol 3–5 mg/kg in children and with 2–3 mg/kg in adults, and alfentanil 20 mcg/kg for both groups. Tracheal intubation was performed without the use of neuromuscular blocking agents, and anesthesia was maintained with 70% nitrous oxide in oxygen and an age-adjusted end-tidal isoflurane concentration of 1 MAC, (1.4–1.6% in children and 1–1.2% in adults). Incremental doses of alfentanil, 10 mcg/kg, were given as required.

Ventilation was controlled to maintain normocapnia. The temperature of the skin overlying the adductor pollicis muscle was monitored and maintained at 32–33°C; nasopharyngeal temperature in the two age groups was maintained at 36–37°C. Concentrations of isoflurane, nitrous oxide, carbon dioxide and oxygen saturation were monitored continuously, and the ulnar nerve was stimulated supramaximally at the wrist, contralateral to the site of the intravenous infusion, with square pulses of 0.2 ms duration delivered in a train-of-four (TOF) sequence at 2 Hz repeated every 15 seconds. An acceleration piezo-electric transducer fastened to the volar surface of the distal phalanx of the thumb was used to assess neuromuscular blockade. For both children and adults, after stabilization of the evoked TOF responses, each patient in the two age groups received a single i.v. bolus of rocuronium 0.6 mg/kg. The onset time of rocuronium-induced neuromuscular block, the time interval between the end of injection of rocuronium and the development of maximum block, and the time required for spontaneous recovery of the first twitch in the TOF response (T_1) to a value of 10% of its control (T_0), were determined for all patients. Neostigmine antagonism was induced at T_1/T_0 of 10%.

Patients in the two age groups were allocated randomly to one of five equal dose blocks each of which consisted of 8 children and 10 adults. Patients in each age group received either no antagonist (control) or one of four doses of neostigmine: 5, 10, 20 or 50 mcg/kg. Atropine 5–20 mcg/kg was administered based on the cardiovascular effects of the neostigmine. No other antagonist was given for the next 10 minutes, and the end-tidal isoflurane concentration was not altered. First twitch height (T1) and TOF ratios (fractional height of the evoked fourth twitch in the TOF response in relation to the first twitch height T_4/T_1) were then recorded continuously for 10 minutes in the control and after the different doses of neostigmine.

Additional doses of neostigmine and atropine were given, if a TOF ratio of 80% was not achieved at the end of the 10-min period. Dose–response curves were constructed using log dose versus probit transformation of antagonist-assisted recovery of TOF ratios. Antagonist-assisted recovery was defined as total recovery minus spontaneous recovery that would have taken place in the absence of neostigmine. This was calculated by subtracting from the total recovery of the TOF ratio the mean spontaneous recovery observed in subjects in the control group. The result was expressed as a percentage of the maximum possible antagonist-assisted recovery, which was equal to 100% minus the percentage mean spontaneous recovery. Linear regression analyses of the dose–response curves were used to calculate the effective doses of neostigmine required to achieve 50% and 80% recovery of the TOF ratio (ED_{50} and ED_{80}, respectively), every minute for 10 minutes after initial administration of neostigmine.

Regression lines were compared using analysis of covariance. First the regression lines were assessed to determine if they deviated from parallelism; if they did not, the *F* test was applied to determine if the elevations were different. If so, Newman–Keuls

multiple comparison test was applied to determine which line differed in elevation. The unpaired *t* test was used to compare the two age groups with respect to:

- overall onset times for neostigmine
- times to 10% recovery of T_1/T_0, T_1 and TOF ratio at 5 and 10 min in the control and after different doses of neostigmine

For each age group, Dunnett's test was used to compare the degree of recovery of T_1 and TOF ratio recorded at 5 and 10 minutes after the different doses of neostigmine to the corresponding values recorded in the control group.

Reported Results

Results were expressed as means (95% confidence intervals) and were considered statistically significant when $p < 0.05$.

All patients in the two age groups developed 100% neuromuscular block in response to the bolus doses of rocuronium. The overall onset time of rocuronium-induced neuromuscular block in children was faster than that in adults [65 (58–72) seconds versus 84 (71–97) seconds; $p < 0.05$].

The time required for 10% spontaneous recovery of T_1/T_0 after rocuronium was shorter in children than in adults [25 (23–28) minutes versus 39 (36–41) minutes; $p < 0.001$]. At the end of surgery, first twitch height always recovered to baseline in the two age groups. Spontaneous and antagonist-assisted recoveries were more rapid in children than in adults. Doses of neostigmine in the range of 10–50 mcg/kg resulted in more than 90% recovery of T_1 and total recovery of the TOF ratio (defined as ≥ 80%) by the end of the 10-min period in children (see the table below). A level of 80% TOF ratio was achieved at 4, 5 and 8 minutes after initial administration of neostigmine 50, 20 and 10 mcg/kg, respectively, in children.

In contrast, only the highest dose of neostigmine (50 mcg/kg) resulted in substantial recovery of T_1 to reach a value of 96 (94–98)% after 10 minutes in adults. Total recovery of 80% TOF ratio was not achieved with any of the four doses of neostigmine in adults within the 10-minute time interval (see the table below). It was noted that, with respect to TOF recovery, neostigmine 5 mcg/kg in children was as effective as 50 mcg/kg in adults after 10 minutes (see Table 25 below).

Table 25. Total recovery of the first twitch in the train-of-four (T_1) in relation to control (T_0) and train-of-four (TOF) ratio (based on Table 1, p. 712 of article)

Treatment Group (doses in mcg/kg)	Recovery Mean (95% Confidence Interval)			
	T_1/T_0 %		TOF Ratio (T_4/T_0 %)	
	5 minutes	10 minutes	5 minutes	10 minutes
Children (n=8 each)				
Control 0 mcg/kg	32 (24–39)*	55 (42–69)*	24 (20-29)*	48 (39–58)*
Neostigmine 5 mcg/kg	62 (47-76)*†	87 (76-99)*†	39 (17–61)*	73 (55–92)*†
Neostigmine 10 mcg/kg	69 (64-74)*†	94 (88.7–98.7)*†	62 (51–73)*†	89 (82–95)*†
Neostigmine 20 mcg/kg	79 (70-88)*†	94 (90-98)*†	85 (74–96)*†	98 (95–99)*†
Neostigmine 50 mcg/kg	85 (80-91)†	96 (92–99)†	93 (86–99)*†	99 (96–100)*†
Adults (n=10 each)				
Control 0 mcg/kg	22 (18–25)	35 (27–45)	51 (0–11)	19 (1–30)
Neostigmine 5 mcg/kg	33 (26–39)†	54 (42–65)†	12 (1–18)	29 (23–36)
Neostigmine 10 mcg/kg	39 (33–45)†	63 (53–73)†	26 (21–31)†	47 (39–56)†
Neostigmine 20 mcg/kg	44 (39–48)†	69 (62–74)†	38 (28–48)†	62 (51–71)†
Neostigmine 50 mcg/kg	82 (76–91)†	96 (94–98)†	62 (51–71)†	78 (67–84)†

* Significantly different from the same dose of neostigmine in adults.
† Significantly different from control in the same age group.

The dose–response curves for antagonist-assisted TOF ratio recovery at 5 and 10 minutes were parallel in the two age groups. For each group, the lines constructed at 10 minutes were shifted significantly to the left from those constructed at 5 min ($p < 0.001$ in children and $p < 0.05$ in adults). The dose–response curves for children were shifted significantly to the left compared with those for adults ($p < 0.001$). The effective doses of neostigmine required to achieve 50% (ED_{50}) and 80% (ED_{80}) antagonist-assisted recovery of the TOF ratios at 10 and 5 min were significantly lower in children compared with adults (see Table 26 below). The ED_{50} values for adults were consistently higher than the ED_{50} and ED_{80} values in children.

Table 26 Calculated effective doses of neostigmine for 50% (ED_{50}) and 80% (ED_{80}) recovery of the TOF in children and adults (based on Table 2, p. 712 of article)

Time after initial injection of neostigmine	Children [mean (95% CI)]	Adults [mean (95% CI)]	p
5 minutes			
ED_{50} (mcg/kg)	10 (8-13)	34 (24-43)	< 0.001
ED_{80} (mcg/kg)	18 (13-23)	101 (81-127)	< 0.001
10 minutes			
ED_{50} (mcg/kg)	4 (3-6)	21 (17-27)	< 0.001
ED_{80} (mcg/kg)	7 (2-10)	57 (46-72)	< 0.001

Discussion

This study provides evidence of efficacy for neostigmine reversing the neuromuscular blocking effects of rocuronium bromide in substantial segments of the pediatric (i.e., healthy 2-10 year olds) and adult (i.e., healthy 18-60 year olds) populations.

The assessment of efficacy is limited in that acceleromyography data, which provide an objective means of assessing neuromuscular function, but are a surrogate marker for the clinically relevant endpoints of reversal of neuromuscular blockade, which were not assessed in the study. Specifically, the ability of patients to maintain a patent airway, without intervention, when extubated and to adequately ventilate the lungs to maintain blood oxygen saturation and end tidal carbon dioxide levels at baseline levels following extubation were not assessed. Furthermore, the authors provided no basis for using a specified TOF value, the ED_{50} or the ED_{80} as the appropriate endpoint for determining that a clinically meaningful reversal of neuromuscular blockade has occurred.

Despite these limitations, the study provides several useful pieces of information:

1. A 10% recovery of T_1 marks the earliest point that 50 mcg/kg doses of neostigmine can be given to pediatric patients with the expectation that nearly complete recovery of TOF, and likely, the nearly complete recovery of neuromuscular function, will occur within 10 minutes.
2. Pediatric patients recover neuromuscular function faster and with lower doses of neostigmine than adult patients.
3. For adult patients, when neostigmine is administered after only 10% recovery of T1, doses substantially greater than 50 mcg/kg are likely to be needed for nearly complete recovery of TOF, and neuromuscular function, to occur within 10 minutes. Doses greater than 70 mcg/kg may not be sufficient in this regard based on the ED_{80} dose estimate.
4. In this study, the continued use of isoflurane during the 10-minute interval following neostigmine administration may have adversely affected neuromuscular recovery; however, it is not possible to tell from this study the extent to which recovery may have been inhibited.

Lastly, the study allowed the use of atropine to compensate for the cardiovascular effects of neostigmine; however, the authors did not describe or discuss the need for or doses of atropine, if any, that were administered. In addition, the authors did not report on any safety issues, if any, that arose during the study.

Adamus et al. (2006)

Adamus M, Belohlavek R, Koutna J, et al. Cisatracurium vs. Rocuronium: A prospective, comparative, randomized study in adult patients under total intravenous anaesthesia. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2006;150:333-8.

The authors compared the pharmacodynamics of neuromuscular blockade induced by single doses of cisatracurium and rocuronium including spontaneous and neostigmine-enhanced recovery.

Methods
A total of 120 adult patients, scheduled for elective general surgery under total intravenous anaesthesia (TIVA) with tracheal intubation, muscle relaxation and mechanical ventilation were enrolled in the study. None of the subjects met any of the exclusion criteria, which included:

1. ASA physical status more than 3
2. Age under 18 or over 75 years
3. Obesity (BMI over > 30 kg/m^2)
4. Taking medication known to interfere with NMBAs (anticonvulsants, amino glycosides or polypeptide antibiotics)
5. Anticipated to be difficult to intubate (modified Mallampati score of 3 or 4)
6. Having a disease affecting neuromuscular transmission (e.g., myopathies)

Subjects were randomized to one of four treatment groups listed in Table 27 below.

Table 27. Study treatment groups

NMBA	Dose (mg/kg)	Type of Recovery	Number of Subjects
Cisatracurium	0.1	Spontaneous	15
		Neostigmine-enhanced	15
	0.15	Spontaneous	15
		Neostigmine-enhanced	15
Rocuronium	0.6	Spontaneous	15
		Neostigmine-enhanced	15
	0.9	Spontaneous	15
		Neostigmine-enhanced	15

Subjects were premedicated with oral diazepam 1 hr before the beginning of surgery. Routine intraoperative monitoring was used throughout the surgical procedure. After preoxygenation, anesthesia was induced with midazolam, sufentanil and propofol. Anesthesia was maintained with a propofol and sufentanil infusions using target control

infusion devices. Neuromuscular blockade was induced with a single bolus dose of study drug. Following maximal depression of the first twitch response (T1) to a train-of-four (TOF) stimulus, direct laryngoscopy and tracheal intubation were performed. Subjects were mechanically ventilated with a mixture of 40% oxygen in air to maintain end-tidal partial pressure of carbon dioxide (ETCO2) between 4.7 and 5.0 kPa. Skin temperature over the thenar muscles, used to monitor the level of neuromuscular blockade, was maintained above 34 °C throughout the study period.

Sufentanil was discontinued 20 min before the end of anesthesia and tracheal extubation was not performed before full recovery from neuromuscular block defined as a TOF-ratio ≥ 0.9.

For each consecutive patient, spontaneous recovery of T1 to 25% of its baseline value was allowed. At this point, subjects randomized to receive neostigmine were administered 0.04 mg/kg of neostigmine with 0.015 mg/kg of atropine.

The following pharmacodynamic parameters were measured in all subjects:

1. ONSET TIME (sec) = time interval from the completion of the intravenous injection of the NMBA to maximal T1 depression
2. CLINICAL DURATION (DUR25) (min) = time interval from the completion of the intravenous injection of the NMBA to spontaneous recovery of T1 to 25 % of the baseline value
3. RECOVERY INDEX (DUR25-75) (min) = time interval from the end of clinical duration (T1 = 25%) to 75 % recovery of T1 (T1 = 75%)
4. DUR25-TOF90 (min) = interval from the end of clinical duration (T1 = 25 %) to TOF-ratio 0.90, which reflects complete recovery from the block
5. For each drug, the VARIABILITY of all pharmacodynamic parameters was determined by subtracting the actual value of a given parameter from its respective mean for the group.

Reported Results

Subjects in each of the treatment groups were comparable with regard to gender, age, weight, height, BSA, BMI, and ASA classification. No complications attributable to the study or anesthesia were observed.

The pharmacodynamic findings, relevant to recovery from the NMBA, are summarized in Table 28 below. Specifically, the recovery times for T1 from 25% to 75% of baseline values, i.e., Recovery Index or DUR25-75, and the recovery time from administration of neostigmine (or lack thereof) to clinical recovery marked by a TOF ratio of 0.9, i.e., DUR25-TOF90.

Table 28. Recovery parameters (taken from Table 3 on p. 336 of the article)

Parameter	Recovery Time Mean (SD) [median]							
	Cisatracurium (0.1 mg/kg)		Cisatracurium (0.15 mg/kg)		Rocuronium (0.6 mg/kg)		Rocuronium (0.9 mg/kg)	
	Spont.	Neost.	Spont.	Neost.	Spont.	Neost.	Spont.	Neost.
Recovery Index DUR25-75 (min)	15.9 (1.8) [16.3]	4.4 (0.9) [4.7]	15.5 (1.7) [15.5]	4.5 (0.8) [4.7]	16.1 (3.7) [15.7]	4.3 (0.8) [4.3]	16.1 (4.0) [16.3]	4.7 (0.7) [4.6]
DUR25-TOF90 Interval (min)	49.2 (8.0) [49]	11.5 (2.8) [12]	52.5 (7.0) [54]	11.7 (2.7) [12]	43.1 (13.1) [41]	9.8 (2.0) [10]	56.7 (12.9) [56]	10.0 (2.7) [10]

The recovery index was similar for all four groups when spontaneous recovery was allowed. The index was also similar for all four groups when the blockade was antagonized with neostigmine. The course of complete recovery from the block (DUR25-TOF90 interval) was more consistent, with lower variability, in the two cisatracurium groups and neostigmine-treated rocuronium groups than for the two spontaneous-recovery rocuronium groups; however, the differences between the means for the two spontaneous-recovery rocuronium groups was less than 10%.

For both sets of recovery parameters and for both doses of both NMBAs, the use of neostigmine significantly reduced the recovery time.

Discussion

Although the study was not blinded, the use of a neuromuscular transmission monitoring device to measure the twitch responses minimized the risk of bias.

The study demonstrated that 40 mcg/kg of neostigmine can reverse rocuronium and cisatracurium even when administered at T1 recovery to only 25% of baseline. The reduction in time, compared to placebo, required to achieve a TOF ratio of 0.9 was substantial: on the order of 30 minutes for the lower doses of rocuronium and cisatracurium, and on the order of 40 minutes for the higher doses. Both of these reduction times are clinically meaningful. The similarity in the responses for the two NMBAs, which are cleared by different mechanisms and have different half lives, suggests that the dose of neostigmine required to achieve a specific level of recovery in a set amount of time can be predicated on the extent of spontaneous recovery that has occurred at the time neostigmine is to be administered rather than on other pharmacokinetic or pharmacodynamic properties of the NMBA.

The authors' reporting on the lack of complications for the study suggests that the 15 mcg/kg dose of atropine administered with the neostigmine was adequate to counteract the cardiovascular effects commonly observed with the anticholinergic agents.

Baurain et al. (1994)

Baurain MJ, Dernovoi BS, D'Hollander AA, Hennart DA. Comparison of neostigmine-induced recovery with spontaneous recovery from mivacurium-induced neuromuscular block. Br J Anaesth 1994;73:791-4.

The authors conducted this study to determine whether neostigmine would reduce the recovery time from mivacurium-induced neuromotor blockade or interfere with mivacurium metabolism by plasma cholinesterase and thereby prolong the block relative to spontaneous recovery.

Methods
A total of 24 subjects were selected from adult, ASA-PS 1 or 2 patients undergoing elective surgery of the lower limb. Subjects were required to have no clinical or routine biochemical evidence of hepatic or renal impairment, be free of neuromuscular disease, not be taking drugs which may interfere with neuromuscular transmission, and have normal plasma cholinesterase activity.

Subjects were premedicated with oral lormetazepam 1 hour before anesthesia. Anesthesia was induced with thiopentone and fentanyl. After loss of consciousness, ventilation was controlled manually with 50% nitrous oxide in oxygen. A force transducer to measure the isometric contraction of the adductor pollicis in response to train-of-four stimuli was applied. After a 3-minute baseline recording of twitch height was obtained, mivacurium was administered, and the trachea was intubated. Ventilation with 65% nitrous oxide in oxygen was then mechanically controlled until the end of the surgical procedure. Ventilation was adjusted to maintain normocapnia defined as an end-tidal carbon dioxide of 4.2 ± 1 kPa. Anesthesia was maintained with an infusion of mivacurium, adjusted to maintain twitch height at 1-5 % of baseline for at least 1 hour, and boluses of fentanyl and thiopentone administered when there was clinical evidence of inadequate analgesia or sedation. Surface temperature of the hypothenar area was maintained at ≥ 35° C.

At the end of the surgical procedure, the mivacurium infusion was discontinued. When the twitch height spontaneously regained 25% of its control value, the subjects were randomized to two groups of 12. Subjects in group NEO were administered 40 mcg/kg of neostigmine with 15 mcg/kg of atropine. Subjects in group SPO were allowed to recover spontaneously from the mivacurium. The following assessments were then made over a 15-minute period in all subjects:

1. Twitch height, measured every 10 s,
2. TOF ratio measured every 3 min.
3. Immediately after the last TOF, 50- and 100-Hz tetanic stimulations of 5-s duration, 1 minute apart, were assessed sequentially in a random fashion but

were limited to a single measurement, performed at 15 minutes immediately after the last TOF assessment.

Reported Results

Subjects in the two groups were comparable in weight, height, plasma cholinesterase, dibucaine number, duration of mivacurium infusion and dose, and spontaneous recovery time from the end of infusion to 25% twitch height (group NEO: mean 7.1 min. (SEM=0.6); group SPO: 6.6 min. (SEM=0.6)).

Twitch height recovery data were used to calculate various indices which are summarized in Table 29 below.

Table 29. Recovery Indices (Table 2 on p. 792 of the article)

Recovery Index	Group NEO Mean (SEM)	Group SPO Mean (SEM)
End of infusion-25% twitch height (min)	7.1 (0.6)	6.6 (0.6)
25-75% twitch height (min)	3 (0.3)	5 (0.5)**
25-90% twitch height (min)	7 (0.6)	8 (0.5)
25% twitch height-70% TOF ratio (min)	5 (0.3)	10 (0.6)***
25% twitch height-90% TOF ratio (min)	10 (0.9)	13 (0.5)**†

***P* < 0.001
****P* < 0.001 (one-way ANOVA)
† *n* = 6

In the figure below, the authors have plotted the recovery of the TOF ratio of the two treatment groups for the 15 minute period starting with return of T1 to 25% of its baseline value. The recovery was significantly faster for the neostigmine-treated subjects at each of the five time points when testing occurred.

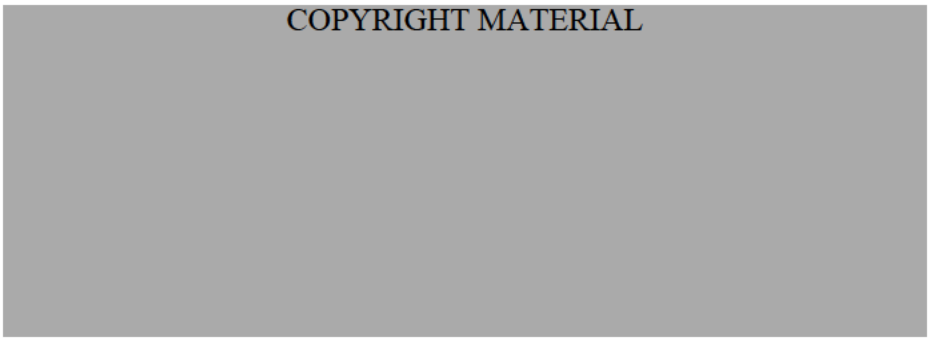


Figure 1. Recovery of TOF ratios during the 15-minute interval following the return of T1 to 25% of its baseline value (Figure 1 on p. 793 of the article)

The authors noted that at the end of the 15 minute interval, the mean TOF ratio for the neostigmine-treated subjects was 0.9, which was significantly higher than the 0.87 for the subjects undergoing spontaneous recovery. They further stated that 40 mcg/kg of neostigmine accelerated recovery of the TOF ratio to 0.9, permitting all patients in group NEO to obtain a TOF ratio of 0.9 within 15 min.

Lastly, 15 minutes after twitch height spontaneously regained 25 % of its control value, there were no significant differences between subjects in the two treatment groups in their responses to the 50-Hz or the 100-Hz, 5-sec tetanic stimulation.

Discussion

Although this study was not blinded, its use of electrical transduction of isometric contractions to assess recovery from neuromotor blockade minimized the risk of bias in these assessments. The authors demonstrated that neostigmine was effective at reversing the effects of mivacurium when a 40 mcg/kg dose was administered at the point when T1 had recovered to 25% of its baseline value, which based on the figure showing the TOF-ratio recoveries, appears to be at a TOF ratio of 0.1.

The authors did not explicitly state it, there findings appear to demonstrate that neostigmine does not interfere with recovery from mivacurium due to any effect it may have on pseudocholinesterase activity.

Baurain et al. (1996)

Baurain MJ, Hoton F, D'Hollander AA and Cantrajne FR: Is recovery of neuromuscular transmission complete after the use of neostigmine to antagonize block produced by rocuronium, vecuronium, atracurium and pancuronium? Br. J. Anaesth. 1996; 77: 496-499.

The authors measured adductor pollicis contraction force (twitch height) in response to 0.1 Hz, train-of-four (TOF) and 100 Hz (RF 100 Hz) ulnar nerve stimulations in 56 adults patients anesthetized with lorazepam, thiopentone, fentanyl, dehydrobenzperidol and nitrous oxide in oxygen. The patients were randomized to one of four groups (n=14) to receive rocuronium (group Roc), vecuronium (group Vec), atracurium (group Atr) or pancuronium (group Pan). Recovery of neuromuscular transmission was studied for 15 min after neostigmine 40 mcg/kg with atropine 15 mcg/kg was given at 25% recovery of twitch height. Fifteen minutes after antagonism, the TOF ratio and RF 100 Hz (the ratio of the force at the end of 5 seconds of stimulation to the strongest force during the stimulation) were assessed for each patient.

At the time of antagonism, when twitch height had regained 25°/o of its baseline value, the mean TOF ratio was 0.07 (SEM=0.003) for all patients (range: 0.02-0.14), and there were no significant differences between the four treatment groups. Evolution of the TOF ratios were similar in patients who received rocuronium 840 mcg/kg, vecuronium 140 mcg/kg, and atracurium 700 mcg/kg, except that the TOF ratio was significantly higher 3 min after neostigmine in patients who received vecuronium compared with those who received rocuronium and atracurium. At 15 minutes after the administration of neostigmine, the TOF ratios were similar for rocuronium, vecuronium and atracurium which were all substantially greater than the two ratios for pancuronium. The findings are summarized in Table 30 below.

Table 30. Summary of study findings

Group	Age (years) [range]	Weight (kg) (SEM)	Height (cm) (SEM)	Clinical Duration of Block (min) (SEM) [range]	TOF Ratio @ 15 min. post tx. (SEM)	RF 100 Hz @ 15 min post tx. (SEM)
Roc	38 [20-56]	75 (3)	176 (2)	68 (5) [43-86]	0.91 (0.01)	0.78 (0.01)
Vec	39 [18-58]	70 (3)	170 (2)	67 (6) [42-96]	0.88 (0.02)	0.79 (0.02)
Atr	35 [18-57]	76 (4)	174 (2)	70 (6) [44-100]	0.92 (0.01)	0.78 (0.01)
Pan	37 [27-47]	73 (3)	174 (3)	68 (5) [45-130]	0.76* (0.01)	0.33* (0.04)

* Significantly different from other groups for the same parameter (P<0.01 based on a one-way analysis of variance using Duncan's multiple classification range tests).

Discussion

These data indicate that a 40 mcg/kg dose of neostigmine at the time of 25% recovery of twitch height following rocuronium and atracurium and perhaps, vecuronium, is likely adequate to allow sufficient ventilation to maintain normoxia 15 minutes following administration, i.e., TOF has recovered to 90%. The data also indicate, however, that this dose of neostigmine given at this time point in recovery is not likely to be adequate to allow adequate ventilation, at least not at 15 minutes later, following pancuronium, i.e., TOF recovers only to 76%.

Baurain et al. (1996)

Baurain MJ, Dernovoi BS, D'Hollander AA, Hennart DA and Cantraine FR: Conditions to optimise the reversal action of neostigmine upon a vecuronium-induced neuromuscular block. Acta Anaesthesia Scandinavica 1996; 40: 574-578

This study characterized the recovery of neuromuscular transmission following a vecuronium-induced block at 15 min after neostigmine administration using different stimulation patterns. It also determined the effects of different doses of neostigmine given at various pre-reversal twitch heights.

Methods
Adductor pollicis (AP) responses to low (0.1 and 2 Hz) and high (50 and 100 Hz) frequency stimulation were recorded 15 min after 20, 40 and 80 mcg/kg doses of neostigmine, given to reverse a vecuronium-induced block at 10, 25 and 50% pre-reversal twitch height (TH).

A total of 54 subjects were enrolled from ASA-PS 1 and 2 adult patients presenting for elective surgery on a lower extremity. Subjects were anesthetized with diazepam, methohexital, fentanyl, and N_2O/O_2. After 3 minutes of recording twitch heights of the adductor pollicis responses to low (0.1 and 2 Hz) and high (50 and 100 Hz) frequency stimulation, neuromuscular blockade was induced with 100 mcg/kg of vecuronium. When twitch heights recovered to 25% of the baseline levels, two additional 20 mcg/kg boluses of vecuronium were administered.

Subjects were randomized into 9 groups of 6 patients each. All subjects received 15 mcg/kg of atropine mixed with either 20 mcg/kg (n=18) or 40 mcg/kg (n=18) or 80 mcg/kg (n=18) of neostigmine. For each treatment group, the timing of neostigmine administration was divided three ways based on the spontaneous recovery of TH. These subgroups included TH recovery to 10% (n=6) or 25% (n=6) or 50% (n=6) of its control value. Thereafter, TH and TOF ratio were recorded for 15 minutes. Immediately after the last TOF assessment, the responses to 5 seconds of tetanic stimulation at 50 (RF50) and 100 Hz (RF100) were assessed sequentially 1 minute apart in a random order. Residual force after tetanic stimulation was calculated as the ratio between the tension at the end of the 5-second stimulation period and the maximal response registered. Because high frequency stimulation can produce marked changes in subsequent TH or TOF ratio, the 50 and 100 Hz tetanic stimulation was limited to one run, 15 min after neostigmine administration.

Reported Results
Pre-reversal TH and neostigmine dose did not influence mean TH and RF50 measured at 15 minutes after neostigmine administration. The TH means were > 95% and the RF50 means were > 80 with the exception of 20 mcg/kg doses of neostigmine

administered at 10% TH for which the mean RF50 was 74%. In comparison, pre-reversal TH level and neostigmine dose did influence mean TOF ratio and RF100 measured at 15 minutes after neostigmine administration. Mean values for the TOF ratio were about 0.9 for all doses of neostigmine when given at pre-reversal TH levels of 25% and 50% and also when 40 mcg/kg of neostigmine was given at a TH of 10%. These findings are summarized in Table 31 and figure below.

Table 31. Mean TH and TOF values at 15 minutes after neostigmine administration (from Table 1 on p. 576 of article)

Neostigmine Dose [mcg/kg]	**TH at Time of Reversal [% of control]**	**TH [% of control] (SEM)**	**TOF [%] (SEM)**
20	10	99 (1)	76 (11)
	25	98 (4)	85 (6)
	50	96 (2)	92 (1)
40	10	100 (4)	86 (2)
	25	99 (3)	86 (2)
	50	100 (3)	94 (1)
80	10	98 (3)	80 (2)
	25	97 (3)	88 (4)
	50	100 (3)	86 (4)

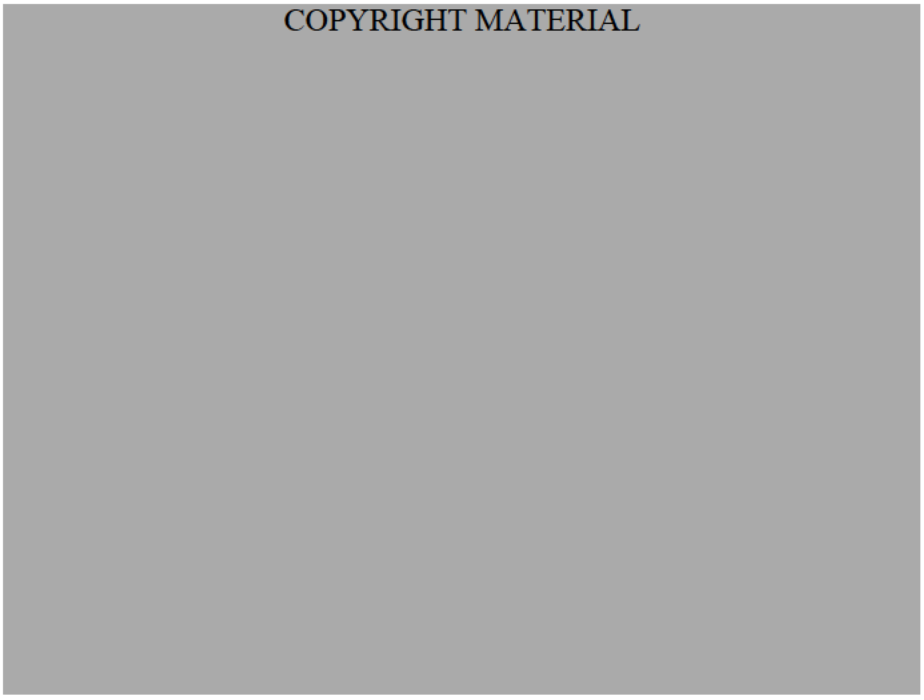


Figure 2. TOF recovery at 15 minutes (mean recovery, %) as a function of neostigmine dose (mcg/kg) and pre-reversal twitch height (% of control) [Figure 1 on p. 576 of article]

The authors conclude that to optimize the reversal action of neostigmine, i.e., to obtain the highest neuromuscular transmission recovery ($TOF_{0.9}$ ratio and RF100) following vecuronium-induced neuromuscular blockade, the 40 mcg/kg dose has to be given at 25 to 50% recovery of TH.

Discussion

This study provides convincing evidence that a neostigmine dose of 40 mcg/kg would be a reasonable dose to reverse vecuronium within 15 minutes provided it were administered when TH has spontaneously recovered to at least 50% of baseline. The data demonstrate the impact of pre-reversal recovery on the dose of neostigmine required to achieve a $TOF_{0.9}$, and suggest that increasing the neostigmine dose, at least within the range studied, may compensate for administering the drug sooner in recovery. While the study did not assess the success rate for extubating the patients and having them maintain a patent airway or adequate level of ventilation, the data indicate that $TOF_{0.9}$ can be achieved with each of the doses of neostigmine when it is administered at TH levels of 50%.

Bevan et al. (1999)

Bevan JC, Collins L, Fowler C, Kahwaji R, Rosen HD, Smith MF, Scheepers L deV, Stephenson CA, and Bevan DR: Early and Late Reversal of Rocuronium and Vecuronium with Neostigmine in Adults and Children. Anesth Analg 1999; 89: 333-9.

The authors conducted a randomized, prospective study examining the influence of the timing of neostigmine administration on the duration of rocuronium and vecuronium neuromuscular blockade (NMB) to determine the feasibility of early reversal of intense NMB. Comparisons were made of reversal in 88 pediatric dental patients and 88 adult patients undergoing gynecological surgery.

Neuromuscular transmission was assessed using the ulnar nerve with supramaximal square wave TOF stimulation at 2.0 Hz and 0.2 ms duration applied every 10 s, and with the evoked EMG response of the adductor pollicis being recorded. To assess the level of neuromuscular recovery, the times to the following endpoints were measured:

- Recovery of the first twitch to 10%, 25%, 75% and 90% of the baseline height, T_{10}, T_{25}, T_{75} and T_{90}, respectively
- TOF ratio of 0.25, 0.5, 0.7, 0.8, and 0.9, $TOF_{0.25}$, $TOF_{0.5}$, $TOF_{0.7}$, $TOF_{0.8}$, and $TOF_{0.9}$, respectively
- Recovery index calculated as the time between T_{25} and T_{75} recovery.

The 88 adult patients were randomized to 11 groups of eight patients. Forty patients received 0.45 mg of rocuronium, 40 received 0.075 mg/kg vecuronium, and 8 were given 1.5 mg/kg succinylcholine 3 min after a defasciculating dose of 0.03 mg/kg rocuronium. Patients receiving rocuronium or vecuronium were further randomized to the control groups for whom no reversal agent was administered or to the study drug treatment group for whom 0.07 mg/kg neostigmine with 0.1 mg/kg glycopyrrolate was administered 5 min after relaxant or at 1% recovery of maximum block (T_1), or T_{10} or T_{25}.

The 80 children were randomized to receive rocuronium or vecuronium with or without neostigmine reversal, as was done with the adult patients. An additional group of eight children received 1.5 mg/kg succinylcholine. The latter was not included in the randomization for children because succinylcholine is no longer used routinely for elective pediatric procedures by all anesthesiologists.

For both the adult and pediatric subjects, the anesthetic was prescribed by the protocol.

Reported Results
The study was terminated in 10 patients before all recovery data had been obtained, partial data analysis was available for all patients, so that the primary analysis was

based on the intent-to-treat population. Within the child and adult groups, there were no differences across the relaxant/reversal groups in demographic variables except that all the adult patients were female.

Rocuronium and vecuronium produced near maximal NMB in all patients. For each relaxant, maximal block occurred more rapidly in children.

Recovery times are summarized in Table 32 below. Recovery to $TOF_{0.9}$ was achieved in most patients. Recovery from NMB was more rapid in children than in adults, but there was no difference in the rate of spontaneous recovery of vecuronium and rocuronium in either age group. Neostigmine accelerated recovery of NMB in all patients. In adults and children, for both vecuronium and rocuronium, the time from administration of relaxant to $TOF_{0.7}$ or $TOF_{0.9}$ was decreased by approximately 30% to 40%. There were no significant differences among the different reversal groups. Times from administration of neostigmine to $TOF_{0.7}$ or $TOF_{0.9}$ decreased as the extent of recovery of NMB when neostigmine was given increased. In all groups, these times were significantly reduced when neostigmine was given at T1 of 25%, compared with administration 5 min after the relaxant.

Table 32. Recovery times from Rocuronium and Vecuronium after Neostigmine administration (based on tables 3 and 4 in the article)

Time of Neostigmine Administration	**Age (yrs) [mean (SD)]**		**Weight (kg) [mean (SD)]**		**Recover Time After Neuromuscular Blocking Agent Administration (min) [mean (SD)]**			
					Rocuronium		Vecuronium	
	Roc	Vec	Roc	Vec	$TOF_{0.7}$	$TOF_{0.9}$	$TOF_{0.7}$	$TOF_{0.9}$
Children	4.4 (1.4)	4.6 (1.8)	18 (4)	19 (6)				
Spontaneous					29 (8)§	35 (10)§	35 (9)‡	44 (12)‡
5 minutes					14 (4)†	17 (5)*	20 (6)†	29 (10)*
T_1 – 1%					17 (6)†	19 (7)*	21 (5)†	25 (7)†
T_1 – 10%					18 (4)†	20 (4)*	26 (6)	29 (8)*
T_1 – 25%					23 (8)†	24 (8)	21 (3)†	23 (4)*
Adults	42 (10)	40 (10)	61 (8)	60 (9)				
Spontaneous					46 (12)	54 (12)	53 (16)	66 (22)
5 minutes					28 (9)	42 (17)†	27 (8)†	35 (12)†
T_1 – 1%					27 (9)†	35 (15)†	27 (6)†	33 (4)†
T_1 – 10%					24 (8)†	27 (9)†	34 (11)*	37 (12)†
T_1 – 25%					26 (9)†	28 (11)†	36 (8)*	38 (10)*

* $p < 0.05$ versus spontaneous recovery
† $p < 0.01$ versus spontaneous recovery
‡ $p < 0.05$ for adult versus pediatric subjects
§ $p < 0.01$ for adult versus pediatric subjects

Discussion

The results indicate that neostigmine substantially reduces recovery time from both vecuronium and rocuronium, compared to spontaneous recovery, in both adult and pediatric patients.

For adults, the data indicate that the timing of neostigmine administration plays a more important role when used to reverse rocuronium than vecuronium. For rocuronium, 90% recovery of the TOF appears more time sensitive than 70% recovery, and the 90% recovery is fastest when T_1 has reached at least 25% recovery at the time neostigmine is administered, i.e., 27 minutes following the last dose of rocuronium. For vecuronium, 90% recovery of the TOF appears no more time sensitive than 70% recovery, and the recovery is between 30 and 40 minutes whether the neostigmine is administered 5 minutes after the last dose of vecuronium or when T_1 has reached 25% recovery.

In children, the data indicate that the timing of neostigmine administration is not affected by whether the neuromuscular blocking agent (NMBA) was rocuronium or vecuronium or whether the reversal agent was given 5 minutes after the last dose of the NMBA or when T_1 had recovered to 25% of its baseline value. Recovery time from rocuronium was reduced by about 30% compared to spontaneous recovery and by almost 50% for vecuronium.

Based on this information, and taking a relatively conservative approach to reversing the effects of an NMBA, this study suggests that administering 0.07 mg/kg of neostigmine following blockade with either rocuronium or vecuronium is effective when T_1 has spontaneously recovered to 25% of its baseline value.

Caldwell et al. (1968)

Caldwell JE, Robertson EN, Baird WLM. Antagonism of profound neuromuscular blockade induced by vecuronium or atracurium. Br J Anaesth 1986; 58: 1285-9.

This study compared the efficacy of neostigmine (0.07 mg/kg) and edrophonium (0.8 mg/kg) for reversing vecuronium and atracurium in 59 healthy adult patients.

Methods
Subjects were paralyzed with doses of vecuronium (1 mg/kg) and atracurium (0.5 mg/kg) that are typically used to allow tracheal intubation. The twitch response was monitored, and 5 minutes after the twitch was completely ablated, study drug was administered except for a control group of subjects who were allowed to recover spontaneously. Recovery was monitored by evaluating the twitch response and the TOF ratio. Twitch responses were monitored initially until they returned to control levels (T_{100}) and then TOF responses were monitored until a TOF ratio of 0.7 (TOF_{70}) was achieved. TOF_{70} was used as the endpoint for recovery.

The anesthetic treatment included premedication with papaveretum [a combination of morphine, codeine and papaverine] (10-20 mg) and hyoscine [scopolamine in the US] (0.2-0.4 mg/kg) given IM followed an hour later by induction with thiopentone 4-5 mg/kg IV and maintenance of anesthesia with 67% nitrous oxide/33% oxygen/1% halothane. A supramaximal stimulus of 0.2 ms duration at a frequency of 0.1 Hz was applied to the ulnar nerve via subcutaneous needle electrodes placed at the wrist, and the evoked responses of the adductor pollicis muscle were recorded. Before the treatment was begun, control responses to single twitch and train-of-four stimulation were recorded for at least 10 minutes to allow stabilization.

Tracheal intubation was performed when the twitch was completely ablated, and mechanical ventilation was initiated. Five minutes after total ablation of the single twitch response, the patients were randomized to one of the three treatment groups: spontaneous recovery, reversal with neostigmine or reversal with edrophonium. All neuromuscular function recovery times were measured from the end of injection of the neuromuscular blocking drug.

Statistical analysis utilized the unpaired Student's test. $P < 0.05$ was considered significant.

Reported Results
Subjects in each of the treatment groups were similar in weight; however, the subjects in the spontaneous recovery treatment group were 15-20 years younger than their counterparts in the active treatment groups: 35 (3) years [mean (SEM)] for the

spontaneous recovery group versus 56 (4) and 49 (6) for the neostigmine and edrophonium groups, respectively.

Table 33 below summarizes the treatment groups and the study results including the time to return of 95% of the baseline twitch response (T_{95}).

Table 33. Summary of the Caldwell et al. study results.

NMBA	Treatment	Number of Subjects	Time to TOF_{70} (min.) [mean (SEM)]	T_{95} (min.) [mean (SEM)]
Vecuronium	Spontaneous Recovery	10	67 (3)	52 (3)
	Neostigmine	10	44 (5)*†	36 (4)*†
	Edrophonium	10	60 (6)‡	48 (4)‡
Atracurium	Spontaneous Recovery	10	66 (2)	59 (2)
	Neostigmine	9	44 (3)*#	39 (3)*#
	Edrophonium	10	49 (4)*	49 (4)%

* Significantly less than spontaneous recovery ($p < 0.01$)
† Significantly less than edrophonium recovery ($p < 0.01$)
% Significantly less than spontaneous recovery ($p < 0.05$)
# Significantly less than edrophonium recovery ($p < 0.05$)
‡ Not significantly less than spontaneous recovery ($p \geq 0.05$)

Discussion

This study demonstrated that reversal of vecuronium and atracurium with neostigmine was superior to both spontaneous recovery and reversal with edrophonium. A dose of 0.07 mg/kg of neostigmine was able to significantly shorten the duration of the NMBAs even when administered prior to the return of a response to peripheral nerve stimulation. Although the ability to successfully extubate the patients with adequate maintenance of a patent airway and ventilation was not assessed, the superiority of neostigmine to spontaneous recovery and to edrophonium for the studied endpoints strongly suggests that it would efficacious, and likely superior to edrophonium, for the purposes of discontinuing mechanical ventilation and removal of the endotracheal tube at the end of a surgical procedure or when ventilatory support is no longer required due to resolution of an underlying medical condition in the intensive care unit setting.

Caldwell et al. (1995)

Caldwell JE. Reversal of residual neuromuscular block with neostigmine at one to four hours after a single intubating dose of vecuronium. Anesth Analg 1995; 80: 1168-74.

The purpose of this study was to measure the degree of residual neuromuscular blockade at different times after a single dose of vecuronium and to evaluate the effectiveness of neostigmine for antagonizing the residual block.

Methods
A total of 60 adult patients, ASA 1 or 2, undergoing a general surgical and an orthopedic procedure were enrolled in the study. None of the subjects had any disease process or was taking a medication that might have affected neuromuscular function.

Patients were premedicated with midazolam and anesthesia was induced with sodium thiopental, isoflurane 1%-2%, and nitrous oxide 60%-70% in oxygen. Vecuronium 0.1 mg/kg was administered to facilitate endotracheal intubation. Anesthesia was maintained with isoflurane 0.5%-1.5% and nitrous oxide 60%-70% and supplemented by fentanyl boluses as needed. Heart rate and ECG were monitored and mean arterial blood pressure (MAP) was measured noninvasively. Neuromuscular function was assessed by stimulation of the ulnar nerve at the wrist and measurement of the force of the evoked twitch tension of the adductor pollicis. Specifically, the amplitudes of the first (T1) and fourth (T4) twitch responses and the TOF ratio (T4/T1) were measured.

Forty patients received a single dose of neostigmine 40 mcg/kg with glycopyrrolate 8 mcg/kg that were administered at 1, 2, 3, or 4 h after vecuronium administration (10 patients at each time point) based on the anticipated duration of surgery. Neuromuscular responses were recorded immediately prior to the injection of neostigmine (control response), at 10 min after the injection (early response), and at the end of the surgical procedure or at 60 min after the neostigmine administration (late response), whichever came earlier. The control TOF response defined the degree of residual neuromuscular block, the early response defined the initial effect of neostigmine, and the late response determined whether the early response was sustained.

In the remaining 20 patients, 20 mc/kg of neostigmine, and 4 mcg/kg of glycopyrrolate were administered at 2 hours (n = 10) and 4 hours (n = 10) after the vecuronium injection in an attempt to identify an effective dose of neostigmine for antagonizing residual neuromuscular block at these different time periods and that was associated with the fewest complications.

Adequate return of neuromuscular function was defined as a TOF ratio of ≥ 0.75 because, the investigators indicated, this is associated with the ability to raise the head for 5 seconds, widely open the eyes, cough, protrude the tongue, and to protect the integrity of the airway. Neostigmine administration was considered successful if 10 minutes after its administration the TOF ratio was increased or unchanged, and was ≥ 0.75. If, at 10 min after neostigmine administration, the TOF ratio was <0.75 this was considered inadequate reversal, and if the neostigmine produced a decreased TOF ratio, even if it remained ≥ 0.75, this was considered an adverse affect.

In all patients, heart rate, rhythm, and MAP were recorded immediately before and at 1-min intervals for 10 min after neostigmine administration. Changes greater than 20% from the pre-neostigmine value were considered clinically significant, as was the development of any cardiac dysrhythmia.

The control, early and late values for T1 and T4 amplitude, and the TOF ratio were compared by repeated measures ANOVA. The control and the early and late values at 2 and 4 h were compared between the patients who received 40 vs 20 mcg/kg of neostigmine by the Mann-Whitney U-test. The maximum changes in heart rate and MAP produced by the two dose combinations of neostigmine and glycopyrrolate were also compared using the Mann-Whitney U-test. The incidence of clinically significant cardiovascular effects was compared by the X^2 test. Statistical significance was inferred at $P < 0.05$.

Reported Results

There were no differences in the ages or weights of the patients in the six study groups. Five study groups had a male to female ratio of 7:3; the remaining (40 mcg/kg neostigmine administered 4 hours after vecuronium) had a ratio of 3:7.

Table 34 below summarizes the median values and ranges for the TOF ratios immediately before administration of neostigmine, 10 minutes later and either at the end of surgery or 1 hour after neostigmine was administered, whichever occurred first.

After 40 mc/kg of neostigmine, the TOF ratio increased or remained unchanged in 32 patients, but decreased in 8 patients. In all patients in whom the TOF ratio decreased, both T1 and T4 amplitudes increased, but the magnitude of the T1 increase was proportionately greater. The lowest TOF ratio recorded in these 8 patients was 0.68. In the patients in whom the TOF ratio decreased, the median time to return to control, i.e., pre-neostigmine values, was 31 min (range, 17-53 min). The decrease in TOF ratio was observed only at 2, 3, or 4 h after vecuronium and was associated with a control TOF ratio of ≥ 0.9. There were no patients in whom the amplitude of the T1 or T4 responses decreased after either dose of neostigmine.

At a dose of 20 mcg/kg, the TOF ratio increased or remained unchanged in all 20 patients. The minimum value for the TOF ratio 10 min after administration of 20 mcg/kg of neostigmine was 0.86. Because, at 4 h after vecuronium, no decrease in the TOF ratio resulted from this smaller dose of neostigmine, the TOF ratio 10 min after 20 mc/kg was greater than after 40 mc/kg.

All patients but one had four TOF responses when neostigmine was given. This one patient received neostigmine 40 mcg/kg 1 h after vecuronium when she had only three TOF responses (TOF ratio = 0.00). In this patient the TOF ratio at 10 min after neostigmine administration was only 0.62; it did not reach 0.75 until 57 min after neostigmine administration. In contrast, all other patients in this group had a TOF ratio of at least 0.77 at 10 min after neostigmine.

Comparison of the early and late responses showed that all initial increases in TOF ratios were sustained until the end of the monitoring period.

Table 34. TOF ratios at different times following vecuronium and neostigmine administration (Table 2 on p. 1170 of the article)

Time after vecuronium (h)	Neostigmine dose (mcg/kg)	TOF ratio before neostigmine [mean (range)] (%)	TOF ratio 10 min after neostigmine [mean (range)] (%)	TOF ratio at end of surgical procedure[A] [mean (range)] (%)
1	40	0.29 (0.00-0.86)	0.86 (0.62-0.96)	0.89 (0.75-0.98)
2	40	0.87 (0.43-0.98)	0.94 (0.75-0.98)	0.97 (0.86-1.00)
3	40	0.90 (0.62-0.98)	0.93 (0.85-1.00)	0.94 (0.87-1.00)
4	40	0.91 (0.81-1.00)	0.83* (0.68-1.00)	0.95 (0.86-1.00)
2	20	0.88 (0.45-0.98)	0.97 (0.86-1.00)	0.96 (0.92-1.00)
4	20	0.92 (0.68-0.98)	0.96* (0.87-1.00)	0.96 (0.87-1.00)

[A] Or at 60 minutes following neostigmine administration, whichever was earlier
* $p < 0.05$ for 40 mcg/kg versus 20 mcg/kg of neostigmine

Cardiovascular monitoring revealed that in the 40 patients who received neostigmine 40 mcg/kg and glycopyrrolate 8 mcg/kg there were 14 episodes of heart rate increase >20%; none of a decrease >20%; 7 episodes of MAP increase >20%; none of >20% decrease; and 4 patients who developed a junctional rhythm. In the 20 patients who received neostigmine 20 mc/kg and glycopyrrolate 4 mcg/kg, there were 5 episodes of heart rate increase >20%; 2 of a decrease >20%; 1 episode of MAP increase >20%; none of a decrease >20%; and 4 patients who developed a junctional rhythm. There were no statistically significant differences in the cardiovascular effects of the two doses of neostigmine and glycopyrrolate.

Discussion

The study results are useful, for the purposes of this application, in showing that a 40 mcg/kg dose of neostigmine administered 1 hour after an intubating dose of vecuronium can restore neuromuscular function to a level where the TOF ratio is greater than 90% within 10 minutes. It also shows that a 40 mcg/kg dose has no more adverse impact on the cardiovascular system than a 20 mcg/kg dose.

Dhonneur et al. (1996)

Dhonneur G, Rebaine C, Slavov V, et al. Neostigmine reversal of vecuronium neuromuscular block and the influence of renal failure. Anesth Analg 1996; 82:134-8.

This study evaluated the pharmacodynamics of vecuronium and its reversal by neostigmine in patients with normal renal function and compared it to patients with renal failure.

Methods

A total of 40 patients with end-stage renal failure (RF), which was not defined in the article, and 40 patients with normal renal function (NL), which was also not defined in the article, were enrolled in this study. Subjects were required to be undergoing elective peripheral surgery under general anesthesia with an expected duration of the surgery to be at least 60 minutes. Patients with neuromuscular disorders and those treated with drugs known to interfere with the neuromuscular blocking effect of vecuronium were excluded from enrollment.

Anesthesia was induced with fentanyl, thiopental, and a single dose of 0.1 mg/kg vecuronium to facilitate tracheal intubation. Anesthesia was maintained with 60% nitrous oxide in oxygen and an end-tidal concentration of isoflurane that was maintained between 0.3% and 1.0% by mechanical ventilation. Monitoring of neuromuscular function consisted of supramaximal train-of-four (TOF) stimulation delivered to the ulnar nerve at the wrist every 12 seconds and measurement of the evoked adductor pollicus response using a force transducer. The control value (T_C) of the twitch height was defined as the height of first evoked twitch response (T_1) to the TOF stimulation immediately before the administration of vecuronium. Monitoring was continued throughout the study.

Vecuronium-induced neuromuscular block was reversed by an intravenous bolus of mixture of 40 mcg/kg neostigmine and 20 mcg/kg atropine. The combination was administered at the time of reappearance of either the second or fourth response to the TOF stimulation, and the following parameters were determined:

1. The spontaneous recovery time, i.e., the time between administration of vecuronium and neostigmine
2. The reversal time, i.e., the time from administration of neostigmine to recovery of the first response to the TOF stimulation to 75% ($T1_{0.75}$) and 90% ($T1_{0.9}$) of its control value,
3. The time to recovery of TOF ratio to 0.7 ($TOF_{0.7}$).
4. The total recovery time, i.e., the sum of the spontaneous recovery time and the reversal time

All pharmacodynamic variables were recorded while the patients were under general anesthesia. The variables were compared between the RF and NL groups using the Student's t-test.

Reported Results

The investigators reported that the age ranges (mean ± SD) were similar in the two groups; 56 ± 16 yr for patients with RF and 51 ± 14 yr for patients with NL, as were the durations of anesthesia NL 79 ± 25 min for NL and 87 ± 32 min for RF patients. Also similar for the two groups were the onset of the maximum neuromuscular blocking effect of vecuronium and the reappearance of the second response to the TOF. The recovery of the fourth response of the TOF was not different for the two groups; it was achieved when the T_1 twitch height was 18% ± 6% in NL patients and 19% ± 9% in patients with RF.

As indicated in Table 35 below, the timing of neostigmine administration, which did not differ between groups, did not significantly affect the spontaneous recovery time. There was no significant difference between treatment groups for any of the recovery parameters evaluated.

Table 35. Summary of pharmacodynamic effects of neostigmine for patients with normal renal function (NL) and end-stage renal disease (RF) [mean (SD)] (based on Table 1 on p. 135 of the article)

Time of Administration of Neostigmine		T_1/T_C at reversal (%)	Spontaneous Recovery Time (min.)	Reversal Time (min.)			Total Recovery Time (min.)		
				$T1_{0.75}$	$T1_{0.9}$	$TOF_{0.7}$	$T1_{0.75}$	$T1_{0.9}$	$TOF_{0.7}$
Reversal at T_2	NL	9 (5)	32 (11)	11 (4)	22 (9)	21(11)	43 (12)	54 (20)	53 (19)
	RF	8 (5)	36 (15)	12 (6)	24 (11)	17 (12)	48 (17)	60 (20)	53 (19)
Reversal at T_4	NL	18 (6)	35 (9)	6 (4)	12 (8)	10(8)	41 (10)	47 (11)	45*(10)
	RF	19 (9)	41 (14)	8 (4)	16 (10)	13 (10)	49 (19)	57 (16)	54 (18)

* Reported as 41 by the authors, but this is not consistent with the definition, i.e., total recovery time = spontaneous recovery time + reversal time.

The investigators compared the total recovery time parameters $T1_{0.75}$ and $T1_{0.9}$ with age for subjects in both groups. A significant correlation was observed for NL patients but not for RF patients. In addition, a significant correlation was observed between age and total recovery time of $TOF_{0.7}$ for NL subjects but not for RF subjects.

Discussion

This study demonstrated that end-stage renal failure, compared to normal renal function, did not affect the dosing requirements or pharmacodynamics of neostigmine when used to reverse vecuronium-induced neuromuscular blockade.

Fisher et al (1983)

Fisher DM, Cronnelly R, Miller RD, Sharma M. The neuromuscular pharmacology of neostigmine in infants and children. Anesthesiology 1983; 59: 220-5.

The investigators determined the dose-response relationship and the time course of action of neostigmine in infants, children, and adults in the study reported in this article.

Methods

To assess dose response to neostigmine in pediatric patients, two groups of patients, infants (3-48 weeks; n = 12) and children (1-8 years; n = 15), undergoing elective nonhepatic, nonrenal surgery were enrolled in the study. No patient had any disease known to alter neuromuscular function. Anesthesia was induced and maintained with nitrous oxide and halothane. Neuromuscular function was monitored by ulnar nerve stimulation at the wrist, using needle electrodes, and measuring the resulting force of contraction of the adductor pollicis muscle. Baseline neuromuscular function was assessed prior to the administration of d-tubocurarine, initially as bolus doses then as an infusion to maintain a constant 90% depression of the twitch response to 0.15 msec impulses delivered at 0.15 Hz. When the twitch response was unchanged for 15 minutes, neostigmine and atropine were administered as an intravenous bolus. Nine subjects (four infants and five children) were assigned to a treatment group and received 6.25, 12.5, or 25 mcg/kg neostigmine and 5, 10, or 20 mcg/kg, respectively, of atropine. After the injection of neostigmine and atropine, the curare infusion and anesthetic were continued as before until the surgical procedure was completed.

The dose response relationship was determined using the percent antagonism calculated as below:

$$\% \text{ antagonism} = \frac{(\text{Peak twitch tension after reversal} - \text{Twitch tension at the time of reversal}) \times 100\%}{100 - \text{Twitch tension at time of reversal}}$$

Equation 1. Percentage of d-Tubocurarine antagonized by neostigmine

For each treatment group, the percentage of antagonism versus logarithm of the dose of neostigmine was analyzed by a least-squares linear regression and ED 50 was calculated from this regression line. Values for adults were obtained from a study conducted by Miller et al. (97) under comparable anesthetic conditions and using similar neuromuscular monitoring techniques. Miller *et al.* administered doses based on body surface area; these values were recalculated by the authors assuming that 1.75 m^2 was

the surface area for a 70 kg person. The slopes and position of the regression lines were compared by analysis of covariance; they are shown in the figure below in the reported results section.

To determine the time course of the onset of antagonism, the authors measured the time from administration of neostigmine to 30%, 50%, and 70% of peak antagonism. Mean values for the low, medium, and high dose for each group were compared by analysis of variance and the Student-Newman-Keuls test. The infusion of dTc was continued until after the peak effect of neostigmine (defined as a 5-min period in which twitch tension did not continue to increase). If time allowed, the authors continued the infusion and followed the course of antagonism until the end of surgery.

The authors also evaluated the pharmacokinetics of neostigmine in 15 patients undergoing surgical procedures with minimal blood loss (< 10 ml/kg). These patients were divided by age into three groups of five: infants (2-10 months), children (1-6 years), and adults (29-48 years). The patients were all treated with atropine 30 mcg/kg in addition to a neostigmine 2-minute infusion, which was dosed as follows:

- 100 mcg/kg for infants
- 70 mcg/kg for children and adults

A larger dose was used for infants, because a preliminary study using 70 mcg/kg demonstrated a short time period during which neostigmine could be detected in serum. The concentration-time curve for neostigmine was fitted, using a least-squares nonlinear regression, to two- and three-compartment pharmacokinetic models adjusted for the infusion. Values were weighted by the inverse-square of the serum concentration. To select between the two- or three-compartment models, the residual sums of squares for each subject were compared using the methods of Boxenbaum *et al.* Using standard formulas, the authors determined the following variables:

- rapid and slow distribution half-lives ($t_{1/2\pi}$; $t_{1/2\alpha}$)
- elimination half-life ($t_{1/2\beta}$)
- volume of the central compartment (V_1)
- steady-state volume of distribution (Vd_{ss})
- total plasma clearance (Cl)

Mean values for the pharmacokinetic data for the three age groups were compared by analysis of variance and the Student-Newman-Keuls test. For all statistical comparisons, $p < 0.05$ was considered significant.

Reported Results

The dose-response regression lines for infants and children were similar in both slope and y-axis intercept; the regression line for adults was parallel but shifted to the right as demonstrated in the figure below. The authors reported the ED_{50} values for the three age groups as:

- infants - 13.1 mcg/kg
- children - 15.5 mcg/kg
- adults - 22.9 mcg/kg

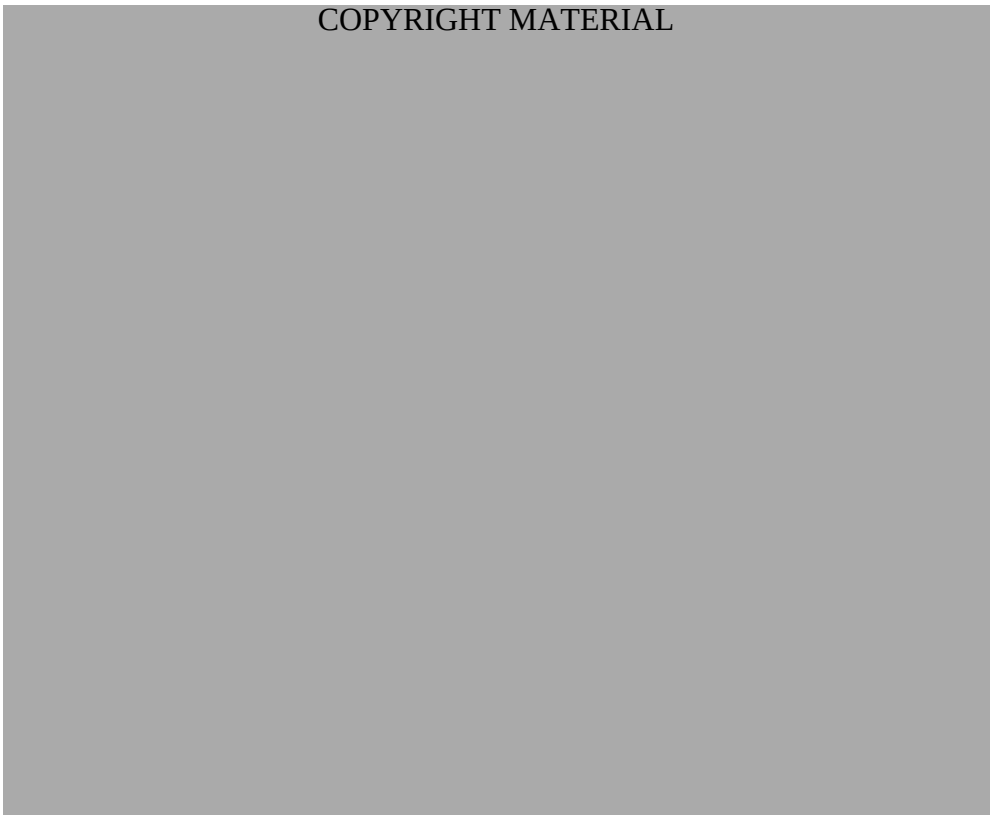


Figure 3. Dose-response curves for neostigmine reversal of d-Tubocurarine (dTC) (Figure 1 on p. 221 of the article)

The time to 30%, 50%, and 70% of peak antagonism was similar for the three groups as indicated in Table 36 below.

Table 36. Time to various percentages of peak antagonism [mean ± SD] from administration of neostigmine (Table 1 on p. 221 of article)

Group	N	Dose (mcg/kg)	Time to 30% antagonism (min)	Time to 50% antagonism (min)	Time to 70% antagonism (min)
Infants	4	6.25	3.0 ± 0.9	5.1 ± 1.7	7.4 ± 2.2
	4	12.5	3.3 ± 0.6	5.6 ± 1.0	8.2 ± 1.5
	4	25.0	2.1 ± 1.2	3.5 ± 1.9	5.1 ± 2.8
Children	5	6.25	2.6 ± 0.8	4.6 ± 1.4	7.1 ± 3.1
	5	12.5	2.8 ± 0.9	5.5 ± 2.3	8.5 ± 3.8
	5	25.0	2.0 ± 0.5	3.2 ± 0.9	5.0 ± 1.2

Group	N	Dose (mcg/kg)	Time to 30% antagonism (min)	Time to 50% antagonism (min)	Time to 70% antagonism (min)
Adults*	5	15.0	3.6 ± 1.3	6.2 ± 2.1	8.3 ± 3.0
	5	30.0	3.2 ± 0.3	5.0 ± 0.5	6.6 ± 1.1
	5	45.0	2.0 ± 0.6	3.2 ± 0.7	4.8 ± 1.3

* Adapted by authors from Miller et al. (97)

In the pharmacokinetic study, neostigmine could be identified in serum for 120-213 minutes after drug administration. The detection period was similar for the three groups. There was statistical support for the three-compartment model. As indicated in Table 37 below, there was no difference in $t_{1/2\pi}$, $t_{1/2\alpha}$, V_1, Vd_{ss}, or Cl. The elimination half-life ($t_{1/2\beta}$) was shorter in infants and children than in adults.

Table 37. Pharmacokinetic parameters for neostigmine (Table 2 on p. 223 of article)

Group	N	$t_{1/2\pi}$ (min)	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)	V_1 (l/kg)	Vd_{ss} (l/kg)	Cl (ml/kg/min)
Infants	5	0.6 ± 0.4	7.7 ± 6.2	39* ± 5	0.08 ± 0.08	0.54 ± 0.17	13.6 ± 2.8
Children	5	1.5 ± 1.4	5.7 ± 2.0	48* ± 16	0.09 ± 0.08	0.49 ± 0.25	11.1 ± 2.7
Adults	5	0.8 ± 0.2	9.2 ± 1.4	67 ± 8	0.04 ± 0.01	0.52 ± 0.15	9.6 ± 2.3

* Different from adults ($p < 0.05$)

Discussion

The results from this study suggest that infants and children have a reduced dosing requirement of neostigmine but a similar time course of action for its reversal effects compared to adults. There appears to be no sharp distinction between infants and children in their dosing requirements, at least not for the purposes of reversing d-Tubocurarine-induced neuromuscular blockade. The study demonstrates that the pharmacokinetics of neostigmine are similar between infants, children and adults with the exception of elimination half-life ($t_{1/2\beta}$), which was shorter in infants and children than in adults.

Fuchs-Buder et al. (2010)

Fuchs-Buder T, Meistelman C, Alla F, et al. Antagonism of low degrees of atracurium-induced neuromuscular blockade: dose-effect relationship for neostigmine. Anesthesiology 2010;112:34-40.

This study was conducted to determine the dose-effect relationship, if one exists, for neostigmine when it is used to reverse paralysis following spontaneous recovery to TOF ratios of 0.4 and 0.6.

Methods
A total of 120 patients (ASA-PS 1-3) scheduled to undergo elective surgery were enrolled in the study. The exclusion criteria included:

1. neuromuscular, hepatic, or renal disease
2. abnormal airway anatomy (Mallampati Score of 3 or 4)
3. body weight exceeding normal limits by ≥ 25%
4. pregnancy
5. being on medication that influences neuromuscular blockade
6. history of allergic reaction to drugs used in the study

Subjects were randomized into the following treatment groups, with 15 subjects per group, with treatment administered based on acceleromyographic measurements of TOF:

TOF = 0.4
A. neostigmine 10 mcg/kg with atropine 15 mcg/kg
B. neostigmine 20 mcg/kg with atropine 15 mcg/kg
C. neostigmine 30 mcg/kg with atropine 15 mcg/kg
D. saline, i.e., no neostigmine or atropine

TOF = 0.6
E. neostigmine 10 mcg/kg with atropine 15 mcg/kg
F. neostigmine 20 mcg/kg with atropine 15 mcg/kg
G. neostigmine 30 mcg/kg with atropine 15 mcg/kg
H. saline, i.e., no neostigmine or atropine

One hour prior to surgery, patients were premedicated with hydroxyzine per os. Routine monitoring was utilized intraoperatively. Anesthesia was induced with propofol and of sufentanil and maintained with a propofol infusion, intermittent bolus doses of sufentanil, and oxygen–nitrous oxide (50%/50%) until the end of surgery and complete neuromuscular recovery. Core temperature was maintained over 35°C and peripheral body temperature measured at the thenar eminence of the palm was maintained at least at 32°C. End-tidal partial pressure of carbon dioxide (PCO2) was maintained

between 32 and 36 mmHg. Following calibration of the acceleromyograph and establishment of a stable baseline reading for 3 minutes, paralysis was induced with 0.5 mg/kg bolus of atracurium, and orotracheal intubation was performed. During surgery, bolus doses of atracurium (0.1 mg/kg) were administered as clinically indicated. At the end of surgery, subjects in treatment groups A, B, C, and D received study drug once the TOF ratio spontaneously recovered to 0.4; subjects in Groups E, F, G, and H received study drug once the TOF ratio spontaneously recovered to 0.6. Neuromuscular monitoring was continued until complete recovery of the acceleromyographic TOF ratio, i.e., baseline values ± 5%.

The following neuromuscular recovery parameters were determined from the acceleromyographic data:

1. The time interval from injection of study drug until a TOF ratio recovery to 0.9 (secondary endpoint) and 1.0 (primary endpoint) was measured.
2. Probability of successful reversal within 10 min after administration of different neostigmine doses and placebo
3. Neostigmine requirements to recover from a TOF ratio of 0.4 and 0.6 to a TOF ratio of 0.9 and 1.0 in 5 and 10 minutes.

Reported Results

The authors reported that there were no significant differences among the treatment groups with respect to age, weight, height, gender distribution, temperature, and cumulative atracurium dose and that all subjects returned to baseline, i.e., TOF ratio of 1.0 during the recovery phase of the study.

The recovery times for each of the treatment groups were summarized by the authors as shown in Table 38. below. They reported that each of the neostigmine doses, whether administered at residual block levels of $TOF_{0.4}$ or $TOF_{0.6}$, significantly reduced the reversal time to both $TOF_{0.9}$ and $TOF_{1.0}$ compared to the placebo treatments.

The authors noted that increasing the neostigmine dose significantly reduced the time needed to recover from $TOF_{0.4}$ to both $TOF_{0.9}$ and $TOF_{1.0}$. However, no such dose-effect relationship was found when neostigmine was given at $TOF_{0.6}$.

Table 38. Recovery time to $TOF_{0.9}$ and $TOF_{1.0}$ (from Table 1 on p. 36 of article)

Prereversal Block	Treatment			
	Placebo	Neostigmine Dose Groups		
		10 µg/kg	20 µg/kg	30 µg/kg
$TOF_{0.4}$				
Recovery to $TOF_{0.9}$ Median (range)	13*† (7-27)	6† (3-12)	6† (4-9)	4† (3-6)
Recovery to $TOF_{1.0}$ Median (range)	19* (11-30)	11 (7-15)	9 (6-13)	6 (4-11)
$TOF_{0.6}$				
Recovery to $TOF_{0.9}$ Median (range)	10*† (5-16)	4‡ (2-9)	3† (2-7)	4† (2-6)
Recovery to $TOF_{1.0}$ Median (range)	15* (8-20)	6 (4-16)	6 (4-14)	5 (3-7)

*p<0.0001 compared with neostigmine
†p<0.0001 compared with $TOF_{1.0}$ recovery
‡p=0.0004 compared with $TOF_{1.0}$ recovery, paired t-test

Using the data, the authors calculated the probability that the different treatments would produce a recovery to $TOF_{0.9}$ and $TOF_{1.0}$ within 10 minutes whether the treatment was administered at a TOF ratio of 0.4 or 0.6. The results are shown in the two figures below.

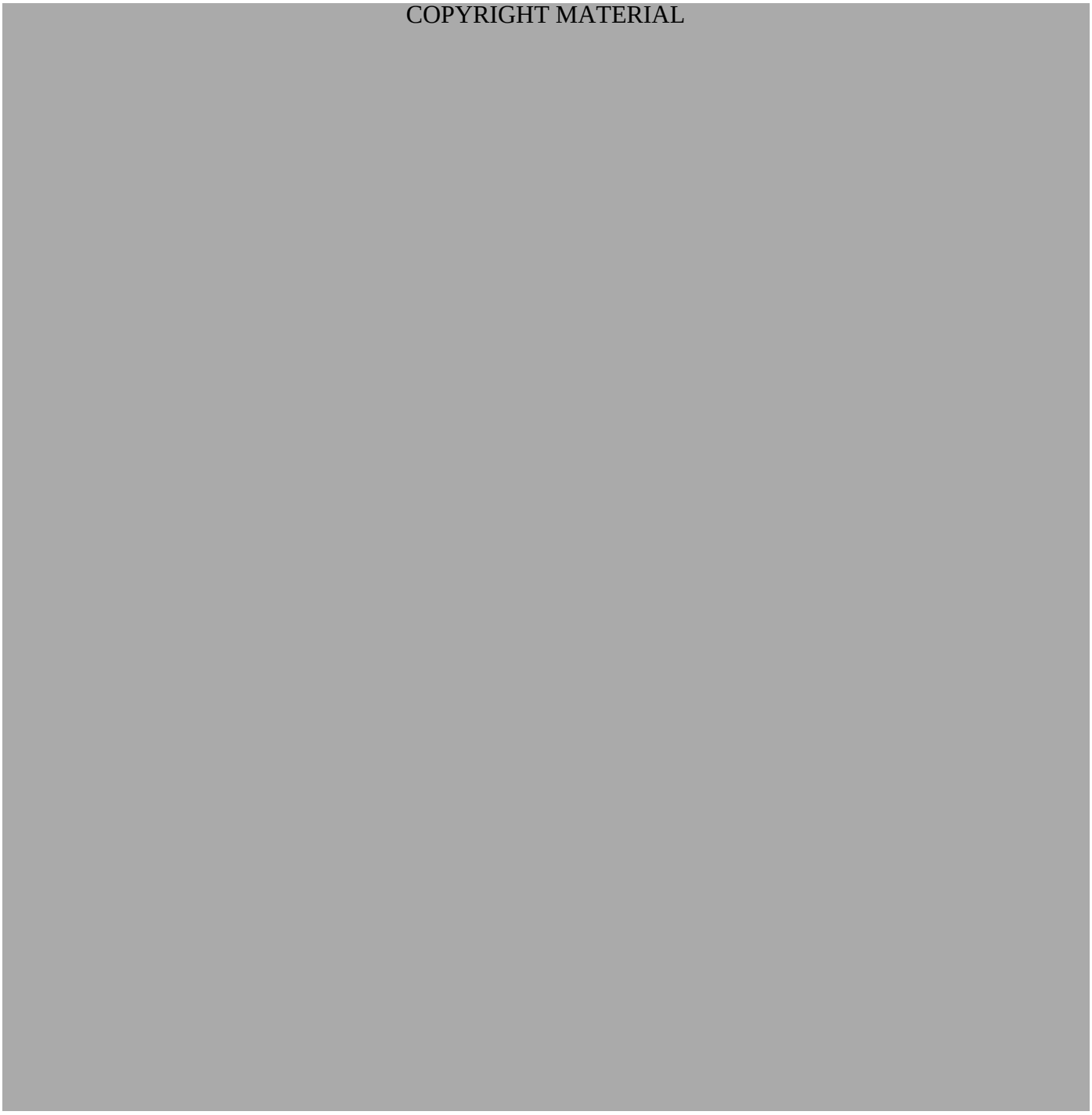


Figure 4. Probability of successful reversal within 10 minutes when treatment is administered at a TOF ration of 0.4 (figure 1 on p. 36 of the article)

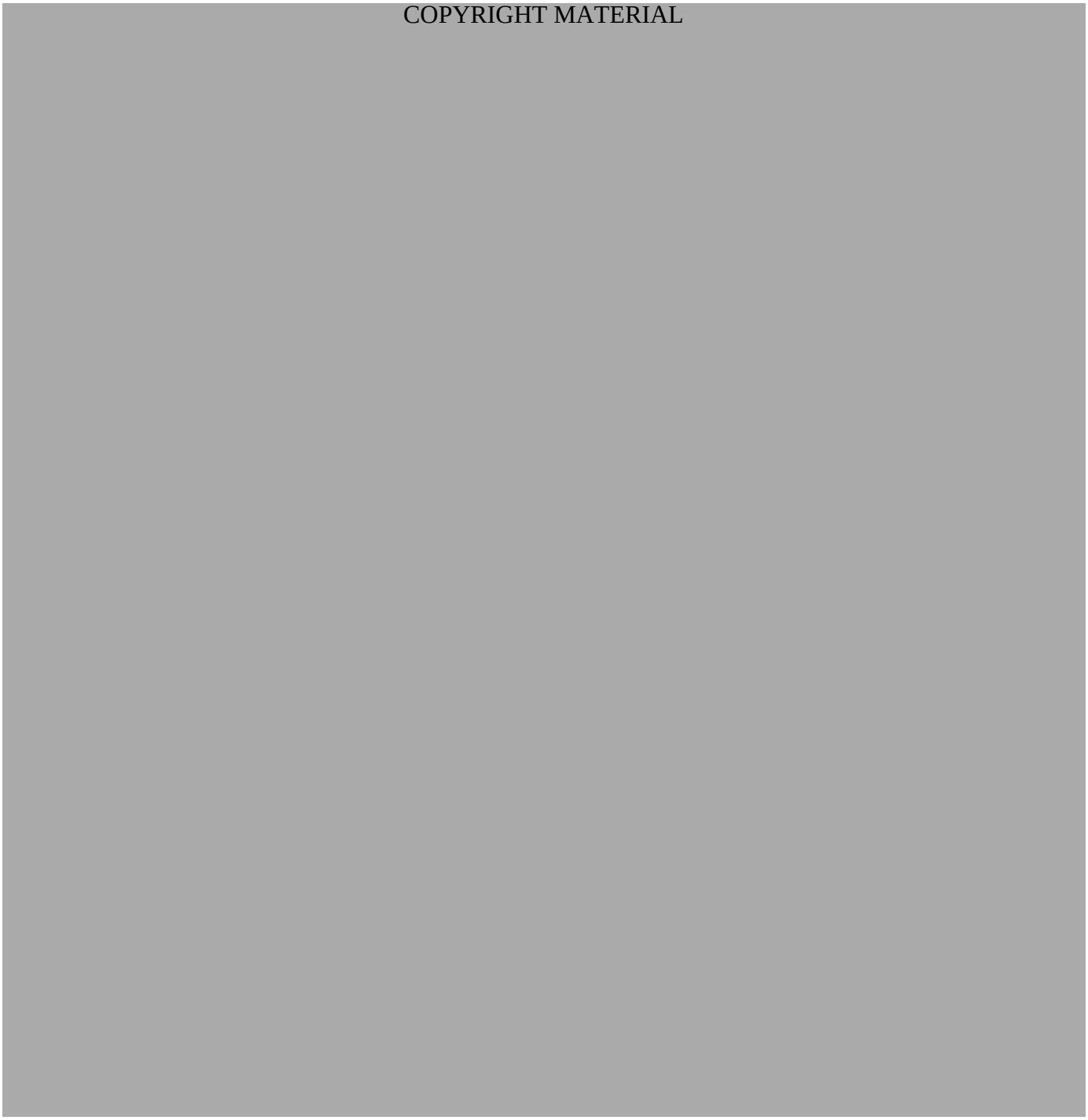


Figure 5. Probability of successful reversal within 10 minutes when treatment is administered at a TOF ration of 0.6 (figure 2 on p. 37 of the article)

The authors utilized their data to estimate the neostigmine doses that would be needed to reach a 0.9 and 1.0 TOF ratio within 5 and 10 minutes after spontaneous recoveries to either $TOF_{0.4}$ or $TOF_{0.6}$. The results are shown in Table 39 below. Based on their calculations, a dose of 30 mcg/kg of neostigmine would be expected to result in a TOF ratio of 1.0 within approximately 5 min, independent of whether it is administered at a TOF ratio of 0.4 or 0.6. Significantly less neostigmine is required to reach a TOF ratio of 0.9 or a time interval of 10 minutes is acceptable.

Table 39. Neostigmine doses needed to recover to $TOF_{0.9}$ and $TOF_{1.0}$ within 5 or 10 minutes (from Table 2 on p. 37 of article)

Timing of Neostigmine Administration	Recovery within 5 min		Recovery within 10 min	
	TOF Ratio 0.9	TOF Ratio 1.0	TOF Ratio 0.9	TOF Ratio 1.0
TOF Ratio 0.4	24 ± 10 mcg/kg*	34 ± 10 mcg/kg*†	8 ± 11 mcg/kg	25 ± 11 mcg/kg†
TOF Ratio 0.6	13 ± 12 mcg/kg*	31 ± 12 mcg/kg*†	—‡	24 ± 13 mcg/kg†

P < 0.001 compared with the corresponding neostigmine dose at 10 min.
† *P* < 0.01 compared with the corresponding neostigmine dose for a 0.9 TOF ratio recovery.
‡ Not calculated because the TOF ratio of 0.9 was already reached in < 10 min in most patients in the placebo group and in all patients who received neostigmine (10, 20, or 30 mcg/kg).

Discussion

This study appears to be well designed and executed. Although not blinded, the risk of bias is reduced by the uniform use of acceleromyographic data to assess the level of neuromuscular blockade.

The findings of the study indicate that doses of neostigmine as low as 10 mcg/kg may effectively reverse atracurium to a TOF ratio of 0.9 within 10 minutes when spontaneous recovery has reached at least $TOF_{0.4}$. Perhaps more apropos to the operating room setting is recovery within 5 minutes of administration of the reversal agent. For this purpose, a 30 mcg/kg dose of neostigmine appears to be adequate even when administered at $TOF_{0.4}$. It is worth noting that the authors explicitly stated that paradoxical weakness after neostigmine did not occur in any patient in this study. This further supports the use of the 30 mcg/kg dose as is neither too low to be fully effective nor too high so as to have a negative effect – at least, not when administered at these points of spontaneous recovery. Expanding the study to include treatment groups with neostigmine doses up to 70 mcg/kg would have been helpful in determining whether the generally touted upper limit of dosing would produce undesired effects, i.e., paradoxical weakness, if it were administered when the TOF ratio was at 0.4 or 0.6.

The authors did not report whether any adverse events were observed for subjects in any of the treatment groups, particularly, whether substantial changes in cardiac rate or

rhythm or blood pressure occurred. Such information would help assess the efficacy of the 15 mcg/kg dose of atropine and the timing of its administration for mitigating or preventing the untoward cardiac effects of neostigmine.

In summary, this study provides strong evidence of the efficacy of neostigmine for reversing atracurium as well as important information regarding the timing of administration and the dosing requirements based on neuromuscular monitoring and onset of its effects.

Gencarelli and Miller (1982)

Gencarelli PJ and Miller RD. Antagonism of Org NC45 (vecuronium) and pancuronium neuromuscular blockage by neostigmine. Br J Anaesth 1982; 54(53): 53-55.

The reversal of vecuronium and pancuronium by administration of neostigmine was evaluated in 29 anesthetized patients. The NMBAs were administered by infusions until the twitch response was reduced to 10% of baseline and maintained at that level for at least 15 minutes. Patients were then randomized to be given a single dose of neostigmine while the NMBA infusion was continued. The changes in twitch responses were measured with a PNS and the dose of neostigmine that effectively produced 50% antagonism (ED_{50}) were determined from the dose-response curves using linear regression techniques. Table 40 below summarizes the doses of neostigmine evaluated.

Table 40. Summary of the Gencarelli et al. study findings.

NMBA	Dose of Neostigmine (mcg/kg)	Number of Subjects	Maximum Twitch Response Following Reversal (% baseline)*
Vecuronium	5	3	30
	10	5	37
	20	4	77
	30	3	78
Pancuronium	5	5	30
	10	5	50
	30	4	82

* Estimated from Figures 1 and 2 on page 54 of the article.

The data indicated a dose-dependent response for the reversal of both agents. It was reported by the authors that the time from its injection to the peak effect of a 10 mcg/kg dose of neostigmine was shorter for vecuronium (5 min) than for pancuronium (11 min). However, the times to peak effect were not different for the two NMBAs with 30 mcg/kg dose of neostigmine.

Discussion

While these data support the efficacy of neostigmine for reversing vecuronium and pancuronium, the study was not designed to allow determination of when neostigmine should be administered or what dose should be used to adequately reverse either of these NMBAs for the purposes of discontinuing mechanical ventilation and extubation of the trachea. Rather, the data indicate that the peak effect from a 30 mcg/kg dose of

neostigmine is likely to be inadequate to reverse the neuromuscular blockade as the TOF ratio fails to reach 90% for either vecuronium or pancuronium-treated patients.

Goldhill et al. (1988)

Goldhill DR, Embree PB, Ali HH, Savarese JJ. Reversal of pancuronium. Neuromuscular and cardiovascular effects of a mixture of neostigmine and glycopyrronium. Anaesthesia 1988;43:443-6.

This study evaluated the efficacy of three doses of neostigmine at reversing pancuronium-induce neuromuscular blockade.

Methods
A total of 51 subjects were enrolled in this study. They were recruited from patients who were ASA 1 or 2, aged 18-65 years, weighed 45-111 kg and were undergoing elective surgery that allowed the use of neuromuscular blocking agents. Patients taking medications that could affect the neuromuscular junction or that might alter cardiac rhythm and patients with abnormal electrolytes were.

Anesthesia was induced with thiopentone and maintained with nitrous oxide (66%) and morphine or fentanyl. Volatile anesthetic agents were not used. Ventilation of the lungs was controlled to maintain end tidal CO_2 of 4-5.3 kPa. Neuromuscular function was assessed using the ulnar nerve stimulation at the wrist and measuring the force of contraction of the adductor pollicus muscle. Pancuronium was administered at an initial dose of 0.08-0.1 mg/kg and increments were given to obtain a desired level of inhibition of the first twitch (T_1) of the TOF response at reversal. Antagonism of residual block was accomplished by administration of a fixed ratio of neostigmine and glycopyrrolate (1 mg of neostigmine with 0.2 mg glycopyrrolate) administered over one minute. Patients were randomly allocated to receive 30 mcg/kg (low dose), 60 mcg/kg (medium dose) or 80 mcg/kg (high dose) of neostigmine.

In 27 patients, the neostigmine was administered when T_1 was 1-9% of the baseline/control level (very deep block), and for 3 patients, the neostigmine was administered when T_1 was 10-19% of control (deep block). Reversal from a moderate block, i.e., when T_1 was between 67% and 80% of control twitch height (T_C), was evaluated in 19 patients. In two subjects, no twitches were present at reversal and they were excluded from the neuromuscular analysis.

Neuromuscular monitoring was continued for 30 minutes in 24 of the subjects reversed from very deep blocks and at least 20 minutes for all the other subjects. If a TOF ratio of 0.75 had not been achieved by the end of these monitoring periods, the patients were assessed clinically and given additional doses of neostigmine as needed.

The amplitude of T_1 at reversal and the time to achieve a T_1 of 95% of T_C and a TOF ratio of 0.75 were recorded. The ECG was recorded continuously and blood pressure

and heart rate taken prior to reversal and at 0, 1 ,2,3,4,5,6,8, 10,15 and 20 minutes post reversal Results were compared by ANOVA and Student's t-test where appropriate

Reported Results

For patients reversed during very deep blockade, at least 20 minutes were required to reach a T_1/T_C of 95% after administration of the low-dose of neostigmine (30 pg/kg). The two higher doses of neostigmine achieved a T_1/T_C of 95% significantly faster than the lower dose ($p < 0.05$). None of the doses of neostigmine reliably produced a TOF ratio of 0.75 ($TOF_{0.75}$) within 30 minutes.

For patients reversed during moderate blockade, recovery to T_1/T_C was achieved within 10 minutes of neostigmine administration for all but 2 subjects, both of whom had received low-dose (30 mcg/kg) neostigmine. Recovery to a $TOF_{0.75}$ took more than 10 minutes in three patients given low-dose neostigmine, 3 patients given the medium dose and 2 patients given the highest dose. There was no statistical difference between the three dosing groups for either time to reach to a T_1/T_C of 95%, or a $TOF_{0.75}$. However two patients in the low-dose neostigmine group failed to achieve a $TOF_{0.75}$ within the 20-minute observation period, and therefore, total times to reach this ratio were not available in this group. The results for both reversal groups, i.e., reversal from very deep and moderate blockade, are summarized in Table 41 below.

Table 41. Summary of recovery indices for the two reversal times and three doses of neostigmine (combined data from Tables 1 and 2, pp. 444 and 445 of the article)

Level of block at reversal	**Very Deep Block**			**Moderate Block**		
Neostigmine dose level	**Low dose**	**Medium dose**	**High dose**	**Low dose**	**Medium dose**	**High dose**
N	9	9	9	6	6	7
T_1 blockade at reversal (% of Tc)	95 (1)	95 (1)	95 (1)	73 (2)	75 (1)	77 (1)
Time to 95% recovery of T_1 (min.)	22 (1) [> 30 for n=1]	16 (3)	15 (2)	11 (2)	7 (1)	7 (1)
Time to $TOF_{0.75}$ (min.)	20 (n=3) [>30 for n=6]	19 (n=3) [>30 for n=5]	21 (n=3) [>30 for n=4]	8 (1) [> 20 for n=2]	10 (2)	8 (1)

The high dose neostigmine (80 mcg/kg) failed to achieve either a T_1/T_C of 95% or a $TOF_{0.75}$ faster than the medium dose (60 mcg/kg) regardless of the level of blockade at the time of reversal. No decrease in the TOF ratio was observed with the high dose of neostigmine, which would have been expected if the antagonist contributed to, rather than reversed, the block.

In all, 17 subjects received low dose reversal, 16 received the medium dose and 18 received the high dose. There was no difference among the groups in the resting heart rates or systolic blood pressures, and the incidence of dysrhythmias was reported as similar in all groups: 5 (29%), 8 (50%) and 4 (22%), for the low, medium and high doses of neostigmine, respectively. All but one of the dysrhythmias was junctional; the other was a first degree AV block. The blood pressures after reversal remained constant and within normal limits. The heart rates in all groups decreased gradually but significantly ($p < 0.01$) over the period of observation, but were generally within normal limits.

Discussion

This study provided some evidence that neostigmine reverses pancuronium blockade as evidenced by the differences in the T_1 recovery times to 95% of control values for both the moderate and very deep block groups. The data also indicated that $TOF_{0.75}$ recovery was faster for moderate blockade reversal than very deep blockade reversal. However, there was no dose dependence of $TOF_{0.75}$ times within the groups; therefore, it is not clear whether the difference was due only to the more advanced state of recovery at the time neostigmine was administered. The lack of spontaneous recovery data precludes further assessment of the contribution of neostigmine in this clinical setting.

The safety data from the study suggest that the combination of glycopyrrolate and neostigmine utilized was generally well tolerated; however, without a comparator group, it cannot be determined whether additional glycopyrrolate would have reduced the incidence of bradycardia and dysrhythmias.

Goldhill et al. (1991)

Goldhill, D. R., Carter, J. A., Suresh, D., Whitehead, J. P., & Flynn, P. J. (1991). Antagonism of atracurium with neostigmine. Effect of dose on speed of recovery. Anaesthesia, 46, 496-499.

This randomized, controlled study was conducted to determine the optimal dose of neostigmine required to antagonize neuromuscular blockade induced with atracurium.

Methods
A total of 36 subjects undergoing elective surgery were enrolled in the study. All subjects were healthy (ASA-PS 1) adults who were not taking medications known to interfere with neuromuscular. Subjects were premedicated with intramuscular papaveretum (a combination of morphine hydrochloride, codeine hydrochloride and papaverine hydrochloride) (15-20 mg) and hyoscine (scopolamine) (0.3-0.4 mg). Anesthesia was induced with fentanyl (1-2 mcg/kg) and thiopentone (4-6 mg/kg) and maintained with oxygen, nitrous oxide (66%) and 0.5% inspired isoflurane. End-tidal $PaCO_2$ was maintained during mechanical ventilation at 4.6 to 5.3 kPa.

The evoked compound electromyogram (EMG) of the adductor pollicis muscle was used to assess the level of neuromuscular blockade with the arm from which recordings were taken wrapped in cotton wool to maintain palm temperature at 34-37°C.
After induction of anesthesia a stable neuromuscular response was established and a single bolus dose of atracurium (0.4 mg/kg or 0.35 mg/kg) was administered. The neuromuscular response was allowed to recover spontaneously until three consecutive TOF stimuli evoked two twitches (point R). At that point, subjects were randomized to either recover spontaneously (n=4) or to receive one of four doses of neostigmine in combination with glycopyrrolate (dose not specified) as follows:

1. neostigmine 15 mcg/kg
2. neostigmine 35 mcg/kg
3. neostigmine 55 mcg/kg
4. neostigmine 75 mcg/kg

The anesthetic was continued throughout the recovery from the neuromuscular block.

The control twitch (T_C) was defined as the T_1 of the TOF when the TOF ratio was 0.9. Prior to the administration of neostigmine, T_1 was recorded and the T_1/T_C ratio was later calculated. TOF ratios were assessed every minute for 10 minutes after this time point, and the time to achieve TOF ratios of 0.5, 0.75 and 0.9 were recorded. For the control group, the onset of recovery began when three consecutive stimuli evoked a response of two twitches (point R).

Differences in recovery times to TOF ratios of 0.5, 0.75 and 0.9 were assessed using one-way analysis of variance (ANOVA) for the four neostigmine-treatment groups and for the three higher dose treatment groups, i.e., 35 mcg/kg, 55 mcg/kg and 75 mcg/kg neostigmine doses. For reasons not described, subjects in the spontaneous recovery/control group were not included in the statistical analysis. Where a significant difference was found, the Student-Newman-Keuls (S-N-K) test was performed to identify differences between the groups. Significance was defined as a $p < 0.05$.

Reported Results

One of the subjects in the 75 mcg/kg neostigmine treatment group exhibited a bimodal pattern of recovery in which initial recovery was followed by an increase in T_1 followed by further recovery of T_4. This patient was excluded from the statistical analysis. In addition, a patient, who received 15 mcg/kg of neostigmine, was only monitored until the TOF ratio was 0.87. The T_1 at this point was taken as the T_C.

The authors reported no significant difference between the treatment groups with regard to age, weight, sex distribution or the T_1/T_C at antagonism. The mean time from the initial bolus of atracurium until point R for patients who received neostigmine was 37 minutes for nine patients given atracurium 0.4 mg/kg, and 31 minutes for the other patients who received 0.35 mg/kg. An average of 23 seconds elapsed from point R until neostigmine was administered.

Table 42 below summarizes the findings of the study. There was a significant difference in times to target TOF ratios between each of the neostigmine-treatment groups: $p = 0.0001$ for $TOF_{0.5}$; $p < 0.0001$ for $TOF_{0.75}$; $p = 0.001$ for $TOF_{0.9}$. The S-N-K test showed a significant difference between the 15 mcg/kg neostigmine-treatment group and the other three groups. There was no significant difference by ANOVA between the neostigmine 35 mcg/kg, 55 mcg/kg and 75 mcg/kg treatment groups in the time to achieve a TOF ratio of 0.5 ($p = 0.62$), 0.75 ($p = 0.73$) and 0.9 ($p = 0.98$). The authors also noted that in the post-anesthesia recovery unit, clinical recovery of muscle power, as determined by head lift and hand grip, was satisfactory for all patients.

Table 42. Recovery of TOF responses (based on Table 2 on p. 497 of the article)

Treatment Group	Number of Subjects	T_1/T_C at Antagonism % (SEM)	Time to Stimulus Response minutes (SEM)		
			$TOF_{0.5}$	$TOF_{0.75}$	$TOF_{0.9}$
Spontaneous Recovery	4	6 (1)‡	29 (5)	36 (4)	45 (3)
Neostigmine 15 mcg/kg	8	12 (2)	10 (1)	13 (1)	16 (1)*
Neostigmine 35 mcg/kg	8	15 (3)	5 (0)	8 (1)	10 (1)
Neostigmine 55 mcg/kg	8	11 (1)	4 (1)	7 (1)	10 (1)
Neostigmine 75 mcg/kg	7	9 (1)	4 (1)	7 (1)	10 (1)

‡ T_1/T_C at point R
* n=7 for this measurement

Discussion

This study demonstrated the efficacy of neostigmine in reversing atracurium-induced neuromuscular blockade. Not only did it demonstrate the superiority of neostigmine to spontaneous recovery, but it also showed a dose-dependent response that had a plateau. The reductions in recovery time, 29-35 minutes at the $TOF_{0.9}$ level, were clinically relevant in addition to being statistically significant. The lack of additional effect for doses greater than 35 mcg/kg suggests that limiting the dose of neostigmine, and thereby potentially limiting its side effects, may be a reasonable initial approach to reversing neuromuscular blockade, at least for atracurium.

Although the study did not appear to be blinded, the manner in which the data were generated and collected, i.e., using electromyographic tracings to dictate when study drug was to be administered and to determine the T_C and TOF parameters, was likely to minimize biasing of the results. The robustness of the results also support reliance on this study to make a finding of efficacy for neostigmine and to recommend a dosing regimen, at least when it is used following neuromuscular blockade induced by atracurium.

Harper et al. (1984)

Harper, N. J., Bradshaw, E. G., & Healy, T. E. (1984). Antagonism of alcuronium with edrophonium or neostigmine. British Journal of Anaesthesia, 56, 1089-1094.

This study compared edrophonium and neostigmine as reversal agents for alcuronium in patients undergoing ophthalmic surgeries.

Methods

Twenty three, healthy (ASA 1 or 2) patients undergoing elective ophthalmic procedures with a general anesthetic that included alcuronium as the muscle relaxant were enrolled in this study. Neuromuscular function was assessed at the ulnar nerve and the adductor pollicis muscle. Patients were randomized to receive either edrophonium 1 mg/kg and atropine 7 mcg/kg or neostigmine 35.7 mcg/kg·(2.5 mg/70 kg) and atropine 14 mcg/kg·when the TOF ratio had recovered spontaneously to 0.1. Three patients were given edrophonium when only one or two contractions were elicited with the TOF stimulus, i.e., during "profound blockade." Patients were monitored for at least 10 minutes after study drug administration; 20 were monitored out to 30 minutes and 9 were monitored for 60 minutes.

Reported Results

There was no significant difference between the T4/T1 ratios recorded before the injection of study drug for either of the treatment groups. Following edrophonium, the train-of-four ratio increased rapidly to reach a mean of 0.75 at 1.5 minutes, after which there was an insignificant decrease in response. Reversal following neostigmine was more gradual, reaching a plateau after approximately 10 minutes followed by a slight increase in response thereafter. The difference between the two groups was significant ($p < 0.01$) for the first 4.5 minutes following injection. The response continued to improve over the remaining 55.5 minutes at which time the TOF ratio was approximately 0.8 for the both treatments.

Discussion

The findings from this study are difficult to interpret. They suggest that edrophonium has a faster onset than neostigmine, but the clinical significance of the differences in time to $TOF_{0.75}$ (1.5 minutes versus 10 minutes for edrophonium and neostigmine, respectively), if there is one, is not readily apparent. Furthermore, the parsing of the limited number of subjects to 2 treatment groups, reversal from two levels of blockade and different durations of monitoring following study drug administration, and the lack of a spontaneous recovery/placebo treatment arm also limit the ability to interpret the results.

Jones et al. (1987)

Jones JE, Hunter JM, Utting JE. Use of neostigmine in the antagonism of residual neuromuscular blockade produced by vecuronium. Br J Anaesth 1987; 59: 1454-1458.

This study evaluated the efficacy of two different doses of neostigmine administered at two different points of spontaneous recovery in reversing vecuronium and compared the recovery to that without a reversal agent.

Methods
Fifty healthy patients presenting for general or gynecological surgery under general anesthesia with vecuronium used as the muscle relaxant were randomized to 5 treatment groups:

- Spontaneous recovery (n=10)
- Neostigmine 2.5 mg when the TOF ratio reached 0.1 (n=10)
- Neostigmine 2.5 mg when the TOF ratio reached 0.5 (n=10)
- Neostigmine 5 mg (two doses of 2.5 mg given 2 minutes apart) when the TOF ratio reached 0.1 (n=10)
- Neostigmine 5 mg (two doses of 2.5 mg given 2 minutes apart) when the TOF ratio reached 0.5 (n=10)

The anesthetic consisted of premedication with promethazine 50 mg PO the night before surgery and, optionally, diazepam 10 mg PO 3 hours before surgery or morphine 10 mg combined with cyclizine 50 mg IM one hour before surgery. Anesthesia was induced with thiopentone, fentanyl and either droperidol or midazolam and was maintained with 70% nitrous oxide, 30% oxygen and a halogenated inhaled anesthetic agent.

A PNS was placed over the ulnar nerve at the wrist and single pulse stimuli were applied at increasing voltages until the maximum height of the resultant twitch was achieved. The voltage was than increased by 25% for application of supramaximal stimulation with TOF stimuli, which were then applied at 12-second intervals. After the baseline responses were recorded, vecuronium 0.1 mg/kg IV was administered and the trachea was intubated.

Recovery from vecuronium was monitored using both the twitch response to the first stimulus compared to the baseline value (A'/A) in the TOF stimuli and the ratio of the last and first twitch responses to the TOF stimuli (D'/A), which were applied at 1-minute intervals. For patients randomized to receive neostigmine, additional vecuronium (0.04 mg/kg up to a maximum of 4 dose) could be administered when A'/A = 0.1. No

additional vecuronium was administered to patients randomized to recover spontaneously.

TOF testing was increased in frequency to every 12 seconds when the administration of neostigmine was imminent, or when A'/A = 0.1 for patients who were to recover spontaneously.

The measurement of recovery times began when A'/A were 0.1 and 0.5 for the group that recovered spontaneously, and when the neostigmine was first administered for the active treatment groups. For the patients treated with neostigmine, it was not to be administered until A'/A was either 0.1 or 0.5. In the group in which recovery was spontaneous, monitoring was continued until D'/A' had reached 70%. Atropine 1.2 mg IV was administered before the neostigmine was administered; if a second dose of neostigmine was administered, a second dose of atropine, 0.6 mg, was administered before the neostigmine.

In patients who received neostigmine, monitoring was continued for at least 10 minutes after the agent had been given in the case of patients with a block of 50% and, in those with *90%* block, at least 20 min or until 70% recovery of the TOF ratio (D'/A') had been achieved and maintained for 10 minutes.

When the measurements were completed, PNS monitoring was discontinued and the patient was allowed to breathe 100% oxygen spontaneously through the tracheal tube until it was considered safe to extubate the trachea. The study did not define how that was to be determined.

Statistical analysis of the differences between the means was carried out using Tukey's method.

Reported Results

There was no clinically relevant difference between treatment groups in the subjects' mean age or weight or in the gender distribution. The recovery times are summarized in Table 43 below.

Table 43. Summary of Jones et al. results (based on Table 2 on page 1456 of article).

Initial Block A'/A at Start of Recovery	Ratio monitored	Time to 70% Recovery of Ratio (min.) [mean (SD)]		
		Spontaneous	Neostigmine 2.5 mg	Neostigmine 5 mg
0.5	A'/A	4.9 (2.7)	1.2 (0.7)	1.1 (0.7)
	D'/A	6.9 (3.2)	2.1 (1.0)	1.5 (0.5)
0.1	A'/A	15.5 (6.8)	3.9 (2.2)	3.4 (1.3)
	D'/A	24.2 (11.4)	9.2 (5.3)	5.6 (3.7)

The results indicate that neostigmine significantly reduces recovery time compared to spontaneous recovery ($p < 0.01$) when administered at the two points and two doses evaluated in this study. The differences in recovery times between the two doses of neostigmine were not significant for either timepoint of administration.

Discussion

In this study, the A'/A ratio is equivalent to a simple twitch response. The data indicate that neostigmine is efficacious at reversing vecuronium-induced neuromuscular blockade when it is administered as early as $T_{0.1}$ at doses as low as 2.5 mg. As the mean weights for the patients who were treated with 2.5 mg of neostigmine at $T_{0.1}$ was 64.4 kg, it would suggest that a 0.04 mg/kg dose of neostigmine produces $TOF_{0.7}$ after 9 minutes on average. Similarly, the data indicate that 5 mg of neostigmine given at $T_{0.1}$, or a mean dose of 0.07 mg/kg, produces $TOF_{0.7}$ after 6 minutes on average.

While this study demonstrates the efficacy of neostigmine as a reversal agent for vecuronium, it does not provide guidance as to the adequacy of reversal in terms of discontinuation of mechanical ventilation or the ability for the patient to maintain a patent airway.

Koscielniak-Nielsen et al. (1992)

Koscielniak-Nielsen ZJ, Law-Min JC, Donati F, et al. Dose-response relations of doxacurium and its reversal with neostigmine in young adults and healthy elderly patients. Anesth Analg 1992; 74: 845-50.

This study examined dose-response relationships for neostigmine reversal of doxacurium in younger (age range: 18-40 years) and older (age range: 70-85 years) adult patients.

Methods

The investigators enrolled 48 patients (24 young and 24 elderly) who were ASA 1 or 2 and were undergoing low- to moderate-risk surgical procedures. The surgery had to be elective and be expected to last a minimum of 90 min. Women of childbearing potential, patients with clinical or biochemical evidence of neuromuscular, cardiovascular, renal, hepatic, or psychiatric disease, patients who were obese or malnourished and patients on medications that could affect neuromuscular function were excluded.

General anesthesia was induced with fentanyl and thiopental and maintained with nitrous oxide in oxygen, isoflurane, and fentanyl boluses. Train-of-four (TOF) stimuli were delivered to the ulnar nerve at the wrist and repeated every 10 seconds while the force of the resulting adductor pollicis muscle contraction was recorded.

When the first twitch (T_1) of the TOF had recovered spontaneously to 25% of control, either an additional dose of doxacurium (5 mcg/kg) or neostigmine was administered. The dose of neostigmine (5, 10, 20, or 40 mcg/kg with 0.6-1.2 mg atropine) was determined by random allocation. After 10 min, an additional dose of neostigmine, for a total of 60 mcg/kg, was injected with 0.6-1.2 mg atropine. Recovery of adductor pollicis response was followed until either 90% of T_1 height or 70% of TOF ratio ($TOF_{0.7}$) was obtained. Isoflurane and nitrous oxide were then discontinued.

Neostigmine dose-response curves were obtained using the amplitude of T_1 and TOF measured 10 minutes after the antagonist was administered. The logit transformation of neostigmine-assisted recovery of T_1 and TOF ratio was plotted against the logarithm of the first dose of neostigmine. Assisted recovery was estimated by subtracting the anticipated spontaneous recovery from the total measured recovery. This was obtained by extrapolating the twitch height linearly from the last 10 minutes before the first dose of neostigmine was administered. The relationship between the TOF ratio and dose of neostigmine was plotted in the same way, except that no extrapolation was attempted because the TOF ratio was zero in all cases when the first dose of neostigmine was injected. Linear regressions were calculated from the log-logit plots. The doses required for 50%, 70%, and 80% assisted recovery (ED_{50}, ED_{70}, and ED_{80}, respectively) for T_1, as well as ED_{50} and ED_{70} for TOF recovery, were then calculated for both groups.

In patients given neostigmine before 25% spontaneous recovery of T_1, the reversal data were not included in the dose-response analysis.

Reported Results

The mean age of the young patients was 28 yr; for the elderly, it was 74 yr. Height and weight were comparable. Twice as many males as females were enrolled in the younger group.

In 6 young and 13 elderly patients neostigmine was administered before 25% recovery was reached because the duration of surgery was shorter than the time to 25% recovery. The dose-response relationships for neostigmine were calculated for the remaining patients (18 young, 11 elderly). The neostigmine ED_{50}, ED_{70},and ED_{80} for T_1 recovery, as well as the ED_{50} and ED_{70} for TOF ratio recovery are presented in Table 44 below. The ED_{50} and ED_{70} values for the TOF ratio are equivalent to $TOF_{0.5}$ and $TOF_{0.7}$, respectively.

The investigators note that the efficacy of neostigmine was similar in both age groups. They also report that for five elderly and eight young patients, the TOF ratio did not recover to 0.7 within 10 minutes after the second dose, i.e., after a total dose of 60 mcg/kg was administered. Among these, eight patients received the first dose of neostigmine before T_1 recovered to 25%, but five (one elderly, four young) received neostigmine at 25% recovery.

Table 44. Dose of neostigmine (mcg/kg) [mean (SEM)] required to achieve various stages of recovery based on the calculated dose-response relationship (from Table 4 on p. 848 of the article)

		Younger Adults (n=18)	Elderly Adults (n=11)	Difference
T_1 Recovery	**ED_{50}**	13 (3)	11 (2)	NS*
	ED_{70}	28 (7)	19 (4)	NS
	ED_{80}	46 (12)	28 (6)	NS
TOF Recovery	**ED_{50} ($TOF_{0.5}$)**	22 (3)	20 (3)	NS
	ED_{70} ($TOF_{0.7}$)	54 (8)	42 (6)	NS

*NS – not significant

Discussion

The study indicates that neostigmine dosing requirements for younger and older patients are similar, based on recovery of T_1 and TOF; although the older subjects appeared to require lower doses of neostigmine to achieve the same response. The investigators noted this finding and indicated that the results were considered potentially biased as fewer elderly patients could be included in the analysis due to the prolonged blockade, compared to surgical duration, which eliminated 13 elderly subjects versus 6

younger subjects. This suggests that the elderly subjects for whom data were available were those who had the fastest rate of spontaneous recovery and who would possibly fare well with lower doses of neostigmine.

Lederer et al. (2010)

Lederer W, Reiner T, Khuenl-Brady KS. Neostigmine injected 5 minutes after low-dose rocuronium accelerates the recovery of neuromuscular function. J Clin Anesth 2010; 22: 420-4.

Methods

Sixty patients undergoing surgical intervention in general anesthesia were enrolled in the study. All subjects were age 18 to 65 years, ASA 1 or 2, with a body mass index (BMI) of between 18 and 28 kg/m^2, and scheduled for elective surgery under general anesthesia with tracheal intubation. Excluded from the study were patients with neuromuscular diseases, known allergy to muscle relaxant, taking medications that interfere with muscle relaxants, or a history of renal or liver impairment.

Subjects were premedicated with either oral midazolam or intramuscular piritramide combined with atropine 30 to 60 minutes before being brought to the operating room. Anesthesia was induced by fentanyl and propofol and was maintained with a propofol infusion and 60% to 70% nitrous oxide in oxygen. Additional doses of fentanyl were given if indicated. Normothermia and normocarbia were maintained throughout the operation.

Patients were randomly assigned to one of three equally sized treatment groups. In Group 1 (n = 20), reversal of rocuronium was achieved with neostigmine 30 mcg/kg and glycopyrrolate 7 mcg/kg; in Group 2 (n = 20), reversal was achieved with neostigmine 50 mcg/kg and glycopyrrolate 10 mcg/kg IV. In Group 3 (n = 20), the control group, the recovery from rocuronium was spontaneous.

For neuromuscular monitoring, an electromyographic (EMG) device was used to obtain the evoked compound EMG of the adductor pollicis muscle. Neuromuscular blockade was assessed by the response to a train-of-four (TOF) stimulation of the ulnar nerve at the wrist. Calibration of the device was performed after induction of anesthesia but prior to administration of the muscle relaxant. For each subject, onset time for maximal twitch depression of T1 (first twitch of TOF), clinical duration until 25% recovery of T1, recovery index (time for T1 to return from 25% to 75%), and time from injection of rocuronium to TOF-ratio of 0.8 and 0.9 were determined.

After induction of anesthesia and calibration of the EMG device, including baseline measurements, 0.4 mg/kg rocuronium was administered over 5 seconds. Neostigmine was administered 5 minutes after the rocuronium to the subjects in Groups 1 and 2, while subjects in the third group recovered spontaneously. Neuromuscular response was recorded until recovery to a TOF ratio of 0.9 occurred.

The Shapiro-Wilk test was used for screening of normal distribution. Mean values were compared using either analysis of variance (ANOVA) with Bonferroni correction at the 5% significance level or Kruskal-Wallis test in the three groups. Differences between two groups were calculated using the Least Significant Difference Method and the Mann-Whitney-U test. Results were deemed significant at a P-value > 0.05.

Reported Results

The demographics for the 3 treatment groups, i.e., age, gender, and BMI were similar.

Onset of muscle relaxation, block maximum, block at 5 minutes, and TOF at 5 minutes after administration of rocuronium did not differ between any of the treatment groups. The recovery times for each of the parameters measured differed significantly for both of the neostigmine groups compared to the control group. The recovery times for the two neostigmine groups did not differ significantly with the exception of the Recovery Index for T1. The results for the recovery period are summarized in Table 45 below.

Table 45. Summary of recovery times [mean (SD)] for each treatment group (from Table 3 on p. 423 of the article)

Recovery Parameter	Group 1 (Neostigmine 30 mcg/kg)	Group 2 (Neostigmine 50 mcg/kg)	Group 3 (Spontaneous Recovery)
25% T1 recovery (min)	9.3 (2.3)	7.7 (1.6)	15.5 (6.5)
Recovery Index T1 (25%-75%)*	7.1 (2.4)	5.7 (4.0)	13.3 (8.3)
TOF 80% recovery (min)	20.2 (5.0)	17.8 (4.8)	36.2 (8.5)
TOF 90% recovery (min)	22.6 (5.9)	19.4 (5.1)	39.0 (8.7)

*The values for each of these parameters are as listed in the article. It is not clear how, barring a typographical error, the values for Groups 1 and 2 were determined to be different at a level of p = 0.014.

Discussion

The study demonstrated that neostigmine in a dose as low as 30 mcg/kg substantially reduces the time to recover from a rocuronium-induced neuromuscular block. It also demonstrated that there was no substantial, or significant, difference between the 30 and 50 mcg/kg neostigmine doses for TOF recovery to 80 and 90%, the most clinically relevant of the recovery parameters.

Lessard et al. (1997)

Lessard MR, Trepanier CA, Rouillard JF. Neostigmine requirements for reversal of neuromuscular blockade following an infusion of mivacurium. Can J Anaesth 1997; 44: 836-42.

This study was designed to assess the efficacy of neostigmine versus placebo for antagonizing mivacurium-induced neuromuscular blockade and to determine the optimal dose of neostigmine for this use.

Methods
A total of 100 patients aged between 18 and 60 years old, who were ASA physical status 1 or 2, and scheduled for an elective surgical procedure of 30-120 min duration under general anesthesia were enrolled in the study. Patients with any neurological, neuromuscular, renal or hepatic disease, intake of any medication known to interfere with neuromuscular function, history of allergy to one of the study medications, extremes of body weight (body mass index <20 kg·m-2, or >30 kg·m-2), and pregnancy were excluded from participation.

Anesthesia was induced with alfentanil and propofol. The lungs were manually ventilated by mask with 0 2 100% while the neuromuscular monitor, an electromyographic device applied over the ulnar nerve that provided a TOF stimulation every 20 seconds, was calibrated. After a stable baseline response was obtained, a bolus of 0.2 mg/kg mivacurium was administered. The trachea was intubated when maximal relaxation was reached. When T_1 had recovered to 5%, an infusion of mivacurium was started at 6 mcg/kg/min and adjusted at 5-minute intervals to maintain 90 to 95% depression of the first twitch of the train-of-four (TOF) for the duration of the surgery. Anesthesia was maintained with incremental doses of alfentanil, an infusion of propofol and a mixture of N20/02 (70%/30%). No other inhalational agent was used at any time during anesthesia.

Patients were randomized into four groups and received one of the following treatments in a blinded fashion:

Group 1: (control) normal saline
Group 2: neostigmine 10 mcg/kg and glycopyrrolate 2.5 mcg/kg
Group 3: neostigmine 20 mcg/kg and glycopyrrolate 5 mcg/kg
Group 4: neostigmine 40 mcg/kg and glycopyrrolate 10 mcg/kg

At the end of surgery, the infusion of mivacurium was stopped and the study medication was administered. A stable level of anesthesia was maintained until adequate recovery from neuromuscular blockade, i.e., the TOF ratio > 0.70. Nitrous oxide and propofol were then discontinued and the trachea was extubated when the patient was awake and able to sustain a five second head lift. If neuromuscular function had not

adequately recovered 20 minutes after the administration of the study medication, neostigmine 40 mcg/kg and glycopyrrolate 10 mcg/kg were given as a rescue reversal medication.

Following tracheal extubation, patients were transferred to the recovery room for standard care and monitoring for at least 60 minutes. The period beginning with discontinuation of the mivacurium infusion and ending with adequate recovery of neuromuscular function defined the Reversal Period.

Neuromuscular blockade was measured using an integrated evoked electromyogram. Responses to supramaximal TOF stimuli, wer measured every 20 seconds. Specifically, the stimuli were applied at the ulnar nerve above the wrist and the evoked EMG responses of the adductor pollicis were recorded. The monitor was calibrated after induction of anesthesia and prior to the administration of mivacurium. Values of the first twitch in the TOF (T_1) were normalized using the value of T_1 prior to administration of mivacurium (T_C) and reported as a percentage (i.e., T_1/T_C x 100) were recorded every 20 sec during the induction phase, every five minutes during the surgical procedure, and again every 20 sec during the reversal period. Also recorded at the same time points were the values of the TOF ratio. Adequate recovery of neuromuscular function was defined as a TOF ratio > 0.70. Since T_1 rarely recovered to 100% of control even when the TOF ratio was > 0.70, the T1 values recorded during the reversal period were recalculated as a percentage of the final T_1 height when TOF ratio had recovered > 0.70. This value was named T_1 corrected (T_1c), and was used in all subsequent analyses. During the reversal period, non-invasive blood pressure and heart rate were measured and recorded every minute. In the recovery room, frequency of postoperative nausea and vomiting (PONV) was recorded during the first 60 minutes after surgery by the attending nurse who was treatment blinded.

Continuous parametric variables were analyzed using ANOVA or repeated measures ANOVA, and the Tukey-Kramer multiple comparisons test when appropriate. Non parametric variables were compared with the Chi-square test with Bonferroni correction for multiple comparisons. A probability level less than 0.05 was considered significant.

Reported Results

Six of the 100 patients were excluded from the analysis due technical failure of the neuromuscular monitor, shortened duration of the surgical procedure preventing the establishment of the mivacurium infusion, prolonged neuromuscular blockade (> 45 minutes) following the bolus dose of mivacurium, and excessive recovery of T_1 at the end of mivacurium infusion (T_1 > 15%).

The investigators reported no difference among groups for age, weight, sex, type of surgical procedure, duration of anesthesia, and the total doses of alfentanil and propofol received. The dose and the duration of mivacurium infusion and the recovery of the first

twitch at the end of infusion (T_1c end of infusion) were not different among the four groups.

The recovery parameters for neuromuscular function are summarized in Table 46 below. Recovery of T_1c and of T_1c 25-75% was reduced in the three neostigmine groups compared with placebo. There was no difference in the recovery of TOF ratio between the placebo and the 10 mcg/kg neostigmine groups, as shown in the figure below; however, the recovery of the TOF ratio was shortened both in the 20 and 40 mcg/kg neostigmine groups compared with these two groups. Compared with control, the time to recovery of TOF ratio > 0.70 was reduced by 5.6 minutes in both the 20 and the 40 mcg/kg neostigmine groups.

Lastly, the investigators noted a slight but significant decrease in heart rate observed at 10 and 15 min in all groups; there was no difference observed between groups. Similarly, a decrease in systolic blood pressure was observed over the 10-minute period after administration of the reversal agent but there were no differences among four groups. Lastly, postoperative nausea and vomiting occurred infrequently in the recovery room, with no differences among the four groups (2,3,1 and 1 patients in the control, and the 10, 20, and 40 mcg/kg neostigmine groups respectively).

Table 46. Summary of findings for neuromuscular function recovery [mean (SD) or ration (%)] (Table 2 on p. 839 of the article)

Parameter	Control	Neostigmine	Neostigmine	Neostigmine
Number of patients	24	25	22	23
Dose of mivacurium (mg)				
- Infusion	24.9 ± 16	28.5 ± 24	40.4 ± 33	25.3 ± 17
- Total dose (initial bolus and infusion)	40.0 ± 18	43.7 ± 25	56.7 ± 34	39.9 ± 19
Duration of infusion (min)	49.6 ± 18	48.8 ± 20	65.4 ± 36	53.6 ± 19
T_1 maximal recovery (% T_1 control)	88.6 ± 15	81.5 ± 14	86.3 ± 17	79.3 ± 16
T_1c end of infusion (%)	5.1 ± 3	7.6 ± 5	6.7 ± 3	6.5 ± 4
Time to T_1c > 95% (min)	16.0 ± 4.5	12.4 ± 3.9†	10.3 ± 2.9‡	10.3 ± 3.6‡
Recovery index (25-75%) (min)	5.6 ± 1.8	4.3 ± 1.6*	3.6 ± 1.1‡	3.5 ± 1.5‡
Time to TOF ratio >70% (min)	17.0 ± 5.1	14.6 ± 4.2	11.4 ± 3.0‡§	11.4 ± 3.5‡§
Mean difference in time to TOF ratio >70%, each neostigmine group minus Control group (95% CI) (min)	--	2.4 (-0.6-5.5)	5.6 (2.5-8.8)	5.6 (2.5-8.7)

* $p < 0.05$ versus control
† $p < 0.01$ versus control

‡ p < 0.001 versus control
§ p < 0.05 versus neostigmine 10 mcg/kg group

Figure 6. Recovery profile of TOF ratios for the 4 treatments over 20 minutes following study drug administration (Figure 2 from p. 839 of the article)

Discussion

The study demonstrates that neostigmine hastens the recovery from mivacurium-induced neuromuscular blockade compared to placebo. It also demonstrates that a dose of at least 20 mcg/kg is required to do so, but that a dose of 40 mcg/kg does not offer any clear advantage over the 20 mcg/kg dose, at least in terms of T_1c and TOF recovery during the first 20 minutes following drug administration.

The study also provided evidence that neostigmine administered with glycopyrrolate, 2.5 mcg of glycopyrrolate /10 mg of neostigmine, is well tolerated in terms of hemodynamic responses and the potential for PONV.

McCarthy et al. (1992)

McCarthy GJ, Cooper R, Stanley JC, Mirakhur RK. Dose-response relationships for neostigmine antagonism of vecuronium-induced neuromuscular block in adults and the elderly. Br J Anaesth 1992;69:281-3.

The investigators examined the dose-response relationship for neostigmine in adult and elderly patients.

Methods
In all, 36 adult (ages 18-50 yr) and 36 elderly (ages > 70 yr) subjects were recruited from patients presenting for elective ophthalmic surgery under general anesthesia. All subjects were classified as ASA-PS 1 or 2, had no hepatic or renal impairment, were not obese, and were not taking medications that are known to interfere with NMBAs. The anesthetic was prescribed by the protocol and included vecuronium as the neuromuscular blocking agent. Neuromuscular blockade was monitored mechanomyographically, using the ulnar nerve and train-of-four (TOF) stimulation.

Six patients of each age group were randomly allocated to receive either neostigmine (at a dose of 5, 15, 25, 35 or 45 mcg/kg) or normal saline when T_1 from the TOF had reached 10% recovery. TOF was then assessed and recorded continuously over the next 10 min. The TOF values at 1-minute intervals from 5 minutes post-study drug administration onwards were used to determine the dose-response relationships.

Reported Results
The physical characteristics of the subjects and recovery time for T_1 are shown in Table 47 below. The difference in the time to spontaneous recovery of T_1 to 10% between the two treatment groups was significant ($P < 0.05$).

Table 47. Subject characteristics (Table 1 on p. 282 of article)

Parameter	Adults	Elderly
N	36	36
Age (years) [mean (range)]	32 (18-50)	78 (70-89)
Weight (kg) [mean (SD)]	64 (11)	62 (9)
Time to recovery of T_1 to 10% (min) [mean (SD)]	24 (5.5)	33 (7.8)

The dose-response curves for neostigmine reported by the authors are shown in the figure below.

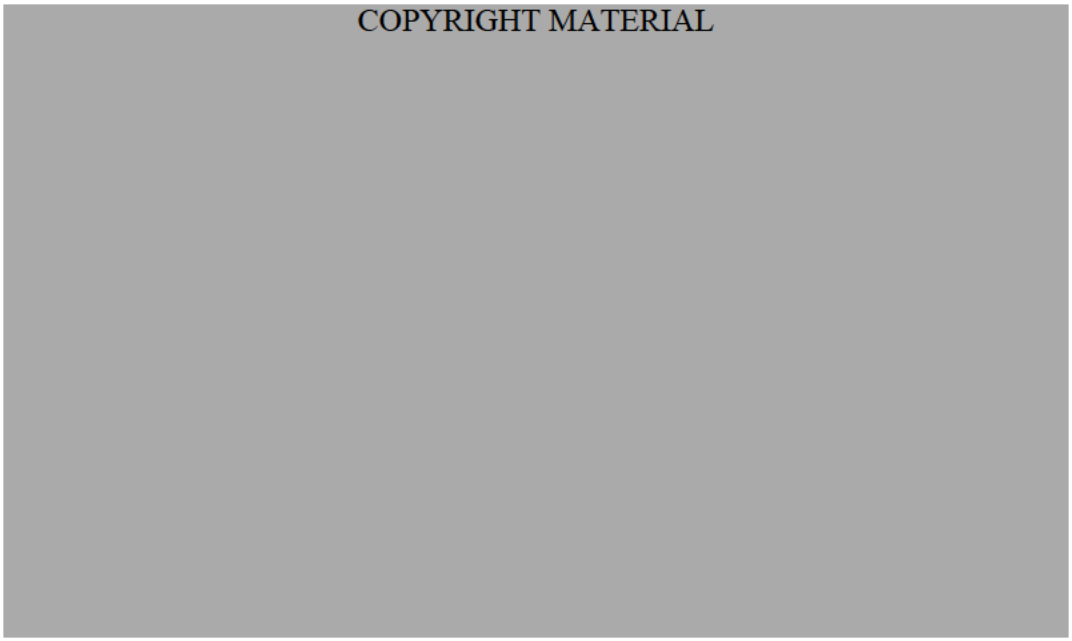


Figure 7. Dose-response curves for TOF ratios at 10 min after administration of neostigmine in adults and the elderly. Mean TOF ratios attained with each dose and the SD bars are shown. (Figure 1 on p. 282 of the article)

The authors note that while the responses were parallel for the two age groups, those for the elderly were significantly shifted to the right of the curves for the adults. They suggest this demonstrates either a lesser relative potency or an increased dosing requirement of neostigmine by the elderly for antagonizing the neuromuscular blocking effects of vecuronium.

Lastly, the TOF ratios for the two treatment groups, listed in Table 48 below, show that increasing doses of neostigmine were associated with faster recovery in both adult and elderly groups. The TOF ratios for the first 5 minutes were small in patients who received placebo indicating little spontaneous recovery. The TOF ratios were generally greater and the recovery apparently faster, according to the authors, with every dose of neostigmine in adults compared with the elderly. They further note that doses of neostigmine 25 mcg/kg or less did not achieve satisfactory antagonism by 10 min from this intensity of block, particularly in the elderly.

Table 48. TOF ratios following administration of study drug to young adult and elderly patients (combined data from Tables 1 and 2 on page 282 of the article)

	TOF Ratio Mean (SD)											
	Adults (18-50 years old)						Elderly (> 70 years old)					
Time (min)	Saline	Dose of neostigmine (mcg/kg)					Saline	Dose of neostigmine (mcg/kg)				
		5	15	25	35	45		5	15	25	35	45
1	NA	6 (10)	5 (8)	3 (7)	18 (15)	32 (14)	NA	NA	NA	8 (12)	5 (8)	10 (13)
2	NA	10 (9)	16 (11)	22 (14)	36 (9)	63 (16)	NA	3(6)	3 (7)	32 (11)	30 (8)	33 (20)
3	NA	16 (6)	24 (7)	31 (13)	46 (10)	72 (16)	NA	5 (8)	15 (13)	40 (10)	43 (9)	49 (15)
4	5 (11)	20 (7)	31 (7)	39 (16)	53 (12)	75 (15)	NA	10 (8)	19 (16)	48 (11)	54 (9)	58 (14)
5	8 (9)	24 (7)	36 (8)	46 (17)	59 (12)	79 (15)	NA	15 (4)	26 (10)	53 (12)	60 (6)	64 (12)
6	11 (9)	29 (8)	42 (9)	51 (18)	63 (13)	80 (12)	5 (9)	19 (5)	32 (10)	56 (14)	65 (6)	69 (12)
7	14 (8)	34 (9)	46 (8)	57 (20)	68 (13)	82 (12)	8 (10)	22(6)	36 (10)	60 (14)	68 (4)	71 (11)
8	18 (7)	38 (10)	50 (9)	61 (19)	70 (13)	81 (11)	12 (11)	24 (8)	43 (10)	62 (12)	70 (3)	74 (11)
9	20 (7)	43 (10)	55 (9)	65 (21)	73 (12)	84 (9)	14 (9)	27 (8)	46 (9)	65 (12)	72 (3)	76 (10)
10	23 (9)	47 (12)	58 (8)	68 (19)	75 (12)	85 (9)	16 (10)	29 (9)	49 (10)	68 (11)	73 (3)	77 (10)

* NA = no TOF ratio present

Discussion

This study demonstrated that neostigmine is efficacious at reversing neuromuscular blockade induced with vecuronium. The results indicate that efficacy of neostigmine in the elderly, i.e., patients over the age of 70 years, is less than that in younger adults, at least for the first 10 minutes following administration. The dose-response curves for the two age groups suggest that the elderly may require about twice the dose of neostigmine to achieve the same TOF ratio as younger adults at 10 minutes.

As the investigators terminated data collection at 10 minutes following study drug administration and neither group had a mean TOF ratio ≥ 90%, it is not possible to determine how much additional time was required for patients to be successfully extubated and able to adequately ventilate without support or airway support.

McCourt et al. (1999)

McCourt KC, Mirakhur RK, Lowry DW, Carroll MT and Sparr HJ: Spontaneous or neostigmine-induced recovery after maintenance of neuromuscular block with Org 9487 (rapacuronium) or rocuronium following an initial dose of Org 9487. Br J Anaesth 1999; 82: 755–6.

This was a report of a randomized, active-controlled, designed study. The aim of the study was to compare spontaneous and neostigmine-induced recovery from neuromuscular blockade following a bolus and three maintenance doses of Org 9487 (rapacuronium bromide: approved in 1999 under NDA 020984 and marketed as Raplon; later withdrawn for reasons of safety), a bolus dose and a 30-min infusion of Org 9487, or a bolus dose of Org 9487 followed by two maintenance doses of rocuronium. The rocuronium groups were included to examine the feasibility of using another rapidly acting drug for maintenance if the use of Org 9487 was found to be associated with prolonged recovery.

Neither the original protocol nor the raw data were provided for review.

Population
Ninety patients were enrolled in this study.

Inclusion Criteria
- Adults (age limits not specified)

Exclusion Criteria
- Pregnant patients
- Patients receiving concurrent treatment with drugs known to interfere with neuromuscular transmission
- Significant hepatic disorder (not defined)
- Significant renal disorder (not defined)

Methods
Patients were anesthetized with propofol 1.5-2.5 mg/kg and alfentanil 30 mcg/kg for induction, followed by maintenance infusions of propofol 6-10 mg/kg/h and alfentanil 30 mcg/kg/h in addition to a 66% nitrous oxide in oxygen breathing mixture. Standard monitoring was applied and the lungs were ventilated to maintain normocapnia. Skin temperature over the adductor pollicis muscle was maintained greater than 32°C by wrapping the arm in cotton wool. The ulnar nerve was stimulated in a train-of-four (TOF) mode every 12 seconds and the force of thumb adduction recorded to assess the level of neuromuscular function.

Patients received an initial dose of Org 9487 1.5 mg/kg followed by one of the following, based on randomization:

- Three maintenance doses of Org 9487 0.5 mg/kg every time T_1 recovered to 25% (groups 1 and 2);
- Infusion of Org 9487 for 30 min after recovery of T_1 to 5% after the bolus dose, at an initial rate of 4.0 mg/kg/h and adjusted to maintain neuromuscular block at 90 ± 10% (groups 3 and 4);
- Two maintenance doses of rocuronium 0.15 mg/kg at recovery of T_1 to 25% (groups 5 and 6).

Neuromuscular block in treatment groups 1, 3 and 5 was allowed to recover spontaneously while patients in groups 2, 4 and 6 received neostigmine 0.05 mg/kg with glycopyrrolate 0.01 mg/kg on recovery of T_1 to 25% after the final bolus dose or cessation of the infusion of neuromuscular blocking agent. Times to various recovery end-points (i.e., TOF of 0.7 and 0.8, and T_1 recovery to 75%) relative to T_1 recovery of 25% were then recorded.

Between-group comparisons were made using analysis of variance followed by pairwise tests. Page's test for ordered alternatives and the Wilcoxon signed rank test were used to analyze the duration of action of maintenance doses of the blockers within each group. The Hochberg – Bonferroni procedure was used to adjust for multiple testing as appropriate. A $p < 0.05$ was taken to represent a significant difference.

Reported Results

Two subjects were excluded from the analysis due to "major study violations." The article did not specify what the violations were or which treatment groups the subjects were assigned to.

The results of the study are summarized in Table 49 below. For each treatment group and for each method of assessing recovery, treatment with neostigmine significantly ($p < 0.05$) reduced recovery time compared to spontaneous recovery.

Table 49. Recovery times, spontaneous and neostigmine induced, from neuromuscular blockade with Org 9487 and rocuronium (based on Table 1 on p. 756 of the article)

Treatment and Recovery	Group	N	Recovery time (minutes) [Mean (SD)]		
			$T_{1\ (25\%)}$ - TOF 0.7	$T_{1\ (25\%)}$ - TOF 0.8	$T_{1\ (25\%)}$ - $T_{1\ (75\%)}$
Org 9487 boluses					
- spontaneous	1	11	58 (12)	72 (17)	25 (14)
- neostigmine	2	14	6 (2)	10 (5)	4 (2)
Org 9487 infusion					
- spontaneous	3	9	53 (18)	66 (27)	24 (11)
- neostigmine	4	10	4 (2)	9 (6)	3 (1)
Rocuronium boluses					
- spontaneous	5	14	29 (14)	37 (16)	14 (8)
- neostigmine	6	12	4 (1)	6 (3)	3 (1)

The article stated that “bronchospasm and/or increased airway pressure, and an erythematous rash” were observed four and three subjects, respectively, following the administration of their initial dose of Org 9487. It did not report any adverse events related to the administration of neostigmine.

Discussion

Although the intent of the study was to compare recovery times from neuromuscular blockade with a bolus dose of Org 9487 followed by either three repeated bolus doses, an infusion or two bolus doses of rocuronium, it demonstrated that neostigmine consistently and substantially reduced recovery time for each of the parameters evaluated. The study did not assess the ability of the subjects to maintain a patent airway and adequately ventilate without assistance following extubation. Indeed, the article did not indicate the length of time following reversal and the achievement of the various efficacy parameters that was required for extubation to occur. Nonetheless, based on the neostigmine-induced substantial reductions in time to reach each of the markers of neuromuscular function studied, it would be more than reasonable to assume that the clinical goal of successful extubation (i.e., the patient is able to maintain a patent airway and adequately ventilate on their own) would be similarly hastened by neostigmine.

In summary, the study demonstrated that neostigmine substantially reduced the time required for neuromuscular recovery, compared to spontaneous recovery times, following neuromuscular blockade that was induce with rapacuronium or rocuronium.

Meistelman et al. (1988)

Meistelman C, Debaene B, d'Hollander A, et al. Importance of the level of paralysis recovery for a rapid antagonism of vecuronium with neostigmine in children during halothane anesthesia. Anesthesiology 1988; 69: 97-9.

The authors studied the antagonism of vecuronium-induced neuromuscular blockade in pedatric patients by administering neostigmine at three predetermined levels of spontaneous recovery.

Methods

Twenty-four children undergoing genito-urinary surgery were enrolled in the study. The patients were ASA class 1 or 1, and aged 3-8 years old. No child had any disease known to alter neuromuscular function. No premedication was used; anesthesia was induced and maintained with halothane and nitrous oxide (60%). Once the patient was unconscious, the ulnar nerve was stimulated at the wrist, train-of-four (TOF) impulses every 20 seconds, and the electromyographic response of the adductor pollicis was monitored with surface electrodes. When the TOF response was stable, a bolus of 100 mcg/kg of vecuronium was administered intravenously. Patients were randomized to have neostigmine (30 mcg/kg) with atropine (10 mcg/kg) administered at one of three levels of spontaneous recovery for the first twitch of the TOF (T_1) compared to the pre-vecuronium control twitch height (T_C):

- Group A – 1% recovery (n=8)
- Group B - 10% recovery (n=8)
- Group C – 25% recovery (n=8)

Both T_1 and TOF ratio were observed every minute during a 12-min period after administration of the neostigmine. Recovery time was determined in the three groups by measuring the time from the beginning of spontaneous reappearance of T_1 to 1 % of control to the return of T_1 to 90% of control. The time elapsed from the beginning of spontaneous reappearance of T_1 to a TOF ratio of 0. 7 ($TOF_{0.7}$) was also determined.

Analysis of variance (ANOVA) was used to detect differences between the three treatment groups. If ANOVA showed significant differences between groups, the Student-Newman-Keuls test was performed. A value of $p < 0.05$ was considered to be significant.

Reported Results

The age and weight of the children did not differ significantly between the three groups. In all patients, T_1 increased rapidly within the first minutes following neostigmine injection. Ten minutes after neostigmine injection, T_1 reached values of 94 ± 6%, 99 ±

1%, and 100% of the initial control values for Group A, Group B, and Group C, respectively.

T_1 values of Groups B and C were always significantly higher than those of Group A up to and including the 10th minute following neostigmine administration; there were no significant differences in T_1 between groups B and C beyond the second minute.

At 10 minutes following neostigmine administration the TOF ratios were (mean ± SD):

- Group A: 0.68 ± 0.22
- Group B: 0.95 ± 0.03,
- Group C: 0.99 ± 0.01 in

At each period of observation, the TOF ratios of Groups B and C were significantly higher than the TOF ratio recorded in group A ($p < 0.01$), and beyond the fourth minute, the TOF ratio did not differ significantly between the two groups. The recovery of the TOF responses for the three groups is shown in the figure below.

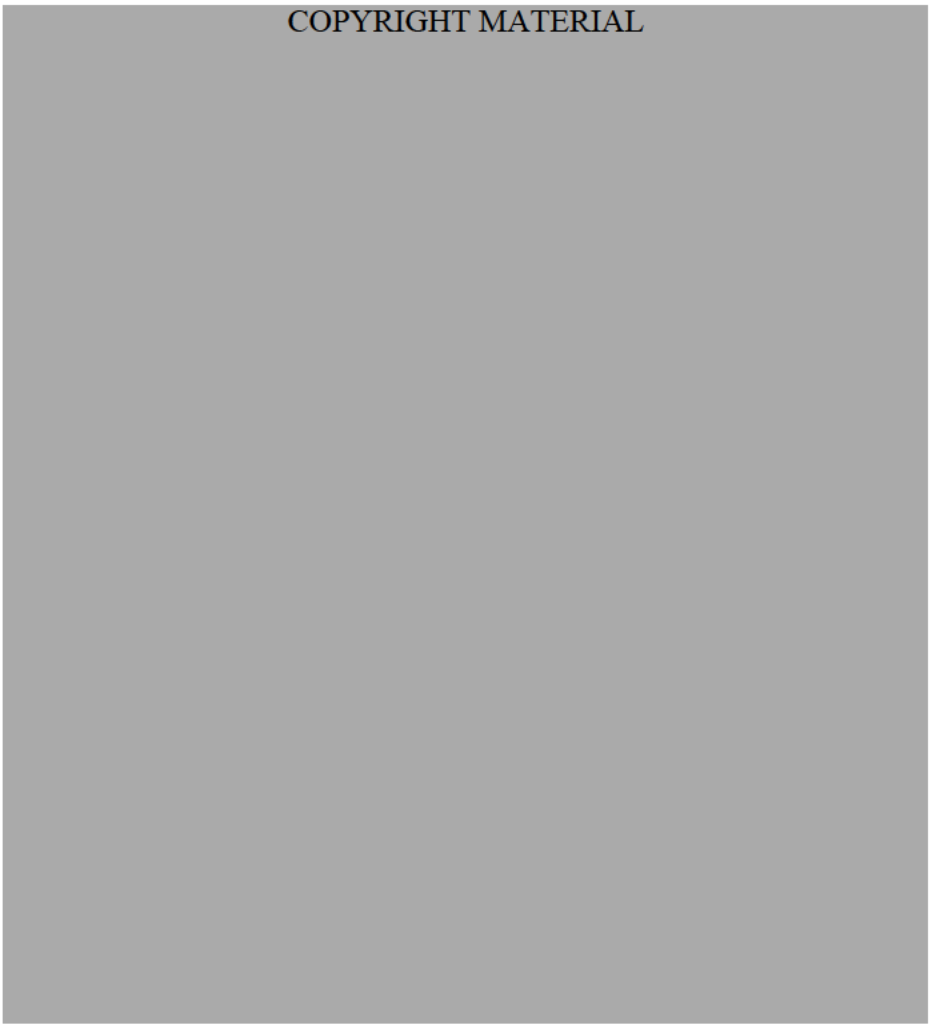


Figure 8. Recovery of the TOF ratio following reversal of vecuronium with neostigmine at three spontaneous recovery endpoints for T_1 of the TOF: 1%, 10% and 25% (Figure 2 on p. 98 of the article)

Recovery time from beginning of spontaneous recovery of T_1 (1 %) to the return of T_1 to 90% of control was similar whether neostigmine was injected at 1, 10, or 25% of control value. The time from 1% spontaneous recovery of T_1 to a TOF ratio of 0.7 was also similar in the three groups as indicated in Table 50 below.

Table 50. Recovery times of T_1 and TOF [mean ± SD] from T_1 of 1% (based on Table 1 on p. 98 of the article)

Group	Time to 90% recovery of T_1 (min)	Time to $TOF_{0.7}$ (min)
A (reversal at T_1 recovery to 1% of control)	8.3 ± 1.9	9.4 ± 3.2
B (reversal at T_1 recovery to 10% of control)	8.1 ± 2.0	9.0 ± 1.9
C (reversal at T_1 recovery to 25% of control)	9.0 ± 1.0	9.8 ± 1.1

Discussion

The study demonstrates that recovery time from vecuronium, in pediatric patients, is not significantly enhanced when 30 mcg/kg of neostigmine are given earlier (T_1 of 1%) compared to later (T_1 of 25%) in the course of spontaneous recovery. However, the data indicate that recovery following neostigmine differs significantly based on the extent to which spontaneous recovery has occurred. In the figure above, it is evident that recovery of TOF ratio to 90% ($TOF_{0.9}$) , a value considered more compatable with successful weaning from mechanical ventilation and extubation of the patient, is strongly influenced by the timing of neostigmine administration. For this study, the times from administration of neostigmine to $TOF_{0.9}$ were approximately 5 and 7.5 minutes when the drug was administered at T_1 recoveries of 25% and 10%, respectively. At 12 minutes following neostigmine administration, the time monitoring of TOF ceased, patients in Group A had reached mean TOF of only 80%, whereas the other two groups had reached levels of nearly 100% recovery.

While it is not known what effect, if any, higher doses of neostigmine would have had in this clinical setting, timing of administration has been demonstrated to play a key role in the extent to which neostigmine efficaciously reverses neuromuscular blockade induced by vecuronium.

Purdy et al. (1999)

Purdy R, Bevan DR, Donati F, Lichtor JL. Early reversal of rapacuronium with neostigmine. Anesthesiology 1999; 91: 51-7.

This study was conducted to assess the efficacy of different doses and timing of administration of neostigmine for the purpose of reversing different doses of rapacuronium.

Methods
A total of 117 adults were enrolled in this study. The subjects were aged 19-64 years, classified as ASA 1-3, free of significant neurologic, renal, or hepatic disease, and not receiving drugs that could interfere with normal neuromuscular function were enrolled in the study. They had to also have had a preoperative evaluation that indicated a difficult tracheal intubation was not anticipated, and they had to have been scheduled for elective surgical procedures expected to last at least 1 hour.

Anesthesia was induced with fentanyl and propofol. It was maintained with oxygen and 60%-70% nitrous oxide and an infusion of propofol as well as incremental doses of fentanyl as needed. Volatile anesthetic agents were not utilized.

Neuromuscular function was monitored by assessing isomeric twitch response of the adductor pollicis to TOF stimulation of the ulnar nerve. After induction, and once the twitch response had stabilized, paralysis was induced with either a 1.5 or 2.5 mg/kg dose of rapacuronium, selected randomly for each patient. Neuromuscular activity was allowed to recover to 90% T1 or a TOF ratio of 0.8 ($TOF_{0.8}$) before further muscle relaxant was administered. Paralysis was reversed at the end of surgery based on patient randomization to one of the following five groups:

1. spontaneous recovery
2. 50 mcg/kg of neostigmine with 10 mcg/kg glycopyrrolate administered at 2 minutes after the rapacuronium
3. 70 mcg/kg of neostigmine with 10 mcg/kg glycopyrrolate administered at 2 minutes after the rapacuronium
4. 50 mcg/kg of neostigmine with 10 mcg/kg glycopyrrolate administered at 5 minutes after the rapacuronium
5. 70 mcg/kg of neostigmine with 10 mcg/kg glycopyrrolate administered at 5 minutes after the rapacuronium

After the conclusion of surgery and transfer to the post anesthesia care unit, the patients were monitored for clinically significant adverse events and postoperative complications.

The recovery of neuromuscular function was characterized by the following:

- T1 recovery of 25%, 50%, 75%, or 90%;
- TOF recovery to 0.7 and 0.8; and
- Calculation of the recovery index defined as the time from 25% to 75% T1 recovery

Reported Results

The authors reported no significant differences in demographic variables (age, weight, height, ASA status, gender) among the 10 reversal groups. They noted, however, that substantially more female patients were recruited than males (104 females and 13 males).

Two subjects were given the wrong dose of rapacuronium, and three others received neostigmine either in the wrong dose or at the wrong time. However, partial data were available for all patients (at least 109 data points for each variable) and the primary analysis was based on the intent-to-treat population, which included all 117 subjects.

Neostigmine was administered during 100% block in 92 patients. Recovery from neuromuscular block was significantly more rapid after the 1.5 mg/kg than after 2.5 mg/kg rapacuronium dose in all subgroups except for:

- $T1_{0.75}$ and the recovery index for the 70 mcg/kg neostigmine dose administered at 5 min in 75% and recovery index
- Recovery index and $TOF_{0.8}$ for the control (spontaneous recovery) group.

Neostigmine accelerated recovery in patients compared with controls at each dose and time administration. There were no significant differences in any of the indices of recovery among groups that had received neostigmine at each dose of rapacuronium. The key findings are summarized in Table 51 below.

Table 51. Summary of TOF recovery (from Table 3 on p. 54 of the article)

	Neostigmine Dose (mcg/kg)	**$TOF_{0.7}$ [mean (SD)] (min.)**	**$TOF_{0.8}$ [mean (SD)] (min.)**
Rapacuronium 1.5 mg/kg	0	38 (10)	43 (12)
	50 @ 2 min	19 (6)	23 (7)
	70 @ 2 min	17 (5)	23 (8)
	50 @ 5 min	17 (3)	19 (4)
	70 @ 5 min	18 (7)	23 (8)
Rapacuronium 2.5 mg/kg	0	54 (13)	60 (11)
	50 @ 2 min	26(7)	31 (8)
	70 @ 2 min	32 (9)	38 (10)
	50 @ 5 min	32 (12)	38 (16)
	70 @ 5 min	28 (10)	35 (13)

No serious adverse events related to rapacuronium were observed. However, probable or possible drug-related effects were reported in 10 patients. In 9 patients, the presenting feature was bronchospasm. One patient with bronchospasm, which developed on arrival in the post-anesthetic care unit (PACU), had a transient rash on the forearm into which rapacuronium had been injected 1 hour earlier. In this case, bronchospasm and oxygen desaturation, pulse oximetry of 88-90%, were relieved by inhalation of salbutamol. In eight patients, transient bronchospasm, 1-6 minuets in duration, occurred during tracheal intubation but subsided spontaneously without treatment.

Discussion

This study demonstrated that neostigmine effectively reverses rapacuronium when administered as early as 2 minutes following administration of a maintenance dose of the paralytic agent. A neostigmine dose of 70 mcg/kg did not offer a substantial reduction in reversal time compared to the 50 mcg/kg dose. Both doses required 20 or more minutes to reverse the lower dose of rapacuronium and 30 or more minutes to reverse the higher dose of rapacuronium to a level of $TOF_{0.8.}$

Based on the author's description of the adverse events, none appeared related to neostigmine. For 8 of the patients, the adverse event occurred prior to administration of neostigmine; however, for the patient who presented with bronchospasm and injection-site rash on admission to the PACU, the possibility that the reactions were due to neostigmine cannot be ruled out.

Sacan et al. (2007)

Sacan O, White PF, Tufanogullari B, Klein: Sugammadex reversal of rocuronium-induced neuromuscular blockade: a comparison with neostigmine-glycopyrrolate and edrophonium-atropine. Anesth Analg 2007 Mar; 104(3): 569-74.

This was a report of a partially randomized, active-controlled, open label, parallel designed study. The study evaluated the return of neuromuscular function following administration of study drug using a train of four (TOF) electrical impulses to stimulate the ulnar nerve and comparing the extent of twitch that occurred with the fourth impulse (T_4) to that of the first (T_1) as a ratio (T_4/T_1). Other assessments of strength were also made as secondary endpoints.

Neither the original protocol nor the raw data were provided for review.

Population
Sixty patients were enrolled who met the following criteria:

Inclusion Criteria
- Adults undergoing elective surgical procedures under general anesthesia
- ASA-PS 1-3

Exclusion Criteria
- History of a difficult tracheal intubation
- Mallampati score of III or IV
- Allergic reactions to opioid analgesics, muscle relaxants, or other medications commonly used during general anesthesia
- Positive pregnancy test (or breast feeding)
- Family history of malignant hyperthermia

Methods
Subjects were given the option to receive sugammadex or not. Those who declined sugammadex were randomized to receive edrophonium or neostigmine. In all, 20 subjects were enrolled in each treatment arm.

The general anesthetic was standardized such that patients were premedicated with midazolam, 20 mcg/kg IV, and fentanyl, 0.5 mcg/kg IV, at 30-45 min and 5-10 minutes, respectively, before induction of anesthesia. Monitoring for induction and throughout the anesthetic included heart rate (HR), mean arterial blood pressure (MAP), and oxygen saturation. Anesthesia was induced with propofol, 2-2.5 mg/kg IV, and maintained with desflurane 4-6% end-tidal, in a 1:1::oxygen:air mixture, in combination

with a remifentanil infusion set at 0.1 mcg/kg/min IV. The end-tidal concentration of desflurane (4 ± 1%) was maintained during the assessment of the study drugs. Ventilation was controlled to maintain the end-tidal CO_2 values between 30 and 35 mm Hg. Nasopharyngeal temperatures were maintained between 35-37°C, and the skin surface temperature of the arm used for monitoring neuromuscular blockade was maintained >32°C, using forced air warming.

To assess neuromuscular function, the twitch response of the adductor pollicis muscle was monitored using a TOF-Watch®SX acceleromyograph, which was calibrated prior to administration of rocuronium. Each subject received a standardized dose of rocuronium, 0.6 mg/kg IV, to facilitate tracheal intubation. Additional bolus doses of rocuronium, 0.15 mg/kg, were administered upon reappearance of the second twitch in a train-of-four (TOF) stimulus to maintain the neuromuscular block during surgery. The study drugs for reversal of the neuromuscular blockade were administered at least 15 minutes after the last dose of rocuronium during steady-state anesthetic conditions and included one of the following intravenous treatments:

- neostigmine (70 mcg/kg) with glycopyrrolate (14 mcg/kg)
- edrophonium (1 mg/kg) with atropine (10 mcg/kg)
- sugammadex (4 mg/kg) alone

Maintenance anesthetic drugs and neuromuscular monitoring were continued for a period of 30 min after administering the reversal drugs. Noninvasive MAP and HR measurements were obtained immediately before the administration of the reversal drugs ("baseline") and subsequently at 2, 5, 10, and 30 minute intervals.

Before the discontinuation of the anesthetics and extubation of the trachea, all patients were required to manifest a sustained tetanic response to ulnar nerve stimulation using a standard neuromuscular stimulator. Extubation times after discontinuation of the maintenance anesthetic drugs were not recorded because the reversal drugs were given at variable times before the end of surgery.

Clinical signs of recovery were assessed at 1 minute intervals after extubation including level of consciousness (3 = awake and oriented, 2 = arousable with minimal stimulation, 1 = responsive only to tactile stimulation) and orientation, after regaining consciousness, by asking their name, the name of the hospital, and the day of the week. Upon regaining orientation, a clinical assessment of muscle strength was performed using the following:

- 5-second head lift test
- asking the patient if they were experiencing general muscle weakness (using a 10-point verbal rating scale from 0 = none to 9 = extremely impaired).

Adverse events (e.g., cardiac arrhythmias, inability to extubate the trachea upon regaining consciousness, dizziness, headaches, dry mouth, nausea and vomiting) were

recorded by a blinded observer in the operating room and upon discharge from the postanesthesia care unit.

Reported Results

A total of 64 subjects were consented for the study. Four subjects were eliminated due to the inability to obtain a stable baseline TOF tracing prior in rocuronium administration. The three treatment groups were similar with respect to their demographic characteristics and total dosages of rocuronium prior to administering the study medication (see Table 52 below).

Table 52. Subject demographics (Table 1 on p. 571 of the article)

Demographic Parameter	Treatment Group		
	Edrophonium/Atropine (n=20)	Neostigmine/Glycopyrrolate (n=20)	Sugammadex (n=20)
Age (yr)	63 ± 12	60 ± 14	60 ± 10
Weight (kg)	86 ± 17	92 ± 27	93 ± 33
Height (cm)	164 ± 10	165 ± 7	165 ± 7
Gender (male/female)	8/12	12/8	14/6
Anesthesia time (min)	134 ± 90	147 ± 92	143 ± 77
Total rocuronium (RCB) dose (mg)	73 ± 30	79 ± 26	73 22
Time to administering reversal after last dose of RCB (min)	40 ± 16	35 ± 18	41 ± 19
Intitial twitch height in TOF at time reversal agent was administered (%)	12 ± 8	12 ± 14	6 ± 7

Although the focus of the article was on the benefits of sugammadex over traditional reversal agents, the focus on the results described below, for the purposes of this review, is on the differences between neostigmine and the approved reversal agent, edrophonium.

The initial twitch heights (T_1) at the time of reversal were reported to be similar in all three treatment groups. The time to achieve TOF ratios of 0.7, 0.8 and 0.9 were shorter with sugammadex and edrophonium than with neostigmine (see Table 53 below). However, more subjects in the neostigmine group achieved TOF ratios of 0.7 and 0.9 within the half hour observation period than in the edrophonium group; both groups had

only 5 subjects achieve a TOF ration of 0.8 in the same period. Only one subject in the neostigmine group had a TOF ratio of 0.9 in ≤ 5 minutes after reversal administration compared with none and 100% in the edrophonium and sugammadex groups, respectively.

Table 53. Summary of results for TOF assessments (based on Table 2 on p. 571 and Table 4 on p. 573 of the article)

Assessment	Edrophonium (n=20)	Neostigmine (n=20)	Sugammadex (n=20)
Initial TOF ratio after reversal administered (%)[A]	30 (14)	16 (7)	73 (16)
Time (min.) to achieve TOF ratio[A]:			
0.7	3.4 (2.9)	10.4 (5.7)	1.2 (0.4)
0.8	4.1 (2.2)	16.5 (7.6)	1.3 (0.6)
0.9	5.5 (0.5)	17.4 (9.8)	1.8 (1.0)
No. of patients within 30 minutes who had a TOF ratio of:			
0.7	7	9	20
0.8	5	5	20
0.9	2	5	20
No. of patients achieved TOF ration of 0.9 at[A]:			
≤ 2 min.	0 (0%)	0 (0%)	15 (75%)
≤ 5 min.	0 (0%)	1 (5%)	20 (100%)
Initial muscle strength assessment:			
Time after extubation (min)[A]	1 ± 1	3 ± 2	1 ± 1
Performed 5-sec head lift	19 (95%)	18 (90%)	20 (100%)
Felt muscle weakness	2 (10%)	4 (20%)	1 (5%)
Median general muscle weakness score (range)[B]	0 (0-6)	0 (0-6)	0 (0-3)

[A] Values are expressed as means ± SD.
[B] Muscle weakness assessment: 0 = no impairment to 9 = severe impairment

Mean arterial blood pressures did not significantly differ between treatment groups at baseline or at 2, 5 or 10 minutes following administration of study drug. None of the values, for any of the treatment groups, exceeded 8% of baseline at these time points. Heart rate values increased more following treatment with neostigmine than with the other agents; however, at each of the time points, the mean increase was less than 10 bpm over baseline for the neostigmine treated subjects. Lastly, the incidence of dry mouth was lower with neostigmine than edrophonium (85% and 95%, respectively).

Discussion

Although the purpose of this study was to compare the efficacy and safety of sugammadex, to neostigmine and edrophonium, the data are useful for the purposes of

this NDA in that they allow comparisons between neostigmine and the approved product, edrophonium. However, in that regard, there are several shortcomings that limit the utility of such a comparison aside from the open-label, partially randomized study design. As stated by the authors:

> Because this study protocol was designed to evaluate the use of sugammadex *(versus* conventional anticholinergic drugs) for the reversal of moderately profound ("deep") neuromuscular blockade, these findings may not be reflective of the difference among these reversal drugs when the patient has recovered 2-4 twitches in a TOF at the end of surgery. Therefore, this study could be criticized for being designed to favor the investigational new drug. Future clinical studies are clearly needed comparing sugammadex to the anticholinesterase drugs when administered after recovery of 2-3 twitches in the TOF.

They go on to state that the "dosages of the anticholinesterase and anticholinergic drugs used in this study were the standard recommended doses; however, higher doses of the anticholinesterases may have been more appropriate, given the degree of residual blockade at the time of reversal." Thus, while the data suggest neostigmine has some efficacy in reversing neuromuscular blockade, they more strongly suggest that the neostigmine dose selected is not adequate for use following the return of a single twitch response to a TOF stimulus.

The authors note that the use of acceleromyography data represents an objective means of assessing return of neuromuscular function. More precisely, it is a surrogate marker for the return of function that is widely used in clinical practice to evaluate whether sufficient strength has been restored to extubate the patient's airway. The clinically relevant endpoints, which were not assessed in the study, are:

- ability to maintain a patent airway, without intervention, when extubated
- ability to adequately ventilate the lungs to maintain blood oxygen saturation and end tidal carbon dioxide levels at baseline levels following extubation

In summary, neostigmine was not demonstrated to be superior to edrophonium at reversing neuromuscular blockade following paralysis induced with rocuronium bromide, when a single twitch has returned following a TOF stimulus. Neostigmine appeared to require more time than edrophonium to achieve a TOF ratio ≥ 7; yet, more subjects treated with neostigmine were able to achieve those TOF ratios within a half-hour observation period. Another clinical marker for assessing adequate strength to extubate a patient, ability to sustain head lift from the horizontal position, favored edrophonium over neostigmine. The safety of the two combination study drugs, neostigmine/glycopyrrolate and edrophonium/atropine appeared to be similar.

Schaller et al. (2010)

Schaller SJ, Fink H, Kurt Ulm K, Blobner M: Sugammadex and Neostigmine Dose-finding Study for Reversal of Shallow Residual Neuromuscular Block. Anesthesiology 2010; 113:1054 – 1060

This single center, randomized, parallel-group, double-blinded study was conducted to determine the dose of neostigmine and sugammadex, which reverses a shallow residual neuromuscular block from a TOF ratio of 0.5 to a ratio of 0.9 or higher in an average of 2 min, with an upper time limit of 5 min for 95% of patients. As a secondary endpoint, the dose needed for a slower reversal, defined as the dose requiring an average time of 5 min for the TOF ratio to reach 0.9 with an upper time limit of 10 min for 95% of patients, was determined.

Population
A total of 99 subjects were enrolled who met the criteria listed below.

Inclusion Criteria
- Aged 18–65 yr.
- American Society of Anesthesiology physical status I to III
- Scheduled for elective surgery under general anesthesia with rocuronium for tracheal intubation

Exclusion Criteria
- Expected to have a difficult airway
- Known neuromuscular disease
- Significant hepatic or renal dysfunction
- Family history of malignant hyperthermia
- Known allergy to one of the drugs used in this protocol
- Intake of any medication that might interact with muscle relaxants
- Pregnant or breastfeeding
- Participation in another clinical study in the past 30 days

Methods
In all, 99 patients were enrolled and anesthetized with propofol and fentanyl for induction, and maintained with propofol, remifentanil, and rocuronium. Patients were artificially ventilated using a laryngeal mask airway to keep arterial oxygen saturation at 96% or higher and to maintain normocapnia. Body temperature was maintained at 35.0°C or higher. Following anesthesia induction, and prior to administration of the rocuronium, neuromuscular monitoring was performed by evoked electromyography of

the adductor pollicis muscle which was calibrated to find individual supramaximal stimulation.

When the surgical procedure no longer required neuromuscular blockade, spontaneous recovery from the neuromuscular block was allowed to a TOF ratio of 0.5. At this point, patients randomly received sugammadex (0.0625, 0.125, 0.25, 0.5, or 1.0 mg/kg), neostigmine (5, 8, 15, 25, or 40 mcg/kg) in a mixture with 1 mcg glycopyrrolate/5 mcg neostigmine, or saline. There were 9 subjects assigned to each dose in each treatment arm. Neuromuscular monitoring was continued until the end of the surgical procedure, and for at least 10 min after the TOF ratio reached 0.9. Any decrease in the TOF ratio below 0.8 was recorded as reoccurrence of neuromuscular block. Heart rate and blood pressure were recorded before the injection of the study medication and then 2, 5, 10, and 20 min afterward. The time between study drug injection, at TOF ratio of 0.5, and postoperative TOF ratio of 0.9 was measured.

The patients were extubated when they were awake following emergence from the anesthetic and monitored in the post-anesthesia care unit (PACU) for at least 60 minutes where oxygen saturation, respiration rate, heart rate, and blood pressure were routinely monitored. Signs of reoccurrence of muscle weakness were recorded, and at 15 minute intervals and immediately before discharge from the PACU, the level of consciousness (*i.e.*, awake and oriented, arousable with minimal stimulation, or responsive only to tactile stimulation) was assessed. Cooperative patients were asked to open their eyes for 5 seconds, perform a 5-second head lift test, a 5-second arm lift test and were asked to swallow a 20-ml bolus of water. Then a test for general muscle weakness was performed using the Medical Research Council Scale [0 = no movement, 1 = flicker is perceptible in the muscle, 2 = movement only if gravity eliminated, 3 = can move limb against gravity, 4 = can move against gravity and some resistance exerted by examiner, 5 = normal power. A blinded safety assessor performed these postoperative clinical assessments. Discharge from the PACU marked the end of a subject's involvement in the study.

The dose-response relationship for each treatment arm was analyzed with a biexponential model using the dose as the independent variable and the logarithm of the recovery time as the dependent variable. Effective doses were interpolated from regression models.

Reported Results

For the purposes of this NDA, only the results of the placebo and neostigmine treatment groups are relevant.

The authors noted that major protocol violations occurred in several subjects:

- Neostigmine was incompletely injected into one subjects as a result of a leaking venous cannula

- Electromyographic response was unstable in three neostigmine-treated subjects (one each in the 5, 8, and 40 mcg/kg dose groups

Because these violations might have affected primary and secondary endpoints, the authors omitted the respective patient data from the analyses, resulting in a per-protocol population of 51 patients for the neostigmine and placebo treatment groups.

The authors stated that the treatment groups did not differ significantly based on gender, age, weight, height, and American Society of Anesthesiology physical status (ASA-PS). Subjects were almost evenly split between males and females, the mean age was 42 years, the mean weight was 76 kg and most of the subjects were ASA-PS 1 or 2.

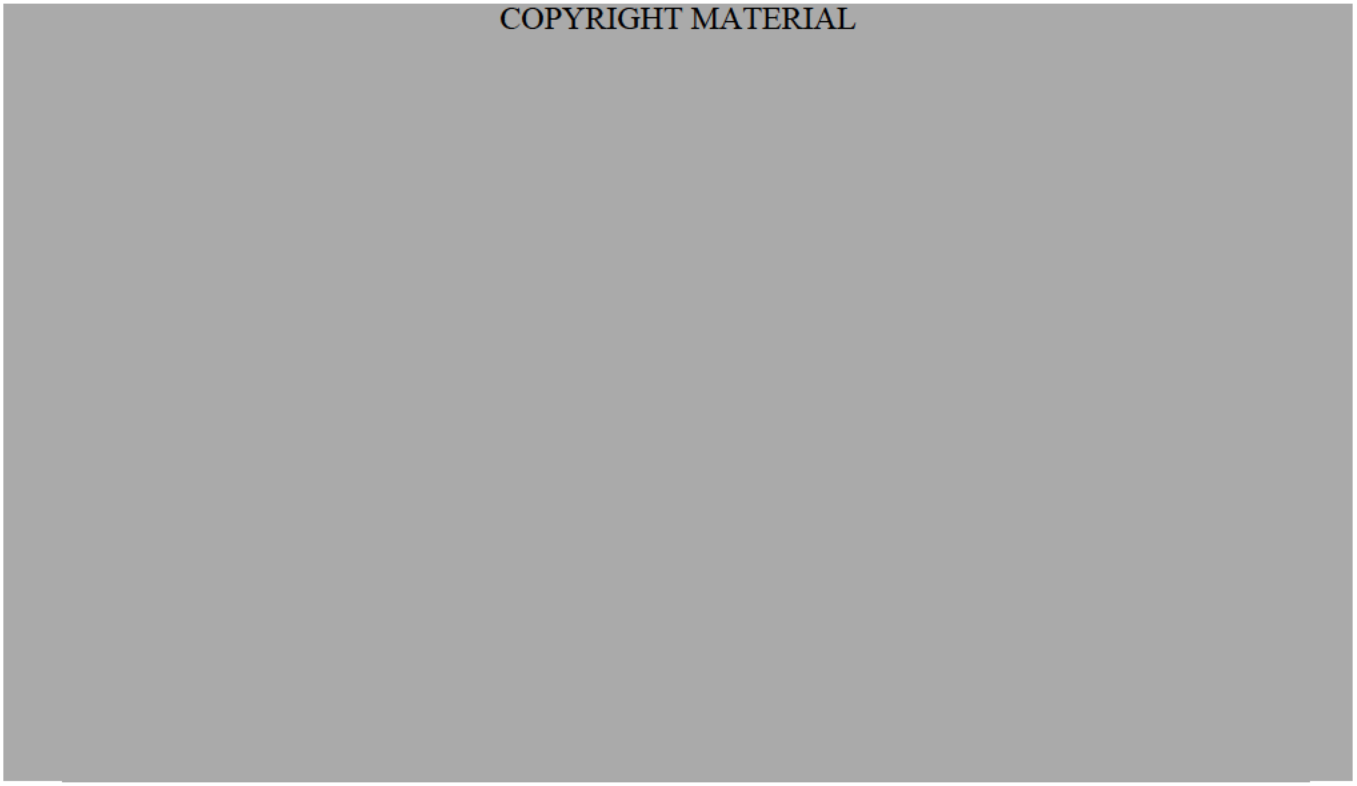
The median time to recover to a TOF ratio of at least 0.9 after injection of the study drugs decreased from 19 min for placebo to 2 min with 40 mcg/kg neostigmine. Table 54 below summarizes the findings for placebo and neostigmine treatments.

Table 54. TOF recovery for placebo and neostigmine (from Table 2 of the article).

Time to TOF Ratio (minutes)	**Placebo (n = 9)**	**Neostigmine Groups by Dose (N=51)**				
		5 mcg/kg (n = 8)	**8 mcg/kg (n = 8)**	**15 mcg/kg (n = 9)**	**25 mcg/kg (n = 9)**	**40 mcg/kg (n = 8)**
≥ 0.7						
Median	5.9	2.7	1.9	1.5	1.3	1.1
Range	3.5–9.8	1.8–3.5	1.5–2.3	1.2–2.5	1.0–2.3	0.7–1.5
≥ 0.8						
Median	10	4.9	2.8	2.3	1.8	1.4
Range	7.2–16	3.3–6.0	2.5–3.3	1.7–3.7	1.2–3.2	1.2–2
≥ 0.9						
Median	19	9.3	5.3	4.0	3.2	2.0
Range	12-33	5.8-15	3.5-8.7	2.8-6.0	1.7-6.2	1.7-4.2

Based on the bi-exponential model used, neostigmine dosing was calculated to be 50 mcg/kg for an average recovery time of 2 minutes; 34 mcg/kg for an upper limit of 5 min for 95% of patients (primary endpoint); 11 mcg/kg for an average recovery time of 5 min; and 10 mcg/kg for an upper limit of 10 min for 95% of patients (secondary endpoint).

The estimated dose-response relationship and the respective 95% CI for recovery from a TOF ratio 0.5 to at least 0.9 for the per-protocol population were plotted by the authors as shown in figure below.



Neostigmine Dose [µg/kg]

Figure 9. Estimate of mean dose-response, by dose, for the time between neostigmine administration to a TOF ratio of 0.9 (Figure 2 from the article)

Using best fit modeling of the dose-response relationship, the authors found that 34 mcg/kg of neostigmine accelerates the recovery from the TOF ratio from 0.5 to at least 0.9 in an average of 2 minutes and within 5 minutes for 95% of all treated patients. No patients showed signs of recurarization after any tested dose of the reversal agent.

The authors noted that clinical muscle function tests and evaluation of consciousness revealed no difference between groups at any time during the postoperative period in the post-anesthesia care unit (PACU). On arrival in the PACU, 13% of the 79 cooperative patients were not able to keep their eyes open for 5 seconds; 6% were not able to lift the head for 5 seconds; 4% were not able to lift the arm for 5 seconds; 13% were not able to swallow 20 ml of water without difficulties; and 46% had not reached normal muscle strength based on the Medical Research Council scale. After 60 minutes in the PACU, all patients were reported to be cooperative and not show any clinical sign of muscle weakness.

After administration of study medication, one or more adverse events (AE) were reported for 28 of the subjects who received neostigmine and 4 subjects who were treated with placebo (see Table 55 below). The majority of AEs were classified by the investigator as mild or moderate. The three most frequently observed AEs following neostigmine treatment were postoperative shivering, bradycardia (defined as a heart rate lower than 40 beats/min), and hypotension. Postoperative shivering was treated with 25-50 mg of meperidine; bradycardia treated with 0.2 mg glycopyrrolate; and hypotension treated with 0.5-2.0 ml of Akrinor (a vasopressor consisting of theophylline, ephedrine, caffeine, and norepinephrine). No dose-response relationship was observed by the authors who also commented that the incidence of bradycardia after neostigmine is a well-known reaction to anticholinergic agents, which appeared even though neostigmine was administered as a premix with glycopyrrolate. They also noted that the bradycardia could be controlled in every patient with an additional 0.2 mg dose of glycopyrrolate.

One patient developed acute lung failure 63 hours postoperatively. This AE was categorized as severe and possibly related to the study medication of 5 mcg/kg neostigmine. The patient was known to have a restrictive lung disorder (vital capacity of 1.9 liters or 35% of normal) following bleomycine chemotherapy.

Table 55. Summary of adverse events (AE) for neostigmine and placebo treatment arms (from table 4 of the article).

Adverse Event	**Neostigmine** [n = 51] **N (%)**	**Placebo** [n = 9] **N (%)**
Hypertension	1 (2)	0
Bradycardia	12 (27)	0
Hypoglycemia	0	1 (11)
Hypokalemia	1 (2)	1 (11)
Hypocalcemia	1 (2)	1 (11)
Hypotension	3 (7)	4 (44)
Desaturation < 90%	3 (7)	0
Paresthesia nervus ulnaris	0	1 (11)
Postoperative nausea and vomiting	0	2 (22)
Postoperative shivering	11 (25)	0
Tachycardia	2 (5)	0
Anesthetic complications (intraoperative cough/movement)	1 (2)	0
Acute lung failure (serious AE)	1 (2)	0
Number of subjects with at least 1 AE	28 (64)	4 (44)

Discussion

This study provides compelling evidence of the efficacy of neostigmine at reversing neuromuscular blockade induced by rocuronium. It indicates that doses of neostigmine

ranging from 5-40 mcg/kg will reverse the blockade to $TOF_{0.9}$ provided they are administered when TOF has spontaneously returned to 50%. A dose of 40 mcg/kg appears to reliably achieve this level of reversal within 5 minutes.

The study also demonstrated that neostigmine, used in this clinical setting is well tolerated with bradycardia, a known side effect of this class of drugs, and post-operative shivering being the adverse events that occurred at rates substantially higher than observed with placebo.

Jones et al. (1987)

Jones JE, Hunter JM, Utting JE. Use of neostigmine in the antagonism of residual neuromuscular blockade produced by vecuronium. Br J Anaesth 1987; 59: 1454-1458.

This study evaluated the efficacy of two different doses of neostigmine administered at two different points of spontaneous recovery in reversing vecuronium and compared the recovery to that without a reversal agent.

Methods
Fifty healthy patients presenting for general or gynecological surgery under general anesthesia with vecuronium used as the muscle relaxant were randomized to 5 treatment groups:

- Spontaneous recovery (n=10)
- Neostigmine 2.5 mg when the TOF ratio reached 0.1 (n=10)
- Neostigmine 2.5 mg when the TOF ratio reached 0.5 (n=10)
- Neostigmine 5 mg (two doses of 2.5 mg given 2 minutes apart) when the TOF ratio reached 0.1 (n=10)
- Neostigmine 5 mg (two doses of 2.5 mg given 2 minutes apart) when the TOF ratio reached 0.5 (n=10)

The anesthetic consisted of premedication with promethazine 50 mg PO the night before surgery and, optionally, diazepam 10 mg PO 3 hours before surgery or morphine 10 mg combined with cyclizine 50 mg IM one hour before surgery. Anesthesia was induced with thiopentone, fentanyl and either droperidol or midazolam and was maintained with 70% nitrous oxide, 30% oxygen and a halogenated inhaled anesthetic agent.

A PNS was placed over the ulnar nerve at the wrist and single pulse stimuli were applied at increasing voltages until the maximum height of the resultant twitch was achieved. The voltage was than increased by 25% for application of supramaximal stimulation with TOF stimuli, which were then applied at 12-second intervals. After the baseline responses were recorded, vecuronium 0.1 mg/kg IV was administered and the trachea was intubated.

Recovery from vecuronium was monitored using both the twitch response to the first stimulus compared to the baseline value (A′/A) in the TOF stimuli and the ratio of the last and first twitch responses to the TOF stimuli (D′/A), which were applied at 1-minute intervals. For patients randomized to receive neostigmine, additional vecuronium (0.04 mg/kg up to a maximum of 4 dose) could be administered when A′/A = 0.1. No additional vecuronium was administered to patients randomized to recover spontaneously.

TOF testing was increased in frequency to every 12 seconds when the administration of neostigmine was imminent, or when A'/A = 0.1 for patients who were to recover spontaneously.

The measurement of recovery times began when A'/A were 0.1 and 0.5 for the group that recovered spontaneously, and when the neostigmine was first administered for the active treatment groups. For the patients treated with neostigmine, it was not to be administered until A'/A was either 0.1 or 0.5. In the group in which recovery was spontaneous, monitoring was continued until D'/A' had reached 70%. Atropine 1.2 mg IV was administered before the neostigmine was administered; if a second dose of neostigmine was administered, a second dose of atropine, 0.6 mg, was administered before the neostigmine.

In patients who received neostigmine, monitoring was continued for at least 10 minutes after the agent had been given in the case of patients with a block of 50% and, in those with *90%* block, at least 20 min or until 70% recovery of the TOF ratio (D'/A') had been achieved and maintained for 10 minutes.

When the measurements were completed, PNS monitoring was discontinued and the patient was allowed to breathe 100% oxygen spontaneously through the tracheal tube until it was considered safe to extubate the trachea. The study did not define how that was to be determined.

Statistical analysis of the differences between the means was carried out using Tukey's method.

Reported Results

There was no clinically relevant difference between treatment groups in the subjects' mean age or weight or in the gender distribution. The recovery times are summarized in Table 56 below.

Table 56. Summary of Jones et al. results (based on Table 2 on page 1456 of article).

Initial Block A'/A at Start of Recovery	Ratio monitored	Time to 70% Recovery of Ratio (min.) [mean (SD)]		
		Spontaneous	Neostigmine 2.5 mg	Neostigmine 5 mg
0.5	A'/A	4.9 (2.7)	1.2 (0.7)	1.1 (0.7)
	D'/A	6.9 (3.2)	2.1 (1.0)	1.5 (0.5)
0.1	A'/A	15.5 (6.8)	3.9 (2.2)	3.4 (1.3)
	D'/A	24.2 (11.4)	9.2 (5.3)	5.6 (3.7)

The results indicate that neostigmine significantly reduces recovery time compared to spontaneous recovery ($p < 0.01$) when administered at the two points and two doses

evaluated in this study. The differences in recovery times between the two doses of neostigmine were not significant for either timepoint of administration.

Discussion

In this study, the A'/A ratio is equivalent to a simple twitch response. The data indicate that neostigmine is efficacious at reversing vecuronium-induced neuromuscular blockade when it is administered as early as $T_{0.1}$ at doses as low as 2.5 mg. As the mean weights for the patients who were treated with 2.5 mg of neostigmine at $T_{0.1}$ was 64.4 kg, it would suggest that a 0.04 mg/kg dose of neostigmine produces $TOF_{0.7}$ after 9 minutes on average. Similarly, the data indicate that 5 mg of neostigmine given at $T_{0.1}$, or a mean dose of 0.07 mg/kg, produces $TOF_{0.7}$ after 6 minutes on average.

While this study demonstrates the efficacy of neostigmine as a reversal agent for vecuronium, it does not provide guidance as to the adequacy of reversal in terms of discontinuation of mechanical ventilation or the ability for the patient to maintain a patent airway.

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

9.3 Advisory Committee Meeting

Input from the Anesthetic and Analgesic Drug Products Advisory Committee was not needed to render a regulatory decision for this application; therefore, an Advisory Committee meeting was not convened.

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/s/

ARTHUR F SIMONE
04/26/2013

CHRISTOPHER D BREDER
04/26/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 204078 **Applicant:** Éclat Pharmaceuticals, LLC **Stamp Date:** July 31, 2012

Drug Name: Neostigmine Methylsulfate Injection **NDA Type:** 3

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	**X**			Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	**X**			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	**X**			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	**X**			
5.	Are all documents submitted in English or are English translations provided when necessary?	**X**			
6.	Is the clinical section legible so that substantive review can begin?	**X**			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	**X**			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	**X**			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	**X**			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	**X**			
11.	Has the applicant submitted a benefit-risk analysis for the product?	**X**			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			**X**	505(b)(2) – the NDA is based solely on published nonclinical and clinical literature.
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? **Location in submission**: Section 4.3 of the ISE	**X**			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	**X**			The Applicant identified five studies reported in the literature that were prospective, randomized, controlled studies

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					measuring the time to $TOF_{0.9}$ following neostigmine administration (an endpoint specified by the Division on 6/30/11)
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	**X**			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	**X**			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		**X**		Most of the studies were conducted in the U.S.; the remainder were conducted in Europe where the population and practice of medicine are similar to those in the U.S.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	**X**			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	**X**			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	**X**			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			**X**	This product is indicated for acute use only.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	**X**			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			**X**	Without case report forms, only terms used in the literature/AERS database were

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					available for the safety analyses.
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	**X**			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			**X**	Without case report forms, only published information could be summarized.
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			**X**	No special clinical studies were requested for this product.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			**X**	This is not an OTC product.
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	**X**			Pediatric assessments have been submitted.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			**X**	This product has no history of abuse.
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		**X**		Most of the studies were conducted in the U.S.; the remainder were conducted in Europe where the population and practice of medicine are similar to those in the U.S.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			**X**	The NDA is literature based; the Applicant tried to secure original protocols and data without any success.
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			**X**	See above.
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			**X**	See above.
34.	Are all datasets to support the critical safety analyses available and complete?			**X**	See above.
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			**X**	See above.
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			**X**	The NDA is literature based; the Applicant tried to secure original protocols and data without any success.
37.	Has the applicant submitted all additional Case Report			**X**	None were requested.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?				
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?			**X**	The NDA is exclusively literature based; the Applicant sponsored none of the published studies.
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			**X**	The NDA is exclusively literature based.

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

(Not applicable)

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None have been identified.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ARTHUR F SIMONE
09/08/2012

CHRISTOPHER D BREDER
09/09/2012