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APPLICATION NUMBER:

203629Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA – Complete Response
Application Number	203629
Supporting Document Nos.	021, 022, and 023
Submit Date(s)	July 11, 2014; August 29, 2014; and October 29, 2014
PDUFA Goal Date	January 11, 2015
Division / Office	DAAAP / ODE 2
Reviewer Name(s)	Arthur Simone, MD, PhD
Review Completion Date	December 16, 2014
Established Name	Neostigmine Methylsulfate Injection, USP
(Proposed) Trade Name	(none Proposed)
Therapeutic Class	Cholinesterase Inhibitor
Applicant	Fresenius Kabi USA, LLC (original applicant was APP Pharmaceuticals, LLC)
Formulation(s)	Injectable solution
Dosing Regimen	(b) (4) -70 mcg/kg intravenously
Indication(s)	Reversal of neuromuscular blockade
Intended Population(s)	Post-surgical 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 now that the deficiency identified in the first cycle has been resolved; specifically, the Office of Compliance has completed its reinspection of the manufacturing facilities and determined the sites to be suitable to produce and package the product within specifications and cGMP standards.

1.2 Risk Benefit Assessment

As indicated in the initial clinical review of this application, 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 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 with 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; they tend to occur soon after the administration of neostigmine 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 both in the original submission and the update in the current submission, the review and analysis by 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 submitted provided 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

This NDA was originally submitted on December 28, 2011. The submission relied solely on published literature for providing evidence of safety, efficacy and appropriate dosing requirements. The original primary clinical review, which was conducted by this reviewer and archived in the Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) on September 18, 2012, should be referred to for the evaluation of safety and efficacy performed during that review cycle. At that time, an approval action was recommended based on the adequacy of the literature submitted to identify appropriate dosing requirements for the desired indication, i.e., reversal of nondepolarizing blocking agents, and to support a finding that the benefits of those doses outweighed the risks. However, one of the manufacturing facilities for the application had failed inspection, which precluded the NDA from being approved at that time.

On January 29, 2013, the Division issued a Complete Response letter citing the following reason for not approving the application:

During a recent inspection of the Grand Island, New York, manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

The letter also advised the Applicant that when they respond to the deficiency, they needed to include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level. The update needed to contain the following:

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

The safety update provided in this submission is reviewed in Section 4 below.

Lastly, the Applicant was also informed in the Complete Response Letter that, based on Section 505(o)(3) of the FDCA, they were required, if the NDA is approved, to conduct the several postmarketing studies and assays that are discussed below in the Preclinical Pharmacology Toxicology Section (3.3).

3. Significant Issues Related to Other Review Disciplines

3.1 Chemistry Manufacturing and Controls

The Chemistry Manufacturing and Controls review team has indicated that the reinspection of the Grand Island, New York, manufacturing facility by the has taken place and all of the deficiencies previously identified have been resolved and no new deficiencies have been identified.

There were no additional CMC issues that needed to be addressed in this submission, and the team reports that there are currently no issues that would preclude the application's approval in this cycle.

3.2 Clinical Microbiology

There were no clinical microbiology issues that needed to be addressed in this submission, and the review team reports that there are no issues that would preclude the application's approval in this cycle.

3.3 Preclinical Pharmacology/Toxicology

The Applicant was also informed that, based on Section 505(o)(3) of the FDCA, they were required, if the NDA is approved, to conduct the postmarketing studies and assays listed below:

1. An in vitro or in vivo assay using mammalian cells for chromosomal damage for neostigmine methylsulfate
2. If an in vivo assay is conducted to address Number 1 above, they needed to conduct a second different in vivo assay for chromosomal damage for neostigmine methylsulfate. Otherwise, they could conduct an in vivo assay for chromosomal damage for neostigmine methylsulfate. In order to address PMRs 1 and 2, they were referred to the options outlined in ICH S2(R1) titled "Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use" and propose an adequate battery of genetic toxicology studies.
3. A fertility and early embryonic development toxicology study in the rat model for neostigmine methylsulfate
4. An embryo-fetal developmental toxicology study using the rat model for neostigmine methylsulfate
5. An embryo-fetal developmental toxicology study using the rabbit model for neostigmine methylsulfate

6. A peri-and post-natal developmental toxicology study in the rat model for neostigmine methylsulfate
7. An adequate extractable/leachable safety assessment for the (b) (4) [redacted] gray (b) (4) [redacted] rubber stopper used in your container closure system – This assessment must include controlled extraction studies to qualitatively and quantitatively determine the chemical species which may migrate into the dosage form, using appropriate solvents that adequately represent the chemical characteristics of the drug product formulation, and leachable data from long-term stability studies (taking into consideration the proposed shelf-life) to determine if the identified/specified extractables also leach into the drug product over time, and a toxicological risk assessment justifying the safety of the extractables and leachables taking into consideration the maximum daily dose of the identified materials for this drug product. For your toxicological risk assessment, any leachable that contains a structural alert for mutagenicity should not exceed 1.5 mcg/day total daily exposure or it will need to be adequately qualified for safety. A toxicological risk assessment should be provided for any non-genotoxic leachable that exceeds 5 mcg/day.

In the current submission, the Applicant has provided study reports addressing the first six of these requirements. The Pharmacology-Toxicology review team is in the process of reviewing these studies. Their overview of the study reports suggests that these requirements may have been satisfied and only the seventh requirement remains to be included in the action letter for this cycle. The team's review of this submission should be consulted for their final determination regarding these requirements.

There were no preclinical issues that needed to be addressed in this submission, and the review team reports that there are no issues that would preclude the application's approval in this cycle.

3.4 Clinical Pharmacology

There were no clinical pharmacology issues that needed to be addressed in this submission, and the review team reports that there are no issues that would preclude the application's approval in this cycle.

4. Review of Safety

As required, the Applicant has provided a clinical safety update with this submission. This update consists of a literature search to identify new information published since the last literature-based update was conducted on October 21, 2013. The literature search was conducted on April 8, 2014 using the PubMed web based portal. The verbatim title search term “neostigmine” was used, and the date range was set at October 21, 2013, through April 8, 2014. An additional filter of “humans” was used as part of the search. This search strategy resulted in 7 articles, which were obtained and reviewed for relevance to the safety update. These articles included:

1. Yoganarasimha N, Raghavendra T, Amitha S, Shridhar K, Radha M. A comparative study between intrathecal clonidine and neostigmine with intrathecal bupivacaine for lower abdominal surgeries. *Indian J Anaesth.* 2014 Jan; 58(1): 43-7.
2. Woo T, Kim KS, Shim YH, Kim MK, Yoon SM, Lim YJ, Yang HS, Phiri P, Chon JY. Sugammadex versus neostigmine reversal of moderate rocuronium-induced neuromuscular blockade in Korean patients. *Korean J Anesthesiol.* 2013 Dec; 65(6): 501-7.
3. Llauradó S, Sabaté A, Ferreres E, Camprubí I, Cabrera A. Postoperative respiratory outcomes in laparoscopic bariatric surgery: Comparison of a prospective group of patients whose neuromuscular blockade was reverted with sugammadex and a historical one reverted with neostigmine. *Rev Esp Anesthesiol Reanim.* 2014 Jan 8.
4. Ledowski T, Falke L, Johnston F, Gillies E, Greenaway M, De Mel A, Tiong WS, Phillips M. Retrospective investigation of postoperative outcome after reversal of residual neuromuscular blockade: Sugammadex, neostigmine or no reversal. *Eur J Anaesthesiol.* 2013 Nov 20. [Epub ahead of print].
5. de Paula Ramos E, Antônio MB, Ambiel CR, Correia-de-Sá P, Alves-Do-Prado W. Paradoxical neostigmine-induced TOFfade: on the role of presynaptic cholinergic and adenosine receptors. *Eur J Pharmacol.* 2014 Jan 15; 723: 389-96.
6. Boogmans T, Vertommen J, Valkenborgh T, Devroe S, Roofthoof E, Van de Velde M. Epidural neostigmine and clonidine improves the quality of combined spinal epidural analgesia in labour: A randomised, double-blind controlled trial. *Eur J Anaesthesiol.* 2014 Apr; 31(4): 190-6.
7. Khorshid AF, Issa YM. Modified carbon paste sensor for the potentiometric determination of neostigmine bromide in pharmaceutical formulations, human plasma and urine. *Biosens Bioelectron.* 2014 Jan 15; 51: 143-9.

Two of these articles met the following selection criteria used by the Applicant for inclusion into this safety summary:

1. The article was not previously submitted to the FDA.
2. Neostigmine was used in a clinical setting primarily for reversal of nondepolarizing neuromuscular blocking agents.
3. The administration of neostigmine was not in the epidural space for caudal anesthesia (these studies were also excluded from the original NDA submission).
4. Some aspect of safety data was included in the article.

The articles identified for inclusion into the clinical safety update were:

- Woo T, Kim KS, Shim YH, Kim MK, Yoon SM, Lim YJ, Yang HS, Phiri P, Chon JY. Sugammadex versus neostigmine reversal of moderate rocuronium-induced neuromuscular blockade in Korean patients. *Korean J Anesthesiol.* 2013 Dec; 65(6): 501-7
- Ledowski T, Falke L, Johnston F, Gillies E, Greenaway M, De Mel A, Tiong WS, Phillips M. Retrospective investigation of postoperative outcome after reversal of residual neuromuscular blockade: Sugammadex, neostigmine or no reversal. *Eur J Anaesthesiol.* 2013 Nov 20. [Epub ahead of print]

These articles are summarized and discussed in Section 5 below. The findings as summarized by the Applicant are contained in the table below. The studies did not provide any new information that significantly affects the previous determinations that the proposed doses of neostigmine are safe and efficacious when used for the proposed indication.

Table 1. Summary of new literature reports related to safety (Table 1, pp 4-5 of Section 2.5 (05 May 2014) in the NDA)

Identification of Literature Source	Neostigmine Dose / Number of Patients or Animals Exposed (N)	Summary of Study Design / Primary Objective(s)	Primary Safety Results
Woo et al. (2013)	<p>50 µg/kg neostigmine with glycopyrrolate 10 µg/kg</p> <p>N=59 patients randomized to neostigmine</p> <p>N=59 patients randomized to sugammadex</p>	<p>Randomized, safety-assessor blinded clinical study</p> <p>The primary efficacy endpoint was the time from sugammadex or neostigmine administration to recovery of TOF ratio to 0.9</p> <p>Safety was also evaluated</p>	<p>The mean time to recovery of the TOF ratio to 0.9 was 1.8 min in the sugammadex group and 14.8 min in the neostigmine group (P < 0.0001)</p> <p>Four patients in the neostigmine group reported AEs thought to be secondary to inadequate reversal of NMB (rocuronium) and included mild amblyopia, mild asthenia and two cases of mild recurrence of NMB</p> <p>PONV was reported in 3 sugammadex and 6 neostigmine patients</p> <p>A lower proportion of AEs was found in Korean patients (85% and 68%, for Caucasian and Korean patients, respectively)</p>
Ledowski (2013)	<p>The mean dose of neostigmine administered was 2.4 mg (range 0.8-3.8)</p> <p>N=212</p>	<p>Retrospective clinical data analysis</p> <p>The primary outcome measure was to assess the incidence of PACU complications or "unwanted events"</p>	<p>The incidence of PONV in the PACU was higher in neostigmine-reversed than sugammadex-reversed patients (21.5 vs. 13.6%; P<0.05)</p> <p>Pulmonary outcome deteriorated significantly in neostigmine reversed patients who were both elderly (>60 years) and with ASA grade 3 or 4 status</p> <p>No differences were found regarding other PACU events, length of PACU stay or hospital stay between the sugammadex or neostigmine groups</p>

5. Appendices

5.1 Literature Review

5.1.1 Sugammadex versus neostigmine reversal of moderate rocuronium-induced neuromuscular blockade in Korean patients.

Woo T, Kim KS, Shim YH, Kim MK, Yoon SM, Lim YJ, Yang HS, Phiri P, Chon JY. Korean J Anesthesiol. 2013 Dec; 65(6): 501-7.

This randomized, safety assessor-blinded trial investigated the efficacy and safety of sugammadex versus neostigmine in Korean patients. The trial was sponsored by Merck Sharp and Dohme Corporation which is the marketer of sugammadex. The trial included Korean patients undergoing general anesthesia and who received rocuronium 0.6 mg/kg prior to intubation with maintenance doses of 0.1-0.2 mg/kg as required during their surgical procedure. Subjects were randomized to receive either sugammadex 2.0 mg/kg or neostigmine 50 µg/kg with glycopyrrolate 10 µg/kg to reverse the residual neuromuscular blockade at the reappearance, after the last rocuronium dose, of the second twitch (T_2) to a train-of-four (TOF) electrical impulses applied over the ulnar nerve. The primary efficacy endpoint was the time from sugammadex or neostigmine administration to recovery of the TOF twitch ratio of the adductor pollicis muscle to 0.9. The safety of these medications was also assessed by evaluation of adverse events occurring over 7 days following study drug administration as well as vital signs, physical examination, and clinical evidence of residual neuromuscular blockade (NMB) and recurrence of NMB.

Of 128 randomized patients, 118 had evaluable data ($n = 59$ in each treatment group). The geometric mean (95% confidence interval) time to recovery of the TOF ratio to 0.9 was 1.8 (1.6, 2.0) minutes in the sugammadex group and 14.8 (12.4, 17.6) minutes in the neostigmine group ($p < 0.0001$).

The percentage of patients who experienced an adverse event (AE) was similar between the groups; most AEs were of mild or moderate intensity. The percentage of subjects reported to have experienced at least one non-serious AE of severe intensity was similar between the treatment groups. Treatment-related AEs (i.e., those that were considered to be possibly or probably related to the study drug) were reported for four (7%) patients in the sugammadex treatment group, and six (10%) patients in the neostigmine treatment group. In the sugammadex group, these were cardiac anesthetic

complication (bradycardia of moderate intensity, n = 1) and headache (n = 3); in the neostigmine group, they were headache (n = 2), nausea, recurrence of NMB, rash, and hypotension (n = 1). Serious AEs were reported for two patients in each treatment group, all of which were considered unlikely to be related to the study drug. In the sugammadex group, these included a severe intestinal anastomosis in a 69-year-old male and a severe postoperative abscess in a 48-year-old female. In the neostigmine group, these were metastases to the bone (severe) in a 56-year old male with maxillary sinus squamous cell carcinoma, and moderate dysuria in a 45-year-old female.

Postoperative nausea and vomiting (PONV) was reported in three patients in the sugammadex group and six patients in the neostigmine group. All patients from both treatment groups who experienced PONV had at least two baseline PONV risk factors. There were no clinically relevant differences between the treatment groups in mean systolic or diastolic blood pressures or heart rate.

No AEs that would be potentially indicative of inadequate reversal of NMB were reported for any sugammadex patients. In the neostigmine group, four patients (7%) reported AEs that were possibly indicative of inadequate reversal (mild amblyopia, mild asthenia and two cases of mild recurrence of NMB).

Based on their findings, the authors concluded that sugammadex 2 mg/kg provided rapid and complete reversal of moderate rocuronium-induced NMB in Korean patients, and the time to recovery of the TOF ratio to 0.9 was significantly (~8.1 times) faster with sugammadex than with neostigmine. The overall efficacy and safety profiles of sugammadex were similar to those previously observed for Caucasian patients in a comparable pivotal study that examined reversal of moderate NMB.

Clinical Comments:

This study was designed to evaluate the efficacy of sugammadex in the Korean patient population. It was powered to evaluate differences between neostigmine and sugammadex in the recovery of rocuronium-induced NMB. The findings relative to the use of neostigmine are consistent with those previously reported in the literature for both safety and efficacy. The results of the trial, therefore, do not affect the determinations of neostigmine's safety and efficacy made in the initial review cycle for this NDA.

5.1.2 Retrospective investigation of postoperative outcome after reversal of residual neuromuscular blockade: sugammadex, neostigmine or no reversal.

Ledowski T, Falke L, Johnston F, Gillies E, Greenaway M, De Mel A, Tiong WS, Phillips M. *Eur J Anaesthesiol.* 2014 Aug; 31(8): 423-9.

The objective of this retrospective data analysis was to investigate the influence of the method of residual of neuromuscular blockate (RNMB) reversal on postoperative outcome with a focus on the use of sugammadex. The study was conducted at a tertiary teaching hospital in Western Australia. The treatments evaluated included neostigmine, sugammadex, and no-reversal.

Data from 1,444 patients who received at least one dose of a non-depolarizing muscle relaxant intraoperatively during the year 2011 were analyzed evaluating the following endpoints:

1. Unwanted events in the postanesthesia care unit (PACU)
2. Symptoms of pulmonary complications within 7 postoperative days using a 0 to 100 outcome score based on 'temperature >38°C,' 'leucocyte count >11 × 10⁹,' 'physical examination consistent with pneumonia' and 'shortness of breath'
3. PACU turnover time
4. Length of hospital stay

The authors reported that of the 1,444 patients, 722 were treated with sugammadex, 212 were treated with neostigmine, and 510 received no-reversal agent. The incidence of postoperative nausea and vomiting (PONV) in PACU was higher in neostigmine-reversed than sugammadex-reversed patients (21.5 vs. 13.6%; P<0.05). No differences were found regarding other PACU incidents, length of PACU stay or hospital stay. Pulmonary outcome deteriorated significantly (outcome score increased) with age and American Society of Anesthesiologists (ASA) physical status. This was observed particularly in ASA 3/4 patients more than 60 years of age in neostigmine-reversed or non-reversed patients, but almost no detrimental effect of age on pulmonary outcome was found in the sugammadex group (P<0.05).

The authors concluded that RNMB reversal with sugammadex was associated with the lowest rate of PONV and the use of sugammadex might reduce the risk of pulmonary complications in elderly patients with an ASA-PS of 3 or 4. However, they also state that prospective randomized controlled studies are required to confirm the effects of sugammadex found in this retrospective analysis.

Clinical Comments:

This study was designed primarily to evaluate whether the use of sugammadex may impact postoperative outcomes. The study was powered to find differences between sugammadex treatment and non-sugammadex treatment; it was not powered to evaluate differences between neostigmine treatment and either sugammadex or spontaneous recovery. The findings relative to the use of neostigmine do not differ in any clinically meaningful way from the findings based on the safety information contained in the initial submission of this NDA.

5.2 Labeling Recommendations

Another neostigmine product with an identical indication (Bloxiverz, NDA 204078) was approved on May 31, 2013. That NDA was also based solely on published literature to support a finding of safety and efficacy for the doses approved for use. As this NDA relies on the same literature to support the same indication, the plan for labeling is to assure that the two products accurately reflect the information contained in the literature and that neither label will differ such that a possible claim of an advantage for one product over the other can be made. Specific recommendations for changes to the proposed label are made in the version to be shared with the Applicant during label negotiations.

5.3 Advisory Committee Meeting

There were no issues that required the input from an advisory committee during the initial review cycle or the current cycle. Therefore, an advisory committee meeting was not convened.

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/s/

ARTHUR F SIMONE
12/16/2014

RIGOBERTO A ROCA
12/16/2014



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

Summary Review for Regulatory Action

Date	January 29, 2013
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia, and Addiction Products
Subject	Division Director Summary Review
NDA #	202788
Applicant Name	Fresenius Kabi USA, LLC
Date of Submission	December 28, 2012
PDUFA Goal Date	October 29, 2012; 3-month extension to January 29, 2013
Proprietary Name / Established (USAN) Name	none / Neostigmine methylsulfate injection
Dosage Forms / Strength	Injectable solution 0.5 mg/ml and 1.0 mg/ml
Proposed Indication	Reversal of non-depolarizing neuromuscular blocking agents
Action:	Complete Response

Material Reviewed/Consulted	
OND Action Package, including:	
CDTL	Christopher D. Breder, M.D., Ph.D.
Clinical Review	Arthur Simone, M.D., Ph.D.
Biostatistics Review	David Petullo, M.S.; Dionne Price, Ph.D.
Pharmacology Toxicology Review	Huiqing Hao, Ph.D.; Dan Mellon, Ph.D.
ONDQA-CMC/Quality Review	Edwin Jao, Ph.D.; Prasad Peri, Ph.D.
OPS/NDMS-Microbiology Review	Vinayak Pawar, Ph.D.; John Metcalfe, Ph.D.
Clinical Pharmacology Review	David Lee, Ph.D.; Yun Xu, Ph.D.
ONDQA-Biopharm	Minerva Hughes, Ph.D.; Angelica Dorantes, Ph.D.
Project Management	Allison Meyer; Parinda Jani
OSE/DMEPA	Denise Baugh, Pharm.D.; Lubna Merchant, Pharm.D.; Scott Dallas, Pharm.D.; Carol Holquist, R.Ph.
OSE/DPVII	Martin Pollock, Pharm.D.; James Kaiser, Pharm.D.; Lauren Choi, Pharm.D.; Bindi Nikhar, M.D.
OMP/OPDP/DDTCP	Eunice Chung-Davies Pharm.D.; L. Shenee Toombs, Pharm.D.
Office of Compliance	Derek Smith, Ph.D.

OND=Office of New Drugs
OMP: Office of Medical Policy
OPDP= Office of Prescription Drug Promotion
DMPP = Division of Medical Policy Programs
DDTCP: Division of Direct-to-Consumer Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention
DPVII=Division of Pharmacovigilance II
CDTL=Cross Discipline Team Leader
ONDQA=Office of New Drug Quality Assessment
OPS/NDMS=Office of Pharmaceutical Sciences/New Drug Microbiology Staff

Introduction

Fresenius Kabi USA, LLC (FK USA), (APP Pharmaceuticals, LLC [APP] at the time of the NDA submission) submitted this 505(b)(2) NDA for their currently marketed but unapproved neostigmine methylsulfate injectable solution. Neostigmine is administered IV for reversing non-depolarizing neuromuscular block. FK USA is referencing published medical literature as the source for much of the clinical data in their application.

The following summary of the pharmacology and clinical use of neostigmine has been reproduced from pages 7 and 8 of Dr. Breder's review:

Scientific Background

Neostigmine, an anticholinesterase agent first synthesized in 1931, 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).

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.

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.

Clinical Background

In general, the goal in reversing an 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 are typically 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 H₂O
 - Tidal volume > 5 mL/kg
 - Vital capacity > 10 mL/kg
 - Respiratory rate < 30 breaths/min
 - Appropriate oxygen saturation and end-tidal CO₂ levels

The clinical benefit 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. However, several potential benefits can be postulated and may be reasonably incorporated into the benefit risk analysis. These include reducing the risks associated with:

- 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.

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

1. Background

As per the following, reproduced from page 6 of Dr. Breder’s review, there were a number of concerns raised by the team during the course of their reviews, all but one of which have been satisfactorily resolved.

Several issues were noted by the reviewers of this NDA at the time of their original discipline reviews, including:

- Nonclinical
 - Structural alerts for impurities and the parent molecule;
 - Phenol content of the drug product;
 - Extractable / Leachable profile of the container closure system;
- Chemistry Manufacturing Controls (CMC)
 - Unsatisfactory manufacturing and controls for the drug substance; The referenced DMF (b) (4) is found inadequate to support this NDA;
 - The recommendation from the Office of Compliance is “Withhold” based on the findings discussed in this and the primary CMC review;
 - Incomplete environmental assessment;
 - Unsatisfactory specifications for total impurities in the drug product;
- Clinical
 - Satisfactory definition of the efficacious dose range and the labeling to describe it.

In the time interval between the completion of the individual discipline reviews and the completion, all of these issues have been resolved to the satisfaction of the disciplines and are clarified in addenda or additions to the original reviews, except the issue of inspection of the manufacturing facility...

I have made a minor recommendation to amend the lower dose in Dr. Simone’s proposed dosing range from 40 to 30 mcg/kg ... This change is reflected in the proposed labeling, which Dr. Simone is in agreement (*sic*).

Based on the available information at the time that Dr. Breder filed his review, he recommended approval, pending satisfactory resolution of the inspection issues. Those inspection issues have not been satisfactorily resolved, and the Office of Compliance has recommended a “Withhold Approval” for this application.

2. CMC

The following has been reproduced from pages 8 through 10 of Dr. Jao's final CMC review:

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The **drug substance** is neostigmine methylsulfate, USP. It is not a NME. The characterization of this compound has been well documented in the literature, and the manufacturer has adequately confirmed the structure of the drug substance they produced. While it contains structural alert moieties ((b) (4) and (b) (4)), it is not genotoxic based on non-clinical data (see pharmtox team review). Neostigmine Methylsulfate, USP is manufactured by (b) (4)

(b) (4) The establishment received "Acceptable" recommendation from the Office of Compliance on 1/22/2012. This compound is prepared through multiple steps of synthesis. The detailed CMC information is incorporated by reference to DMF (b) (4) which is considered adequate to support this NDA. The proposed drug substance specification meets and exceeds that required by the USP monograph for neostigmine methylsulfate. The quality and stability of the registration batches of the drug substance Neostigmine Methylsulfate, USP are adequately demonstrated by release and stability data. The drug substance is packaged (b) (4). There are no safety concerns for the container/closure system. The proposed retest period of (b) (4) months is supported by real time stability data.

The drug product is Neostigmine Methylsulfate Injection, USP, 0.5 mg/mL and 1.0 mg/mL, (b) (4) in 10 ml Type I USP glass vials, with rubber stopper and aluminum seal. Neostigmine Methylsulfate injection has been approved only for animal use (21CFR 522.1503), but not for human. Neostigmine Methylsulfate OPHTHALMIC SOLUTION was approved on 5/4/1939 (NDA 000654), but was withdrawn on 4/12/1996. Currently there are three companies marketing Neostigmine Methylsulfate injection (American Reagent, APP, and West-Ward Pharmaceuticals), and none of them have an approved NDA. Neostigmine Methylsulfate injection is on the drug shortage list. There is a current USP monograph for neostigmine methylsulfate injection. The excipients used in the formulation are liquefied phenol, sodium acetate, and water for injection. All the excipients are compendial. Liquefied Phenol (used as preservative) has been approved for IV drug product for up to 0.5% based on Inactive Ingredients database. There is no safety issue from CMC perspective. The drug product is manufactured by Fresenius Kabi USA, LLC (formerly APP). This establishment received a Withhold recommendation from the Office of Compliance on 2/24/2012, which remains effective. The environmental assessment for the drug product was submitted on 9/20, and considered acceptable by Dr. Raanan Bloom.

The manufacturing process of the drug product involves (b) (4) Adequate in-process and material controls are in place. The proposed drug product specification meets and exceeds that required by the USP monograph for neostigmine methylsulfate, injection. The sterilization process and sterility controls have been evaluated by the microbiology team and are considered acceptable. Given that the drug product is an aqueous solution for injection, USP Type I glass generally satisfy safety and quality concerns. DMF (b) (4) is referenced for the rubber stoppers, and is found adequate to support this NDA. Due to the presence of (b) (4) % phenol in the formulation, there is potential for leachables from the rubber stoppers to be present in the drug product. Depending on the assessment of leachable data, additional controls might be necessary. However, since the same rubber stoppers are already used in two approved drug products with similar formulations and route of administration and given the marketing history of this drug product, the pharmtox team considers this issue can be further managed post approval. Release and stability data from two batches (pilot scale) each for the two strengths of the drug product are provided. Release batch data are acceptable per specification. Twelve months of stability data from the registration batches are provided. No significant trend is observed. Up to 45 months of supporting stability data (impurity profiles of the last testing points only) from historical batches (7 batches) are also

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provided. The requested shelf life of 24 months is supported by historical and registration stability data. All comments pertinent to labeling have been conveyed to applicant and satisfactorily resolved.

B. Description of How the Drug Product is Intended to be Used

Neostigmine Methylsulfate Injection is administered IV for reversing non-depolarizing neuromuscular block

C. Basis for Approvability or Not-Approval Recommendation

1. *The applicant of the NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product.*
2. *The recommendation from the Office of Compliance for this NDA is "withhold".*

The current inspection of Fresenius Kabi revealed that the firm is not GMP compliant. Observations cited in Form 483 were related to various deficiencies observed in the (b) (4) insects and arachnids in the building, procedures not followed for cleaning and maintenance, etc. Although these observations were not specific to neostigmine, they suggest that there is no assurance that the neostigmine manufacturing area or line will be clean or without (b) (4) contamination, or that the product will be manufactured under GMP regulations having high quality standard. Based on these findings, the Compliance review team recommended a "Withhold" for this application. I concur with the review team that this product's quality has not been adequately established and, indeed, may be of sufficient concern to block distribution of the unapproved product.

3. Nonclinical Pharmacology/Toxicology

The following summary of the nonclinical pharmacology and toxicology data and review has been reproduced from page 4 of Dr. Mellon's secondary pharmacology/toxicology review:

The primary pharmacology toxicology review was completed by Dr. Huiqing Hao. Dr. Hao originally recommended a complete response based on the lack of adequate genetic toxicology data for the parent and drug substance impurities. A subsequent submission from the Sponsor (8/29/2012) addressed this concern. Based on the second review from Dr. Hao, she is recommending that the application can be approved at this time pending agreement on labeling and with post-marketing requirements (PMRs). I concur with this approval recommendation and with the recommendation for the PMRs.

As discussed in the 2009 preIND meeting with the Sponsor, given the long clinical history of neostigmine use, no new nonclinical pharmacology or toxicology studies for the drug substance were required to support approval of this NDA. The pharmacology toxicology review therefore focused on the safety of the drug substance impurities and drug product degradants, the container closure system, and the drug product excipients. As noted in her reviews, adequate data were available to support the safety of the container closure system, the drug substance impurity specifications, and the drug product degradant specifications. In terms of excipient safety qualification, the total daily dose of the preservative phenol via this drug product formulation does exceed that of previously approved drug products that are administered as a single bolus injection; however, we recognize that previous clinical experience exists that may justify the safety in this product (see medical officer review).

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As noted in the preIND meeting minutes from 2009, the Sponsor was also 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. Based on the lack of adequate data in the published literature to inform labeling, these studies are recommended as post-marketing requirements.

The following summary of the team's conclusion has been reproduced from pages 9 and 10 of Dr. Mellon's review:

1.3 Recommendations

1.3.1 Approvability

Approval. From a nonclinical pharmacology toxicology perspective, adequate information has been provided to support approval of this NDA. If approved in this or a second cycle, post-marketing requirements for the remaining two genetic toxicology studies, the complete battery of reproductive and developmental toxicology studies, and an adequate extractable/leachable assessment of the container closure system are also recommended.

1.3.2 Additional Non Clinical Recommendations

Based on the data submitted to date, the following studies are recommended as post-marketing requirements (PMRs) should this NDA be approved:

1. Conduct an in vitro or in vivo assay using mammalian cells for chromosomal damage for neostigmine methylsulfate.
2. If you conducted an in vivo assay to address number 1 above, conduct a second in vivo assay for chromosomal damage for neostigmine methylsulfate; otherwise conduct an in vivo assay for chromosomal damage for neostigmine methylsulfate. NOTE: To address PMRs 1-2, you may refer to the options outlined in ICH S2(R1) titled "Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use" and propose an adequate battery of genetic toxicology studies.
3. Conduct a fertility and early embryonic development toxicology study in the rat model for neostigmine methylsulfate.
4. Conduct an embryo-fetal developmental toxicology study using the rat model for neostigmine methylsulfate.
5. Conduct an embryo-fetal developmental toxicology study using the rabbit model for neostigmine methylsulfate.
6. Conduct a peri- and post-natal developmental toxicology study in the rat model for neostigmine methylsulfate.
7. Conduct an adequate extractable/leachable safety assessment for the (b) (4) gray (b) (4) rubber stopper used in your container closure system. This assessment must include controlled extraction studies to qualitatively and quantitatively determine the chemical species which may migrate into the dosage form using appropriate solvents that adequately represent the chemical characteristics of the drug product formulation, and leachable data from long-term stability studies (taking into consideration the proposed shelf-life) to determine if the identified/specified extractables also leach into the drug product over time, and a toxicological risk assessment justifying the

safety of the extractables and leachables taking into consideration the maximum daily dose of the identified materials for this drug product. For your toxicological risk assessment, any leachable that contains a structural alert for mutagenicity should not exceed 1.5 mcg/day total daily exposure or be adequately qualified for safety. A toxicological risk assessment should be provided for any non-genotoxic leachable that exceeds 5 mcg/day.

I concur with the review team that there are no outstanding pharmacology or toxicology concerns that would preclude approval of this application.

4. Clinical Pharmacology/Biopharmaceutics

The following summary of the clinical pharmacology data and review has been reproduced from pages 18 through 21 of Dr. Breder's review:

The Applicant submitted 8 and 5 publications under clinical pharmacology and biopharmaceutics (assay methodology), respectively. A cursory review was conducted by the Applicant and presented as below in a table format. All publications were reviewed by Dr. Lee based on the current review practice. In particular, study design, dosage administration, blood sampling scheme, and analytical methodology information were focused during the review.

3.3.2. General clinical pharmacology/biopharmaceutics considerations

Dr. Lee presented the following table that summarized the clinical pharmacology findings as presented by the applicant:

Table 2 Clinical Pharmacology findings presented by the Applicant

Author	Treatment		PK parameters			
	Neo	Other meds	Cmax, T _{ax} , AUC	T _{1/2} (min)	CL (mL/min/kg)	V _d (L/kg)
Williams	Neo methylsulfate 5 mg iv	Atropine sulfate 1.2 mg iv	Conc. profile	24	Not reported	6.2
Chan (Analytical method)	Neo bromide 5 mg iv	Not reported	Conc. profile	Not reported	Not reported	Not reported
De Ruyter (Analytical method)	Neo 0.05 mg/kg	Not reported	Conc. profile	Not reported	Not reported	Not reported
Fisher De Ruyter method	Infants 100 µg/kg iv Children and adults 70 µg/kg iv	Atropine 30 µg/kg iv	Conc. profile	Infants: 39 Children: 48 Adults: 67	Infants: 13.6 mL/min/kg Children: 11.1 Adults: 9.6	Infants: 0.08 Children: 0.09 Adults: 0.04
Calvey	Neo methyl 68.9-103 µg/kg iv	Atropine sulfate 1.2 mg iv	Conc. profile	25.4	5.72	0.12
Morris De Ruyter method	Neo methyl 70 µg/kg iv	Atropine sulfate 1.0 mg iv	Not reported	a=3.4 b=77	9.2	0.74
Broggini Authors' own HPLC method	Neo 0.5 mg iv	Not reported	C _{max} : 8.84 T _{max} : 0.08 h AUC=126.8 (ng.h/mL)	1.88 h or (112.8 min)	0.7 L/h/kg	0.18 MRT 2.83 h
Cronnelly Chan method	Neo 70 µg/kg iv	Atropine 0.03 mg/kg iv	Conc. profile	Normal: 79.8 Anephric: 181.1 Transplant: 104.7	Normal: 16.7 Anephric: 7.8 Transplant: 18.8	Normal: 1.4 Anephric: 1.6 Transplant: 2.1

Dr. Lee determined that all of the publications submitted in the application do not have adequate analytical information (e.g., QCs, recovery, stability, validations, etc.). According to his review, based on the current clinical pharmacology standards, none of the publications are adequate and are not optimal in presenting the information needed for the Labeling purpose. However, it appears to him that the following information (**Sections 3.3.2.1 - 3.3.2.3**) is consistent throughout the publication regardless which analytical methods used.

3.3.2.1. Drug-drug interactions

Dr. Lee noted that the pharmacokinetic interaction between neostigmine and other drugs has not been studied. He advised that since neostigmine is metabolized by microsomal enzymes in the liver, one should use with caution when using neostigmine with other drugs which may alter the activity of metabolizing enzymes or transporters.

3.3.2.2. Metabolism and Pathway of Elimination

- Neostigmine half life ranged from 77 to 113 minutes after a single intravenous administration.
- Nonclinical information suggested that neostigmine is eliminated in the urine and feces (unabsorbed material given by routes other than IV) unchanged and undergoes hepatic metabolism in the liver microsomes. 3-Hydroxyphenytrimethyl ammonium (PTMA) is the primary metabolite, which then becomes glucuronide conjugated PTMA.

3.3.2.3. Demographic interactions/special populations

Age – Elderly

The only significant difference between the young and elderly was initial volume of distribution (V1), which was lower in the elderly. Numerically the clearance in elderly (23.4 ± 4 mL/kg/min) is also lower compared to younger patients (33.5 ± 4 mL/kg/min). Overall the duration of maximum response to neostigmine was significantly prolonged in the elderly (42 ± 10 minutes) compared to the younger group (13.14 ± 2.4 minutes).

Age – Pediatrics

From a study by Fisher et al, Dr. Lee noted elimination half-life for infants, children and adults were 39 ± 5 min, 48 ± 16 min, and 67 ± 8 min (mean \pm SD), respectively. Clearance for infants (2-10 months), children (1-6 years), and adults (29-48 years) were 13.6 ± 2.8 , 11.1 ± 2.7 and 9.6 ± 2.3 mL/min/kg (mean \pm SD), respectively.

Renally Impaired

From his review, Dr. Lee determined that clearances for normal, transplant and anephric patients were 16.7 ± 5.4 , 18.8 ± 5.8 and 7.8 ± 2.6 mL/min/kg (mean \pm SD), respectively. The clearance in patients with impaired renal function is lower compared to patients with normal renal functions. Use with caution in patients with impaired renal functions.

Hepatically Impaired

The pharmacokinetics of neostigmine in patients with hepatic impairment has not been studied. Dr. Lee noted that since neostigmine is metabolized by microsomal enzymes in the liver, caution should be exercised with the use in patients with impaired hepatic functions.

3.3.3. Biopharmaceutics

During a pre-IND meeting held on 12/22/09, the Agency stated that the Applicant may submit their NDA based the literature information, including to support a biowaiver request, pending the formulations used in the literature are appropriate for reference. Specifically, the Agency stated that “the formal review of submitted information in the NDA application will determine the adequacy of literature to support a request to waive pharmacokinetic/bioavailability studies for the proposed adult and pediatric subjects.” Therefore, the Applicant requested to waive in vivo pharmacokinetic / bioavailability studies. With respect to bioavailability/bioequivalence requirement as per the 21 CFR320, there are no concerns due to the fact that 1) the bioavailability is “self-evidence” since the Applicant’s formulation is for intravenous use; and, 2) that the Applicant and intravenous formulations described in the literature (based on the descriptions provided in the publications, e.g., neostigmine, preservatives (phenol) and saline) appear to be simple solutions.

3.3.4. Thorough QT study or other QT assessment

No information was submitted to characterize neostigmine effect on the QT interval. There did not seem to be a signal from the postmarketing surveillance investigation or from the literature reviewed by Dr. Simone or Martin Pollock (see Sections 3.5.3.3.3.6, 3.5.3.3.6.1.2, and 3.5.3.3.6.1.3). In as much as the Clinical Pharmacology group did not believe this to be a deficiency requiring further study before or after approval, I concur with this position considering the long clinical use without an apparent related safety signal.

The following has been reproduced from page 4 of Dr. Hughes' review of the biopharmaceutics data:

CONCLUSIONS:

The scientific bridge to the literature bioavailability data has been appropriately established for only the intravenous literature studies. As there are no listed drugs for reference, an additional waiver of bioequivalence studies does not apply for this product.

The submitted literature, if acceptable, can be used to satisfy the "evidence" of bioavailability requirement as per §320.24(b)(6). Therefore, from the perspective of Biopharmaceutics, additional studies are not necessary to meet the bioavailability data submission requirement. However, it should be noted that the adequacy of the submitted PK data to support bioavailability, clinical, and labeling decisions are two different issues. The adequacy of the literature PK (bioavailability) data is under the purview of the Office of Clinical Pharmacology, assigned primary reviewer Dr. David Lee. Additional PK studies may be requested, if deemed appropriate by the Office of Clinical Pharmacology, irrespective of the literature data submitted.

APPROVAL RECOMMENDATION:

Approval from the perspective of Biopharmaceutics.

I concur with the review team that there are no outstanding concerns regarding the clinical pharmacokinetic and biopharmaceutics data that would preclude approval of this application.

5. Clinical Microbiology

No clinical microbiology data were necessary for this application.

6. Clinical/Statistical-Efficacy

The following summary of the efficacy data and reviews has been reproduced from pages 23 and 24 of Dr. Breder's review:

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 meaningful efficacy data. Studies in which multiple doses of neostigmine were evaluated and those in which the timing of administration of a fixed dose of neostigmine was varied were also considered as providing meaningful efficacy data.

The Applicant did not identify any of these studies as pivotal or perform any efficacy analyses of the studies or the data contained within them. For the purposes of this review, Dr. Simone identified 11 studies reported in the literature that can be considered as pivotal, i.e., prospective, randomized, controlled studies involving recovery of the ToF ratio to 90% (**Table 1**)

Table 1 Studies considered by the Primary Medical Reviewer to be Pivotal in the Review of NDA 203629¹

Source	NMBA Reversed	Dose(s) of Neostigmine (mcg/kg)	Comparator(s)	Study Population
Abdulatif (63)	Rocuronium	5	Spontaneous recovery and a range of neostigmine doses	Pediatric and adult
		10		
		20		
		50		
Baurain (28)	Rocuronium	40	Different neuromuscular blocking agents	Adults
	Vecuronium			
	Atracurium			
	Pancuronium			
Baurain (29)	Vecuronium	20	Doses of neostigmine and timing of administration based on extent of spontaneous recovery	Adults
		40		
		80		
Bevan (41)	Rocuronium	70	Timing of administration based on extent of spontaneous recovery	Pediatric and adult
	Vecuronium	70		
Caldwell (27)	Vecuronium	40	Timing of administration based on time lapsed after vecuronium administration	Adults
Goldhill (17)	Atracurium	15	Spontaneous recovery and a range of neostigmine doses	Adults
		35		
		55		
		75		
Lederer (53)	Rocuronium	30	Spontaneous recovery and two neostigmine doses	Adults
		50		
McCourt (37)	Rapacuronium boluses	50	Spontaneous recovery	Adults
	Rapacuronium infusion			
	Rocuronium			
Meistelman (58)	Vecuronium	30	Timing of administration based on extent of spontaneous recovery	Adults
Sacan (68)	Rocuronium	70	Edrophonium and sugammadex	Adults
Source	NMBA Reversed	Dose(s) of Neostigmine (mcg/kg)	Comparator(s)	Study Population
Schaller (52)	Rocuronium	5	Placebo and a range of neostigmine doses	Adults
		8		
		15		
		25		
		40		

¹ Numbers in parentheses below the author's names represent the number in the References from Dr. Simone's review.

The following discussion of the analysis of the primary endpoints has been reproduced from 25 of Dr. Breder's review:

The Applicant did not perform an analysis of primary endpoints.

The reversal of neuromuscular blockade is most widely assessed, in both clinical practice and clinical research, by assessing the twitch response to a ToF electrical impulses and comparing the ratio of the magnitude of the fourth twitch to that of the first. Furthermore, 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 $\geq 90\%$. 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%. In the literature, 11 articles described clinical studies assessed recovery to these higher ToF ratios...visual inspection of [a] Table supplied by Dr. Simone suggests that for doses in the range of ~ 20 mcg/kg and higher, adequate reversal (ToF ~ 0.9) occurred in a timely manner (~ 10 min.).

Mr. Petullo performed a statistical verification of the analysis of the primary endpoint, and a summary of the results of that analysis has been reproduced below from pages 28 through 30 of Dr. Breder's review:

After a preliminary review of the 42 published articles submitted to support the efficacy of neostigmine, Mr. Petullo focused his analysis on the study by Schaller et al., 2010 to determine if there was a difference between the reversal times for neostigmine and placebo in achieving a ToF ratio of 0.9. The values for the sugammadex treatment groups are not of interest and were not to be included in the review.

According to the authors of Schaller et al., the primary aim of this study was to determine the dose of neostigmine and sugammadex which reversed a shallow residual neuromuscular block from a ToF ratio of 0.5 to a ToF ratio ≥ 0.9 . In this study, ninety-nine patients were equally randomized to 1 of 11 treatments: sugammadex (0.0625, 0.125, 0.25, 0.5, or 1.0 mg/kg), neostigmine (5, 8, 15, 25, or 40 $\mu\text{g}/\text{kg}$), or placebo (saline). A neuromuscular block was applied after induction of anesthesia using rocuronium. When the block was no longer required, spontaneous recovery was allowed until a ToF ratio of 0.5 was achieved. The study drug was then administered according to randomization. The time required to reach a ToF ratio greater than or equal to 0.7, 0.8, and 0.9 was recorded for all patients. The authors reported the median, minimum, and maximum times for each treatment group. There were no comparisons of the recovery times for the individual doses of neostigmine or sugammadex to placebo group as that was not the intent of this study.

The authors presented the individual data points in a dose-response curve for the time to a recovery ratio of 0.9 (Figure 1). Three patients were excluded due to major protocol violations, one each in 5, 8, and 40 $\mu\text{g}/\text{kg}$ neostigmine. Since the minimum, median, and maximum times were known, Mr. Petullo approximated the values that were above and below the median but within the reported range by visual examination of Figure 1. His approximations, along with the known values, are shown in Table 5. He compared each dose of neostigmine to placebo using a log-rank test. Results are shown in Table 6.

Figure 1 Dose Response Curve for Neostigmine based on Schaller, et al., 2010
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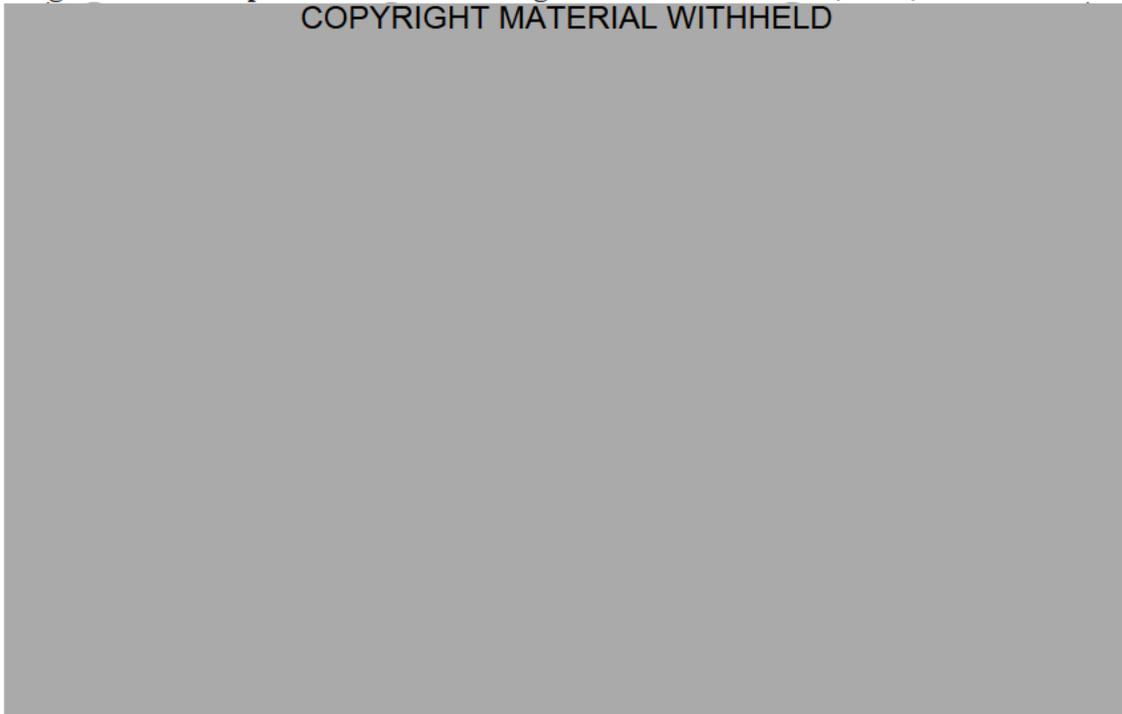


Table 5 Time (minutes) for reversal of Neuromuscular Block to ToF Ratio 0.9

Treatment	n	Time to TOF \geq 0.9 (minutes)
Placebo	9	12, 15.1, 15.5, 16, 19, 22, 23, 27, 33
Neostigmine 5 μ g/kg	8	5.8, 7, 7.1, 8.3, 10.3, 11.5, 12.1, 15
Neostigmine 8 μ g/kg	8	3.5, 3.7, 4.0, 5.3, 5.3, 5.5, 6.0, 8.7
Neostigmine 15 μ g/kg	9	2.8, 3.5, 3.6, 3.9, 4.0, 4.2, 5.1, 5.2, 6.0
Neostigmine 25 μ g/kg	9	1.7, 2.1, 2.5, 3, 3.2, 4.9, 5, 5.8, 6.2
Neostigmine 40 μ g/kg	8	1.7, 1.8, 1.8, 2.0, 2.0, 2.8, 2.8, 4.2

Source: Reviewer

Table 6 Comparison of Time to a ToF ≥ 0.9 Approximated from the Schaller et al., 2010 Reference

Treatment	Time to TOF ≥ 0.9 (minutes)		p-values*	
	Median	Range	raw	Sidak
Placebo	19	[12,33]	-	-
Neostigmine 5 $\mu\text{g}/\text{kg}$	9.3	[5.8, 15]	0.01	0.07
Neostigmine 8 $\mu\text{g}/\text{kg}$	5.3	[3.5, 8.7]	<0.0001	0.0001
Neostigmine 15 $\mu\text{g}/\text{kg}$	4.0	[2.8, 6.0]	<0.0001	<0.0001
Neostigmine 25 $\mu\text{g}/\text{kg}$	3.2	[1.7, 6.2]	<0.0001	<0.0001
Neostigmine 40 $\mu\text{g}/\text{kg}$	2.0	[1.7, 4.2]	<0.0001	<0.0001

* Log Rank Test with Sidak adjustment

Source: Reviewer

Based on his analysis of data provided in Schaller et al, he found that neostigmine reduces the recovery time required to reach ToF ratio ≥ 0.9 when administered at a ToF ratio of 0.5. He therefore concluded that there is evidence to support the use of neostigmine to reverse neuromuscular blocks.

Since the usual practice of administering reversal is to administer the neostigmine sooner than when ToF is 0.5, but rather when it is closer to a ToF of 0.1, I would not recommend using doses as low as 5 or 8 mcg/kg unless dictated by clinical circumstances (e.g., the patient has spontaneously reversed to a degree of ToF greater than 0.5)

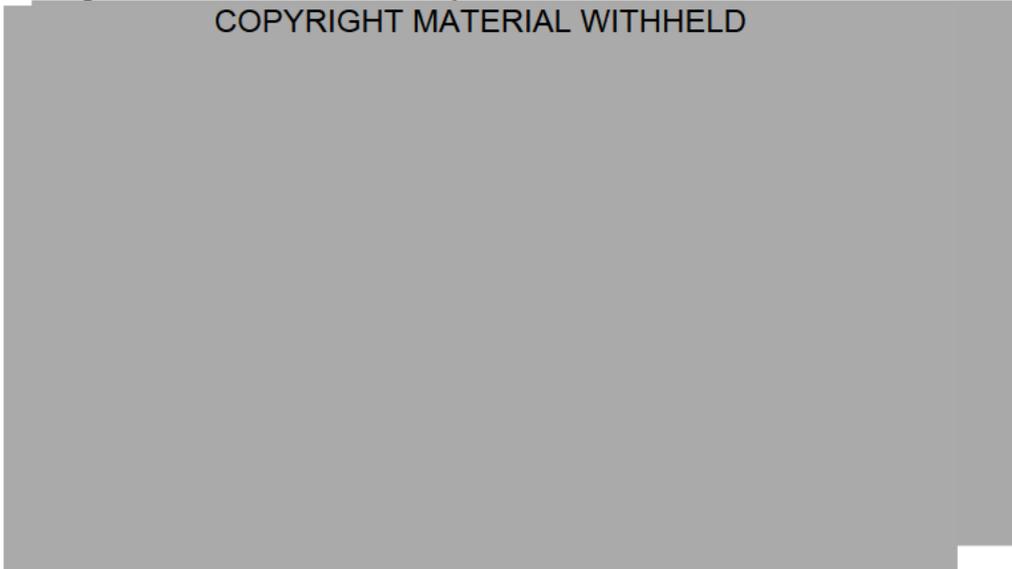
In regard to subpopulations, there was no evidence to suggest that neostigmine's efficacy would be affected by race or sex. The following summary of the review team's assessment of the efficacy of neostigmine for pediatric and elderly patients has been reproduced from pages 30 to 32 of Dr. Breder's review:

Age (Elderly)

Of the studies cited by Dr. Simone regarding the use of neostigmine in the geriatric population, McCarthy et al. seemed to most systematically examine the dose-response relationship for neostigmine in the elderly.

In this study, neostigmine doses included 5, 15, 25, 35, and 45 mcg/kg. The ToF values at 1-minute intervals from 5 minutes post-study drug administration onwards were used to determine the dose-response relationships. The difference in the time to spontaneous recovery of T1 to 10% between the two treatment groups was significant: 24 minutes (SD = 6) and 33 minutes (SD = 8) for the younger and older adults, respectively. The dose-response curves for neostigmine reported by the authors are shown in **Figure 2**. 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, suggesting either a lesser relative potency or an increased dosing requirement of neostigmine by the elderly for antagonizing the neuromuscular blocking effects of vecuronium. Furthermore, the ToF ratios for the two treatment groups showed that increasing doses of neostigmine were associated with faster recovery in both adult and elderly groups; however, 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.

Figure 2 Dose-response curves for ToF ratios at 10 min after administration of neostigmine in adults and the elderly.



In summary, the results of this study indicated that the 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 and suggests that the elderly may require about twice the dose of neostigmine to achieve the same ToF ratio as younger adults at 10 minutes.

Age (Pediatrics)

Dr. Simone analyzed and summarized ...the unintegrated literature provided by the Sponsor. In general the data suggest the following:

- Neostigmine seems to be similarly effective in the reversal of neuromuscular blockade of non-depolarizing neuromuscular blocking agents as it is in adults;
- The effect of the dose range (~20-70 mcg/kg) seems similar to that observed in adults. Doses as low as 10 mcg/kg may be effective in certain circumstances (see the following bullet)
- Similar considerations for dose selection within the recommended dose range seem to apply for pediatric patients as in adults (e.g., lower doses with short-acting non-depolarizing neuromuscular blocking agents or when the patient has spontaneously recovered to a greater extent than a single twitch on the ToF);
- There seems to be an increasing effect with increasing dose up to the highest doses tested (~70 mcg/kg).
- Excessive dosing of neostigmine (e.g., high doses in the setting of almost complete reversal of blockade before administration) may result in a paradoxical weakness

The data presented by the Sponsor spans the age range of 0-16 years old. There were notably fewer studies involving those in the youngest part of this population (i.e., <3 mo). However, Dr. Simone and I concur that there does not seem to be any notable deviation of the effects of neostigmine in this age group. Dr. Simone also notes throughout his review that the reversal of NMBAs involves not only the use of neostigmine but also requires a rigorous paradigm of clinical evaluation that should be more than adequate to account for any individual variability in the response to administration of neostigmine according to the proposed labeling.

Dr. Breder provided the following explanation for his dosing recommendation in an e-mail dated January 25, 2013:

The lower dose of 30 mcg/kg is supported by the literature provided by the Sponsor and the summary table of findings from the pivotal studies...While there seems little downside for recommending a higher limit to the low end of the dosing range, there are circumstances noted by both Dr Simone and myself in our reviews, where the clinician would need to administer a lower dose (e.g., short or intermediate acting NMBAs, situations where the patient has achieved a greater degree of spontaneous recovery). As Dr. Simone notes in his review, "...an excessive dose of neostigmine may also lead to a depolarizing block, similar to succinylcholine, due to excess acetylcholine (Ach) in the neuromuscular synapses" (p.88 AS review). Therefore since the efficacy of 30 mcg/kg is supported by the literature and since there are situations where the practitioner has need of a low, yet effective dose, I believe it is a sound recommendation for the lower end of the recommended dose range.

I concur with the review team that the applicant has provided sufficient evidence to support the conclusion that the product is effective for the proposed indicated use. I also concur with Dr. Breder's conclusion regarding the dosing recommendation.

7. Safety

The following summary of the exposure data has been reproduced from page 76 of Dr. Simone's review:

The Applicant did not analyze the available safety data to determine overall exposure, exposure at clinically relevant doses or the demographics of the exposed population. Based on Table 2.7.4-1 in the original NDA submission, 26 articles were identified by the Applicant as providing clinical safety information. These articles provided a database of 1,747 adult patients who were exposed to neostigmine in doses ranging from 10 mcg/kg to 80 mcg/kg. This population included a substantial numbers of both male and female patients as well as geriatric patients. Race of the patients was rarely reported. Similarly, Table 2.7.4-3 in the original NDA submission listed three studies in which clinical safety was assessed in a total of 56 pediatric patients.

The following summary of the data regarding deaths has been reproduced from page 79 of Dr. Simone's review:

The Applicant reviewed historical reports in the literature dating back to 1949 and identified 3 reports of acute cardiac arrest and death in anaesthetized patients following the rapid intravenous administration of neostigmine. The etiologies of these deaths were attributed to the rapid administration of neostigmine leading to bradycardia or inappropriate timing of administration of an anticholinergic agent (atropine).

The table below presents a summary of the deaths. The Applicant did not attempt to secure access to the raw data from these reports; therefore, no case report forms (CRFs) or patient narratives were submitted.

Table 11. Summary of deaths reported in the literature (Table 2.7.4-7 from original NDA submission)

Author (Year) Reference	Age	Sex	Neostigmine Dose (mg)	Diagnosis	Cause of Death	Other Medications	Other Medical Conditions
Clutton-Brock (1949) (84)	62 years	Female	2.0 mg	Common bile duct obstruction	Cardiac arrest	Atropine (0.65mg)	Intra-operative cardiac "irregularities"
Hill (1949) (85)	7 months	Not reported	0.25 mg	Congenital atresia of the bile duct	Cardiac arrest	Atropine (0.22 mg)	Autopsy findings normal with exception of bile duct
Macintosh (1949) (86)	38 years	Male	2.5 mg	Acute surgical abdomen	Cardiac arrest	Atropine (0.65mg)	Cardiac hypertrophy and generalized peritonitis found at autopsy

The following summary of the serious adverse events has been reproduced from page 82 of Dr. Simone's review:

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.

The following summary of the adverse events leading to discontinuation has been reproduced from page 82 of Dr. Simone's review:

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.

The following summary of the common adverse events has been reproduced from pages 83 and 84 of Dr. Simone's review:

Based on the literature submitted by the Applicant and the AERS database and literature review performed by DPV-2, the adverse events commonly reported for neostigmine were those related to its anticholinesterase activity and contained in the label for the currently marketed, unapproved product. These adverse events are identical to those proposed by the Applicant for inclusion if the product is approved, include those reported for uses of neostigmine outside the scope of the proposed indication, and are listed below:

- **Neurological:** Dizziness, weakness, convulsions, loss of consciousness, drowsiness, headache, dysarthria, miosis and visual changes

- **Cardiovascular:** Cardiac arrhythmias (including bradycardia, tachycardia, atrioventricular block and nodal rhythm) and nonspecific electrocardiogram changes have been reported, as well as cardiac arrest, syncope and hypotension
- **Respiratory:** Increased oral, pharyngeal and bronchial secretions, dyspnea, respiratory depression, respiratory arrest and bronchospasm
- **Dermatologic:** Diaphoresis, flushing, rash and urticaria
- **Gastrointestinal:** Nausea, emesis, flatulence and increased peristalsis
- **Genitourinary:** Urinary frequency
- **Musculoskeletal:** Muscle cramps and spasm, arthralgia

In the only study that reported a detailed list of adverse events for neostigmine and a comparator, Schaller (2010)(52) evaluated the efficacy and safety of neostigmine in doses of 5, 8, 15, 25, or 40 mcg/kg in a mixture with 1 mcg glycopyrrolate/5 mcg neostigmine to sugammadex and saline. The adverse events for all doses of neostigmine were combined for tabular display in the article. The table below lists the findings for the neostigmine and placebo (normal saline) treatment arms of the study.

Table12. Adverse events [n (%)] following neostigmine and placebo treatments (from Table 4 on p. 1059 of the article)

Adverse Event	Neostigmine (n = 51)	Placebo (n = 9)
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)
Oxygen desaturation < 90%	3 (7)	0
Paresthesia <i>nervus ulnaris</i>	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
At least 1 AE	28 (64)	4 (44)

* One patient developed acute lung failure 63 h 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 l, *i.e.*, 35% of normal) after bleomycine chemotherapy.

The unexpected finding of Schaller's study was the high incidence of postoperative shivering for neostigmine-treated patients. The authors reported that there were no dose-related responses to any of the adverse events. However, it should be noted that all but one of the neostigmine doses studied were less than 30 mcg/kg, and therefore, this study does not fully characterize its risk profile.

The following summary of the applicant's post-marketing safety review has been reproduced from pages 90 and 91 of Dr. Simone's review:

The Applicant reported that they have an established clinical safety database for neostigmine, and that 7 adverse drug events have been reported to the company since March 2003. Three events were considered non-serious; four were classified as serious adverse events (SAE). Each is described below.

Of the non-SAEs reported, two involved episodes of hypoventilation following drug administration and one involved an incident of decreased effect with no associated adverse events.

Of the 4 SAEs, two of the events were described by the Applicant as expected based on the product label of neostigmine. One of these involved a patient who experienced a decreased effect of neostigmine given for neuromuscular blockade reversal during eye surgery. The patient was hospitalized and recovered with no sequelae. The other event involved a patient with an extensive history of hypersensitivity who developed an anaphylactic reaction during an unspecified procedure in which she was administered an anesthetic that included propofol, vecuronium, midazolam, dexamethasone, cefazolin, and, at the end of the procedure, neostigmine to reverse the vecuronium. The patient was hospitalized for two days and recovered with no sequelae. The anesthesiologist suspected vecuronium as the most probable drug causing the event. The two remaining SAEs were reported in a literature article and were deemed unexpected based on the currently available (unapproved) product label. Both events were cases of non-cardiogenic pulmonary edema (NCPE) that began after administration of a combination of neostigmine and glycopyrrolate, which were used to reverse residual neuromuscular blockade. One of the patients was undergoing excision of a hemangioma on lower lip. Anesthesia was induced with thiopentone and suxamethonium. The patient was intubated and an oropharyngeal pack was inserted prior to the procedure. Anesthesia was maintained with propofol, N₂O:O₂ (50:50) and vecuronium. At the end of the procedure, after oropharyngeal suctioning and removal of oropharyngeal pack, the patient received neostigmine and glycopyrrolate. Shortly afterwards, the patient developed signs and symptoms of non-cardiogenic adult respiratory distress syndrome (ARDS). A chest x-ray was suggestive of pulmonary edema. The patient was mechanically ventilated overnight and was discharged after 2 days without complications. The second incident of NCPE after administration of neostigmine involved a pediatric patient who was undergoing corneal repair surgery. Anesthesia was induced with thiopentone and suxamethonium, and the patient was intubated. Anesthesia was maintained with propofol, N₂O:O₂ (50:50) and vecuronium. After the surgery the patient was extubated and administered neostigmine and glycopyrrolate. Shortly after extubation, the patient exhibited decreased oxygen saturation, crepitus sounds were heard during auscultation of the lungs, and frothy secretions were observed on laryngoscopy. The patient was treated and transferred to the pediatric intensive care unit. The patient's outcome was not reported.

Dr. Pollack and his colleagues completed a review of the AERS data for neostigmine. They concluded that the analysis of all events reported in the case series did not find any new

safety issue for which the proposed label can be strengthened or new events could be added.

The DPVII team also performed a literature review. The following summary of their review and conclusions has been reproduced from pages 93 and 94 of Dr. Simone's review:

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 five deaths that were included in the review, two of which involved the proposed indicated use. The first was reported by Middleton et al. (1957)(92) 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 than neuromuscular blockade and did not attribute the death to neostigmine. The second death was reported by Buzello et al. (1982)(93) 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.

On page 8 of his review, Dr. Simone provides the following summary regarding the risks associated with the administration of neostigmine to reverse neuromuscular blockade:

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.

I concur with the review team that the safety profile of neostigmine, based on the medical literature and AERS data, appears to be well defined; and that there are well-established clinical procedures for addressing the potential adverse events associated with this drug.

8. Advisory Committee Meeting

This application was not taken to advisory committee as it is a well understood product that has been used clinically for decades, and there were no specific efficacy or new safety concerns noted at the time of filing, or during the course of the review.

9. Pediatrics

The following summary of the pediatric issues related to this application has been reproduced from pages 52 and 53 of Dr. Breder's review:

The Division made a case to the PeRC that the NDA contained sufficient information for pediatric labeling and that further studies would not likely result in a further refinement of the dosing guidance or additional safety findings. This was based on the following rationale:

Pediatric efficacy...

The efficacy studies were similar in design to the studies conducted in adult patients and had similar limitations for deriving a uniform method of using neostigmine to reverse the effects of NMBAs. Nonetheless, the findings for pediatric patients were similar to those for adults as they relate to when the drug should be given relative to the extent of spontaneous recovery, the range of dosing (by body weight) that should be administered, and the recovery times of the ToF ratios. The data indicate that neostigmine is equally efficacious across pediatric age groups when adult dosing paradigms are applied. Furthermore, the efficacy results were similar for the NMBAs more commonly used in the pediatric patient population.

Pediatric pharmacokinetics...

The available pharmacokinetic data, summarized in the last table below, indicate that PK parameters are similar across pediatric age groups and are also similar to those measured in adults.

Pediatric safety...

The safety findings reported in the published literature were limited and were supplemented by a review of available safety data in the literature and the AERS database by conducted by the Division of Pharmacovigilance 2. There were three key findings:

1. The reported adverse events for pediatric patients were similar to those observed in the adult population and were neither severe nor life-threatening.
2. No unexpected adverse events occurred in pediatric patients that raised a safety concern.
3. The use of anticholinergic agents (atropine and glycopyrrolate) counteracted the well-known and predictable effects of neostigmine at the sites of muscarinic cholinergic transmission occurring in the parasympathetic, postganglionic receptors of the autonomic nervous system (most notably bradycardia and bronchoconstriction). The timing of administration and dosing (by weight) of these agents in pediatric patients was the same as for adults;

In light of this data, the Division had the following summary findings upon which it derived its recommendation to the PeRC:

- The evidence supporting the use of 30 to 70 mcg/kg in the pediatric population is adequate. Dosing in the youngest group (0 to 3 months) seems to be similar to that of older pediatric age groups and adults.

- Given the influence of confounding factors (different PK of different NMBA, different concomitant adjunctive medications used in anesthesia), further studies of dosing for neostigmine in the pediatric population are not likely to result in a more refined dosing guidance than that which is proposed by the Sponsor.
- Given the extensive monitoring of patients after neostigmine administration, which is detailed in the proposed labeling, further study in the pediatric population is not likely to result in the description of a safer paradigm of clinical use of neostigmine.

The PeRC agreed with the Division's position without further comment and requested a copy of the final pediatric labeling be sent to them.

10. Other Relevant Regulatory Issues

There are no other regulatory concerns for this application

11. Labeling

The review team and the applicant have reached agreement on all aspects of the product labeling. There were no major disagreements during the course of the review and discussions with the applicant.

12. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Complete Response

- Risk Benefit Assessment

The applicant has provided sufficient evidence to demonstrate the safety and effectiveness of their neostigmine product. However, the quality of their product remains of concern. Based on systemic problems at APP's manufacturing plant, it is possible that their injectable products are not sterile, and may be adulterated or contaminated, including this neostigmine product. As such, this application cannot be approved until the manufacturing facility has been demonstrated to be functioning under strict compliance with GMP processes, procedures and controls.

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/s/

BOB A RAPPAPORT
01/29/2013

CLINICAL REVIEW

Application Type: NDA
Application Number(s): 203629
Priority or Standard: Standard

Submit Date(s): December 28, 2011
Received Date(s): December 29, 2011
PDUFA Goal Date: October 29, 2012
Division / Office: DAAAP / ODE 2

Reviewer Name(s): Arthur Simone, MD, PhD
Review Completion Date: September 9, 2012

Established Name: Neostigmine Methylsulfate
Injection, USP
(Proposed) Trade Name: (none proposed)
Therapeutic Class: Cholinesterase Inhibitor
Applicant: APP Pharmaceuticals, LLC

Formulation(s): Injectable solution
Dosing Regimen: (b) (4) -70 mcg/kg intravenously
Indication(s): Reversal of neuromuscular
blockade
Intended Population(s): Post-surgical 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 once the issues identified by the Chemistry, Manufacturing and Controls team have been resolved to the team's satisfaction and the Office of Compliance has completed its reinspection of the manufacturing facilities and determined the sites to be suitable to produce and package the product within specifications and cGMP standards.

1.2 Benefit Risk 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 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 with 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; they tend to occur soon after the administration of neostigmine 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 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 submitted provided 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[®] for the symptomatic treatment of adynamic ileus. However, at the present time, the drug is not listed in the Orange Book and is marketed in the US without an FDA approval.

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 Tables of 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 overdose.

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 overdose.

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 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 related to edrophonium:

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 December 22, 2009, to discuss the information that would be necessary to file an NDA. The meeting package was submitted under PIND 106574. The key discussion points of the meeting are summarized below.

1. The clinical information for the NDA was to be obtained solely from the published literature.
 - a. The Division indicated that each published study should be critically reviewed and its data organized to allow an organized assessment of efficacy and safety.
 - b. The Division also indicated that the safety data should be integrated, to the extent possible, to create a safety database that can be analyzed

according to subject demographics, dose of neostigmine evaluated, use of an anticholinergic, and neuromuscular blocking agent reversed. The efficacy data should be integrated according to the same parameters as the safety data.

- c. The Applicant indicated that they believed there were sufficient data from well-designed, randomized, blinded, controlled studies to support a finding of safety and efficacy. The Division indicated that this would be a review issue and that the Applicant should make a good faith effort to acquire protocols and the original clinical data from the studies.
 - d. The Applicant sought approval of neostigmine only for the reversal of neuromuscular blocking agents and not for the other indication currently listed on the current product label. The Division encouraged the Applicant to pursue approval for those other indications (e.g., myasthenia crisis, central anticholinergic syndrome) as well, if only in a subsequent fashion after an NDA was submitted for the planned indication.
 - e. The safety analyses should focus on patients receiving neostigmine for the indication of reversal of the neuromuscular blocking effects of nondepolarizing muscle relaxants. However, the safety of neostigmine when used for other indications should also be included in the NDA, but should be easily identified as such; the safety analyses should be conducted with and without the supporting safety data.
2. The Division stated that the approach taken for the pediatric patient population PK, safety and efficacy data should be similar to that used for the adults and that information for each of these should be provided for each of the pediatric subpopulations:
 - a. Neonate (< 1 month)
 - b. Infant (1-24 months)
 - c. Child (pre-school) (2-6 years)
 - d. Child (school-age) (6-12 years)
 - e. Adolescent (12-16 years)

Furthermore, needed information that was not found or not adequately addressed in the literature would need to be supplemented by clinical trials in this patient population.

3. The Division indicated that if the drug product contains impurities, degradants, or leachables which exceed generally allowable levels and are not qualified for safety, it may be necessary to demonstrate that the proposed to-be-marketed product will not expose the public to a less safe version of neostigmine than other products currently found on the market. It was specifically noted that any impurity or degradation product that exceeds ICH

- thresholds may need to be adequately qualified for safety as per ICHQ3A(R) and ICHQ3B(R) at the time of NDA submission. Adequate qualification would include:
- a. Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies) with the isolated impurity tested up to the limit dose for the assay.
 - b. Repeat dose toxicology of appropriate duration to support the proposed indication.
 - c. Any impurities or degradation products that contain structural alerts for mutagenicity may be held to more stringent standards of control.
 - d. Impurities greater than the ICHQ3B threshold can potentially be justified for the NDA through comparison against currently marketed products as can excipients provided the levels and duration of exposure for each are the same as or exceed that of neostigmine when administered at the proposed doses.
4. The Division also noted that neostigmine does not appear to have information related to genetic or reproductive toxicology to inform the product label. While normally required for approval, these studies will not be required pre-approval but would be Post-Marketing Requirements unless sufficient data is provided to address these concerns and allow for adequate labeling.
5. Submission of two exhibit batches for each of the two strengths of Neostigmine Methylsulfate Injection, USP would be sufficient to support a 505(b)(2) marketing application provided impurities and degradants are monitored and reported as per ICHQ3B. For impurities that contain a structural alert for mutagenicity, appropriate assay(s) will be needed to detect these substances at levels called for in ICHQ2.
6. To support the shelf life of the product the following points were made:
- a. Real-time data, obtained from testing only at $25 \pm 2^\circ \text{C}$, $60 \pm 5\%$ relative humidity (RH) through 6 months, and accelerated data, obtained from testing at $40 \pm 2^\circ \text{C}$, $75 \pm 5\%$ RH through 6 months may be acceptable for filing, but might not support a shelf life of 24 months.
 - b. Expiration dating will be assessed as per ICHQ1E during the NDA review and will be based on available real time primary and supporting stability data and statistical analysis evaluation, if applicable.
 - c. It was strongly recommend that the maximum available stability data for the primary stability batches be provided at the time of NDA submission as data submitted afterwards may not be reviewable within the time allotted by GRMP.
 - d. The following were also to be provided in the NDA submission:
 - Photostability data, as per ICHQ1B
 - Data on physicochemical compatibility with atropine, other co-administered drugs and diluents

- Data on particulates, neostigmine assay and levels of impurities/degradants.
- e. If the stability data for the registration and stability lots can be statistically pooled and support a 24-month shelf life, a 24-month shelf life may be requested in the NDA submission provided the formulation of the proposed drug product is the same as the currently marketed product and that the formulation and container closure system of the drug product in the marketing application are identical to the currently marketed product.
 - f. Expiration dating will be determined during the NDA review and will be based on ICH Q1E (Evaluation of Stability Data) requirements.
7. An in vitro physicochemical compatibility study should be conducted assessing the combinations of neostigmine and atropine and neostigmine and glycopyrrolate as these two anticholinergics are frequently mixed in the same syringe in clinical practice.
 8. A specification for osmolality for the drug product will need to be provided in the NDA.
 9. A list of all manufacturing and testing facilities, in alphabetical order, a statement about their cGMP status and whether they are ready for inspections at the time of NDA submission will need to be provided in the NDA submission. In addition, for each manufacturing site, a contact name, telephone number, facsimile number and email address will need to be provided along with specification of the responsibilities of each facility in the manufacturing process. Specification as to which sites are intended to be primary and which are to be alternate sites of production needs to be made.
 10. Facilities with unacceptable cGMP compliance may jeopardize the approvability of the NDA.
 11. All available Clinical Pharmacology information related to pharmacokinetics, distribution, metabolism, elimination, dose-response, and special populations (such as drug-drug interactions, hepatic impairment, renal impairment, elderly, gender, pediatrics, etc) needs to be summarized in the NDA. All aspects of Clinical Pharmacology information included under the Physician Labeling Rule for the content of the clinical pharmacology section of the label need to be addressed.
 12. In the absence of PK studies conducted with the to-be-marketed formulation, a biowaver will be required as per 505 (b)(2) regulations. The waver request can be restricted to the proposed indication and route of administration and may be justified by providing evidence that the to-be-marketed formulation was used in the PK or clinical studies cited in the literature. If the PK or

clinical literature articles did not use the to-be-marketed formulation, then an effort should be made to relate the formulations used in the clinical literature to the to-be-marketed formulation.

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

There were several inconsistencies related to the Applicant's referencing of the literature; however, 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 conducted by Drs. Edwin Jao and Prasad Peri. At the time this review was filed, there were several CMC issues waiting to be resolved each which needed to be satisfactorily addressed before they could recommend that the application be approved. Specifically, the following issues are pending resolution:

1. Reinspection of the manufacturing site(s) with confirmation by the Office of Compliance that CMC issues identified on the initial inspection have been appropriately resolved.
2. The environmental assessment needs to be submitted.
3. The drug substance manufacturing and controls (DMF (b) (4)) evaluation resulted in a letter being issued to the Applicant requiring several changes in the processes and requesting additional information needed to complete the CMC review. These included the following, for which a response from the Applicant has not been received:
 - a. Neostigmine (b) (4)
 - b. The Manufacture of Neostigmine (b) (4) needs to be included in section 5.3.10 Control of Critical Steps together with validated critical process parameters.
 - c. Control for residual (b) (4) in the drug substance specification, which should include the acceptance criterion and testing method, needs to be provided.
 - d. Acceptance criterion for (b) (4) need to be reduced to NMT (b) (4) %.
 - e. The names of the manufacturers, specifications, and representative certificate of analysis for the (b) (4) (b) (4) used as the container/closure system for the drug substance need to be provided.
 - f. Verification that all components of the (b) (4), (b) (4) conform to the pertinent 21 CFR requirements for direct food contact needs to be provided.

The CMC review team otherwise notes that the specifications for the drug substance are generally acceptable; the controls for impurities, which might be genotoxic, are acceptable for the proposed dosing regimen; and the batch release; stability data

support a retesting period of (b) (4) months; and the requested shelf life of 24 months is supported by historical and registration stability data.

4.2 Clinical Microbiology

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

4.3 Preclinical Pharmacology/Toxicology

The Pharmacology Toxicology review was conducted by Drs. Huiqing Hao and R. Daniel Mellon. The information below is taken from Dr. Mellon's secondary review in which he notes that no new toxicology studies for neostigmine were required to support approval of this NDA because of 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 provided to support the safety of the container closure, and drug product degradants. However, the levels of the preservative phenol in this drug product formulation exceed that of previously approved drug products administered as a single bolus injection. They defer to the clinical team to determine if the adequate clinical experience exists to justify the safety of the phenol levels in this product.

[Reviewer Note: An information request was issued to the Applicant asking how long they have marketed the phenol-containing product and how many units of that product have been sold. This information was needed to determine whether the clinical experience reflects enough exposure to the phenol to make an assessment to the risk it may pose. In an e-mail sent on September 5, 2012, the Applicant provided the following information:

We confirm that there is no change in the amount of phenol used in the formulation of registration batches for Neostigmine NDA 203629 as compared to the formulation of the historical batches. Further, a comparison of the two Neostigmine codes is shown in the table below:

Attribute	Product Code 38210	Product Code 38310
Neostigmine Methylsulfate	0.5 mg/mL	1.0 mg/mL
Phenol	4.5 mg/mL	4.5 mg/mL
Fill Volume	10 mL	10 mL

This information supplemented marketing data that were sent by e-mail on August 29, 2012:

We have been marketing these formulations for over 20 years. The distribution data for the past 10 years is provided in the table below:

Year	Neostigmine code 38210 (# of units)	Neostigmine code 38310 (# of units)	Neostigmine Total (# of units)
2002	(b) (4)		
2003			
2004			
2005			
2006			
2007			
2008			
2009			
2010			
2011			
2012 (year to date)			

Based on the information provided, if any safety issues related to the bolus administration of the amounts of phenol in the product exist, they would likely have been apparent by this point in time. It should be noted that the safety concern was related to the bolus administration of this dose of phenol; similar doses, and therefore daily exposures, are contained in approved products that are also 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, at the 2009 meeting, 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 assess these toxicities and render a recommendation for approval; however, they consider the data in the published literature inadequate to inform labeling. Therefore, they recommend that these studies be conducted as post-marketing 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. Lee 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 make no recommendation 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.

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, they note 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.

Neostigmine’s half life ranged from 77 to 113 minutes after a single intravenous administration. No information was submitted to characterize neostigmine pharmacokinetics by race or gender. The pharmacokinetic interaction between neostigmine and other drugs has not been studied. The pharmacokinetics of neostigmine in patients with hepatic impairment has not been studied. Neostigmine is metabolized by microsomal enzymes in the liver; therefore, they recommend it be used with caution when it is administered with other drugs which may alter the activity of metabolizing enzymes or transporters. The clearance in patients with impaired renal function is lower compared to patients with normal renal functions; therefore, they recommend that it should be used with caution in patients with impaired renal functions including elderly patients with declining renal function.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The Applicant did not conduct any clinical studies to assess the safety, efficacy or dosing requirements of neostigmine for the proposed indication. Instead, they submitted a number of published study reports containing data pertaining to the safety and efficacy of various dosing regimens of neostigmine when used for the reversal of the following non-depolarizing neuromuscular blocking agents (NMBAs):

- vecuronium
- pancuronium
- atracurium
- rocuronium
- cisatracurium
- tubocurarine

The literature submitted to the application was selected from the published study reports identified by two literature searches, one conducted in July 2011 and the other in May 2012. The Applicant conducted these searches through the PubMed web-based portal at <http://www.ncbi.nlm.nih.gov/sites/entrez> using the verbatim title search term “neostigmine.” Additional filters included “humans”, “clinical trials”, and “English text only”.

The date range, for the May 2012 search, was set for the past ten years, which also included the published literature since the cutoff for previous literature searches (July 2011). The search identified 52 articles which were screened by the Applicant for relevance by title and by reviewing the abstracts where abstracts were available. Articles not relevant to the indication for this application were excluded. The majority of these exclusions reported the use of neostigmine for regional or caudal anesthesia (n=40); the others were provided in the original NDA submission (n=3). This left nine articles that met the selection criteria for the update, the majority of which (8/9) used neostigmine as a comparator to the currently unapproved product, sugammadex.

The study reports for both literature searches were analyzed by the Applicant for safety and efficacy. Neither the original protocols nor the raw data from any of these studies were requested or obtained by the Applicant.

The following tables summarize the findings of literature search for reports of the efficacy of neostigmine for reversal of non-depolarizing neuromuscular blocking agents in adults and pediatric patients.

Table 1. Applicant's summary of neostigmine clinical efficacy studies in adults (based on Table 2.7.3-1 from the original NDA and Table 1 of the June 15, 2012, submission)

Citation	Number of Patients Exposed	Dose of neostigmine (mg) or (mg/kg)	Dose of Atropine or Glycopyrrolate (mg or µg/kg)	Agent(s) Reversed
■ Ostheimer (1)	305	2.5 mg	atropine (1.0 mg) glycopyrrolate (0.5 mg)	d-tubocurarine or pancuronium
■ Mirakhur et al. (2)	40	2.5 mg	atropine (1.2 mg) glycopyrrolate (0.5 mg)	tubocurarine or pancuronium
■ Brock-Utne (3)	20	2.5 mg 5.0 mg	glycopyrrolate (0.6 mg)	suxamethonium
■ Delisle and Bevan (4)	30	2.5 mg	atropine (1.6 mg)	pancuronium
Gencarelli and Miller (5)	29	0.005-0.03 mg/kg	Not reported	vecuronium or pancuronium
Harper et al. (6)	12	2.5 mg	atropine (7 or 14 µg/kg)	alcuronium
■ Salem and Ahearn (7)	115	5 mg	atropine (1.2 or 1.8 mg); glycopyrrolate (0.6 mg or 0.9 mg)	pancuronium

Citation	Number of Patients Exposed	Dose of neostigmine (mg) or (mg/kg)	Dose of Atropine or Glycopyrrolate (mg or µg/kg)	Agent(s) Reversed
Caldwell et al. (8)	19	0.07 mg/kg	atropine (1.2 mg)	vecuronium or atracurium
Jones et al. (9)	40	2.5 mg 5.0 mg	atropine (1.2 mg) 0.6 mg for subsequent doses	vecuronium
King et al. (10)	19	2.5 mg	atropine (1.2 mg)	tubocurarine
Goldhill et al. (11)	51	0.01 – 0.08 mg/kg	glycopyrrolate (0.2 mg)	pancuronium
Johnson and Harper (12)	26	0.01 – 0.04 mg/kg	atropine (0.4 mg/1.0 mg neostigmine)	vecuronium
Nagiub and Gomaa (13)	70	0.04 – 0.06 mg/kg	atropine (0.014-0.04 mg/kg)	pancuronium
Donati et al. (14)	14	0.01 – 0.04 mg/kg	atropine (0.6-10.0 µg/kg) glycopyrrolate (0.3-0.5 µg/kg)	atracurium

Citation	Number of Patients Exposed	Dose of neostigmine (mg) or (mg/kg)	Dose of Atropine or Glycopyrrolate (mg or µg/kg)	Agent(s) Reversed
Magorian, et al. (15)	30	0.07 mg/kg	glycopyrrolate (15µg/kg)	vecuronium
Wetterslev, et al. (16)	55	0.035 mg/kg	atropine (8.0 µg/kg) glycopyrrolate (7.0 µg/kg)	gallamine
Goldhill, et al. (17)	32	0.015 – 0.075 mg/kg	glycopyrrolate (dose not reported)	atracurium
Suresh, et al. (18)	32	0.015 – 0.075 mg/kg	glycopyrrolate (3.0-15.0 µg/kg)	atracurium
Koscielniak-Nielsen, et al. (19)	48	0.005 – 0.04 mg/kg	atropine (0.6-1.2 mg)	doxacurium
McCarthy et al. (20)	72	0.005 – 0.045 mg/kg	glycopyrrolate (dose not reported)	vecuronium
Orlowski and Pollard (21)	52	0.05 mg/kg	glycopyrrolate (0.01 mg/kg)	vecuronium

Citation	Number of Patients Exposed	Dose of neostigmine (mg) or (mg/kg)	Dose of Atropine or Glycopyrrolate (mg or µg/kg)	Agent(s) Reversed
Van den Broek et al. (22)	40	0.04 mg/kg	methyl-atropine (7.0µg/kg)	rocuronium
Boeke et al. (23)	40	1.5 mg	atropine (0.5mg)	vecuronium
Harper et al. (24)	57	0.02 – 0.08 mg/kg	atropine (0.4mg/1mg neostigmine)	atracurium
Nielsen et al. (1995) (25)	45	0.035 – 0.070 mg/kg	atropine (14-28 µg/kg)	atracurium or vecuronium
Nielsen et al. (1995) (26)	46	0.036 mg/kg	atropine (14µg/kg)	vecuronium
Caldwell et al. (27)	60	0.02 – 0.04 mg/kg	glycopyrrolate (4.0 or 8.0µg/kg)	vecuronium

Citation	Number of Patients Exposed	Dose of neostigmine (mg) or (mg/kg)	Dose of Atropine or Glycopyrrolate (mg or µg/kg)	Agent(s) Reversed
Baurain et al. (1996a) (28)	56	0.04 mg/kg	atropine (15µg/kg)	atracurium vecuronium rocuronium pancuronium
Baurain et al. (1996b) (29)	54	0.02 – 0.08 mg/kg	atropine (15µg/kg)	vecuronium
Dhonneur et al. (30)	80	0.04 mg/kg	atropine (20µg/kg)	vecuronium
Kirkegaard-Nielsen et al. (31)	83	0.07 mg/kg	atropine (28µg/kg)	atracurium
Hovorka et al. (32)	80	2.0 mg	glycopyrrolate (0.4mg)	mivacurium
Lessard et al. (33)	70	0.010 – 0.04 mg/kg	glycopyrrolate (0.25, 0.5, or 1.0mg)	mivacurium

Citation	Number of Patients Exposed	Dose of neostigmine (mg) or (mg/kg)	Dose of Atropine or Glycopyrrolate (mg or µg/kg)	Agent(s) Reversed
Fuchs-Buder et al. (34)	24	0.02 mg/kg	atropine (10µg/kg)	vecuronium
Morita et al. (35)	90	0.04 mg/kg	atropine (15µg/kg)	vecuronium
Joshi et al. (36)	40	2.5 mg	glycopyrrolate (0.5mg)	mivacurium or rocuronium
McCourt et al. (1999a) (37)	36	0.05 mg/kg	glycopyrrolate (10µg/kg)	rapacuronium with and without rocuronium
McCourt et al. (1999b) (38)	110	0.02 – 0.05 mg/kg	glycopyrrolate (10µg/kg); atropine (20µg/kg)	rocuronium

Citation	Number of Patients Exposed	Dose of neostigmine (mg) or (mg/kg)	Dose of Atropine or Glycopyrrolate (mg or µg/kg)	Agent(s) Reversed
Lien et al. (39)	8	0.05 mg/kg	glycopyrrolate (10µg/kg)	mivacurium
Purdy et al. (40)	117	0.05 – 0.07 mg/kg	glycopyrrolate (0.01mg/kg)	rapacuronium
Bevan et al. (41)	80	0.07 mg/kg	glycopyrrolate 0.01mg/kg; atropine (0.02 mg/kg)	rocuronium or vecuronium
Reid et al. (42)	120	0.05 mg/kg	glycopyrrolate (10µg/kg)	rocuronium
Hayes et al. (43)	15	0.05 mg/kg	Not reported	rapacuronium

Citation	Number of Patients Exposed	Dose of neostigmine (mg) or (mg/kg)	Dose of Atropine or Glycopyrrolate (mg or µg/kg)	Agent(s) Reversed
Larijani et al. (44)	119	0.05 mg/kg	glycopyrrolate (10µg/kg)	rapacuronium
Kirkegaard-Nielsen et al. (45)	20	0.07 mg/kg	glycopyrrolate (15µg/kg)	cisatracurium
Tribuddharat et al. (46)	46	2.5 mg	atropine (0.9 or 1.2 mg)	vecuronium
Dahaba et al. (47)	24	0.05 mg/kg	glycopyrrolate (10µg/kg)	rocuronium
Carron et al. (48)	1	0.07 mg/kg	Atropine (15 µg/kg)	rocuronium
Gaszynski et al. (49)	35	0.05 mg/kg	Atropine (20 µg/kg)	rocuronium
Adamus et al. (50)	10	0.04 mg/kg	Atropine (20µg/kg)	rocuronium

Citation	Number of Patients Exposed	Dose of neostigmine (mg) or (mg/kg)	Dose of Atropine or Glycopyrrolate (mg or µg/kg)	Agent(s) Reversed
Illman et al. (51)	23	0.05 mg/kg	Glycopyrrolate (10µg/kg)	rocuronium
Schaller et al. (52)	45	0.005, 0.008, 0.015, 0.025, and 0.04 mg/kg	Glycopyrrolate (1µg/5µg neostigmine)	rocuronium
Lederer et al. (53)	40	0.03 and 0.05 mg/kg	Glycopyrrolate (7 and 10µg/kg)	rocuronium
Blobner et al. (54)	48	0.05 mg/kg	Glycopyrrolate (10µg/kg)	rocuronium
Khuenl-Brady et al. (55)	45	0.05 mg/kg	Glycopyrrolate (10µg/kg)	vecuronium

These studies were not considered in the evaluation of efficacy as they either focused on the effects of glycopyrrolate and atropine, did not have suitable comparators (e.g., sugammadex), or endpoints that did not include TOF assessments.

Table 2. Applicant's summary of neostigmine clinical efficacy studies in pediatric patients (Table 2.7.3-4 from the NDA)

Citation	Number of Patients Exposed	Dose of neostigmine (mg) or (mg/kg)	Dose of Atropine or Glycopyrrolate (mg or µg/kg)	Agent Reversed
Salem et al. (56)	20	0.05 mg/kg	atropine (20 µg/kg)	tubocurarine
Fisher et al. (57)	27	0.00625 – 0.025 mg/kg	atropine (30 µg/kg)	d-tubocurarine
Meistelman et al. (58)	24	0.03 mg/kg	atropine (10 µg/kg)	vecuronium
Debaene et al. (59)	18	0.03 mg/kg	atropine (10 µg/kg)	vecuronium
Gwinnutt et al. (60)	18	0.05 – 0.10 mg/kg	atropine (20 µg/kg)	atracurium
Bevan et al. (61)	48	0.005 – 0.060 mg/kg	atropine (0-15 µg/kg)	doxacurium or pancuronium

Citation	Number of Patients Exposed	Dose of neostigmine (mg) or (mg/kg)	Dose of Atropine or Glycopyrrolate (mg or µg/kg)	Agent Reversed
Kirkegaard-Nielsen et al. (1995) (62)	40	0.050 mg/kg	atropine (20 µg/kg)	atracurium
Abdulatif et al. (63)	40	0.01 – 0.05 mg/kg	atropine (5-20 µg/kg)	rocuronium
Bevan et al (1996) (64)	24	0.005 – 0.050 mg/kg	atropine (2,4,8 or 20 µg/kg)	mivacurium

* These studies were not considered in the evaluation of efficacy as they either focused on the effects of glycopyrrolate and atropine, did not have suitable comparators (e.g., sugammadex), or endpoints that did not include TOF assessments.

The following tables were provided by the Applicant as a listing of their search of the literature for reports of the safety of neostigmine for reversal of non-depolarizing neuromuscular blocking agents in adults and pediatric patients.

Table 3. Applicant's summary of neostigmine clinical safety studies in adults (Table 2.7.4-1 from the NDA)

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. (1)	305	Safety assessment between atropine and glycopyrrolate	2.5 mg	atropine (1.0 mg) glycopyrrolate (0.5 mg)	d-tubocurarine or pancuronium
Mirakhur et al. (2)	40	Safety assessment between atropine and glycopyrrolate	2.5 mg	atropine (1.2 mg) glycopyrrolate (0.5 mg)	tubocurarine or pancuronium
Brock-Utne et al. (3)	20	Lower esophageal tone	2.5 mg 5.0 mg	glycopyrrolate (0.6 mg)	suxamethonium
Salem et al. (7)	115	Postoperative heart rate and oral secretions	5 mg	atropine (1.2 or 1.8 mg); glycopyrrolate (0.6 mg or 0.9 mg)	pancuronium
King et al. (10)	19	Incidence of postoperative nausea and vomiting	2.5 mg	atropine (1.2 mg)	tubocurarine
Goldhill et al. (11)	51	Incidence of dysrhythmias, abnormal heart rate and BP	0.01 – 0.08 mg/kg	glycopyrrolate (0.2 mg)	pancuronium
Johnson et al. (12)	26	ECG, and arterial pressure	0.01 – 0.04 mg/kg	atropine (0.4 mg/1.0 mg neostigmine)	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
Naguib and Gomaa (13)	70	Change in heart rate via ECG	0.04 – 0.06 mg/kg	atropine (0.014-0.04 mg/kg)	pancuronium
Wetterslev et al. (65)	55	Change in heart rate via ECG	0.035 mg/kg	atropine (8.0 µg/kg) glycopyrrolate (7.0 µg/kg)	gallamine
Suresh et al. (18)	32	Dose response to cardiovascular changes	0.015 – 0.075 mg/kg	glycopyrrolate (3.0-15.0 µg/kg)	atracurium
Van den Broek et al. (66)	40	Cardiovascular safety and rate of recovery from neuromuscular block	0.04 mg/kg	methyl-atropine (7.0µg/kg)	rocuronium
Boeke et al. (23)	40	Incidence of postoperative nausea and vomiting	1.5 mg	atropine (0.5mg)	vecuronium
Harper et al. (24)	57	Monitoring of vital signs, ECG, capnography and pulse oximetry	0.02 – 0.08 mg/kg	atropine (0.4mg/1mg neostigmine)	atracurium
Caldwell et al. (27)	60	Monitoring of ECG and non-invasive MAP	0.02 – 0.04 mg/kg	glycopyrrolate (4.0 or 8.0µg/kg)	vecuronium
Dhonneur et al. (30)	80	Effect of renal failure on reversal from neuromuscular block	0.04 mg/kg	atropine (20µg/kg)	vecuronium

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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. (32)	80	Incidence of postoperative nausea and vomiting	2.0 mg	glycopyrrolate (0.4mg)	mivacurium
Lessard et al. (33)	70	Monitoring of ECG, pulse oximetry and non-invasive MAP	0.010 – 0.04 mg/kg	glycopyrrolate (0.25, 0.5, or 1.0mg)	mivacurium
Fuchs-Buder et al. (34)	24	Incidence of bradycardia	0.02 mg/kg	atropine (10µg/kg)	vecuronium
Joshi et al. (36)	40	Incidence of postoperative nausea and vomiting	2.5 mg	glycopyrrolate (0.5mg)	mivacurium or rocuronium
McCourt et al. (37)	36	Monitoring of ECG, pulse oximetry and non-invasive MAP	0.05 mg/kg	glycopyrrolate (10µg/kg)	rapacuronium with and without rocuronium
McCourt et al. (38)	110	Incidence of emetic symptoms	0.02 – 0.05 mg/kg	glycopyrrolate (10µg/kg); atropine (20µg/kg)	rocuronium
Purdy et al. (40)	117	Postanesthetic AEs and SAEs	0.05 – 0.07 mg/kg	glycopyrrolate (0.01mg/kg)	rapacuronium

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
Bevan et al. (41)	80	Monitoring of ECG, pulse oximetry and non-invasive MAP	0.07 mg/kg	glycopyrrolate 0.01mg/kg; atropine (0.02 mg/kg)	rocuronium or vecuronium
Hayes et al. (43)	15	Monitoring of ECG, pulse oximetry and non-invasive MAP	0.05 mg/kg	Not reported	rapacuronium
Larijani et al. (44)	119	Heart rate and incidence of bronchospasm	0.05 mg/kg	glycopyrrolate (10µg/kg)	rapacuronium
Tribuddharat et al. (46)	46	Role of different doses of atropine on cardiovascular effects	2.5 mg	atropine (0.9 or 1.2 mg)	vecuronium
Symington et al. (67)	10	Monitoring of ECG, pulse oximetry and non-invasive MAP	0.04 mg/kg	glycopyrrolate (10 µg/kg)	mivacurium
Sacan et al. (68)	20	Monitoring of ECG, and non-invasive MAP	0.07 mg/kg	glycopyrrolate (14µg/kg)	rocuronium
Jones et al. (69)	37	PE, vital signs, AEs, SAEs, blood chemistry	0.07 mg/kg	glycopyrrolate (14µg/kg)	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
Flockton et al. (70)	39	PE, vital signs, AEs, SAEs, blood chemistry	0.05 mg/kg	glycopyrrolate (10µg/kg)	cisatracurium

Table 4. Applicant's summary of neostigmine clinical safety studies in pediatric patients (Table 2.7.4-3 from the NDA)

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
Salem et al. (56)	20	Hemodynamic response to atropine-neostigmine antagonism of neuro-muscular block	0.05 mg/kg	atropine (20 µg/kg)	tubocurarine
Debaene et al. (71)	18	Monitoring of ECG, pulse oximetry and non-invasive MAP	0.03 mg/kg	atropine (10 µg/kg)	vecuronium
Gwinnutt et al. (60)	18	Monitoring of ECG, pulse oximetry and non-invasive MAP	0.05 – 0.10 mg/kg	atropine (20 µg/kg)	atracurium

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 meaningful efficacy data as well as 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 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 are summarized in section 9 where those that were considered pivotal are described in greater detail.

6 Review of Efficacy

Efficacy Summary

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 at 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 10 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.
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% ($\text{TOF}_{0.9}$) 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.

The clinical benefit 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:

Neostigmine Methylsulfate Injection is indicated for reversal of nondepolarizing neuromuscular blocking agents.

(b) (4)

(b) (4)

6.1.1 Methods

Background

In general, the goal in reversing an 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 H₂O
 - Tidal volume > 5 mL/kg
 - Vital capacity > 10 mL/kg
 - Respiratory rate < 30 breaths/min
 - Appropriate oxygen saturation and end-tidal CO₂ 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 fourth 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.

In the literature, a TOF ratio of 0.7 ($\text{TOF}_{0.7}$) was often used as the "gold standard" cut-off point for adequate reversal of an NMBA to allow resumption of spontaneous ventilation and maintenance of a patent airway. However, Eriksson and colleagues (72,73) 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 (74) found that pharyngeal dysfunction and aspiration (defined as laryngeal penetration by secretions) occur with partial paralysis by vecuronium when the TOF ratio is less than 90% as measured at the adductor pollicis following ulnar nerve stimulation.

The adequacy of TOF_{0.7} is further challenged by the findings of Eikermann et al. (75) 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 (FIV₁), peak expiratory force (PEF), and peak inspiratory force (PIF). A clinically relevant ($\geq 10\%$) 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. (76) 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 [$\text{MEF}_{50}/\text{MIF}_{50}$] > 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 $\geq 10\%$ 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. (77) 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 retropharyngeal and retroglottal 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.

Lastly, Berg et al. (78) examined the effect of residual neuromuscular block on the incidence of postoperative pulmonary complications (POPC). Specifically, they evaluated POPC following the use of pancuronium, atracurium, and vecuronium. Defining residual block as a TOF ratio < 0.7 , they found its incidence to be significantly higher in the pancuronium group (26%) than in the atracurium/vecuronium groups (5%). In the pancuronium group, more patients with residual block developed POPC (17%) as compared to patients without residual block (5%). In the atracurium/vecuronium groups, the incidence of POPC was not significantly different in patients with or without residual block, 4% and 5%, respectively. Using multiple regression analysis the authors found that abdominal surgery, age, longer duration of surgery, and a TOF ratio < 0.7 following the use of pancuronium were potential risk factors for the development of POPC.

Based on the information above, 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}) may be a more clinically relevant end-point for defining adequate recovery of neuromuscular transmission than TOF_{0.7}.

Based on the information above, 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.

Overall Efficacy

The Applicant has submitted a number of clinical studies published in the literature that they purport demonstrate the efficacy of neostigmine for reversing neuromuscular blockade induced by nondepolarizing NMBAs. These studies include placebo-controlled and dose-controlled studies, some of which evaluated pediatric or geriatric

patients. The Applicant did not identify any of these studies as pivotal or perform any efficacy analyses of the studies or the data contained within them.

For the purposes of this review, I have identified 11 studies reported in the literature that can be considered as pivotal, i.e., prospective, randomized, controlled studies involving recovery of the TOF ratio to 90%. These studies are listed in the table below. In Section 9.1 of this review, the methods, endpoints and results of these and other studies relevant to safety, efficacy or pharmacokinetics/pharmacodynamics are described in more detail.

Table 5. Summary of the pivotal studies from the literature to support efficacy.

Source	NMBA Reversed	Dose(s) of Neostigmine (mcg/kg)	Comparator(s)	Study Population
Abdulatif (63)	Rocuronium	5	Spontaneous recovery and a range of neostigmine doses	Pediatric and adult
		10		
		20		
		50		
Baurain (28)	Rocuronium	40	Different neuromuscular blocking agents	Adults
	Vecuronium			
	Atracurium			
	Pancuronium			
Baurain (29)	Vecuronium	20	Doses of neostigmine and timing of administration based on extent of spontaneous recovery	Adults
		40		
		80		
Bevan (41)	Rocuronium	70	Timing of administration based on extent of spontaneous recovery	Pediatric and adult
	Vecuronium	70		
Caldwell (27)	Vecuronium	40	Timing of administration based on time lapsed after vecuronium administration	Adults
Goldhill (17)	Atracurium	15	Spontaneous recovery and a range of neostigmine doses	Adults
		35		
		55		
		75		
Lederer (53)	Rocuronium	30	Spontaneous recovery and two neostigmine doses	Adults
		50		
McCourt (37)	Rapacuronium boluses	50	Spontaneous recovery	Adults
	Rapacuronium infusion			
	Rocuronium			
Meistelman (58)	Vecuronium	30	Timing of administration based on extent of spontaneous recovery	Adults
Sacan (68)	Rocuronium	70	Edrophonium and sugammadex	Adults

Source	NMBA Reversed	Dose(s) of Neostigmine (mcg/kg)	Comparator(s)	Study Population
Schaller (52)	Rocuronium	5	Placebo and a range of neostigmine doses	Adults
		8		
		15		
		25		
		40		

The studies provided the following evidence of efficacy:

1. Neostigmine significantly reduced recovery time to TOF_{0.9} compared to placebo or spontaneous recovery.
2. A dose effect was demonstrated for neostigmine; however, there appears to be an upper limit beyond which additional neostigmine does not hasten the recovery, i.e., the dose-response curve plateaus.
3. The extent to which neostigmine shortened recovery times varied due to a number of factors; however, the range appears to be on the order of 10 to 60 minutes, which is clinically relevant for reducing patient exposure to anesthetic medications as well as reducing the duration of mechanical ventilation and presence of an endotracheal tube.
4. Neostigmine reduced recovery times for all the nondepolarizing neuromuscular blocking agents assessed, although the extent of its effect was variable and appeared to be influenced by a number of factors:
 - a. Extent of spontaneous recovery at the time of its administration
 - b. Concurrent use of volatile anesthetic agents
 - c. Use of certain concomitant medications, e.g., some antibiotics, magnesium sulfate

6.1.2 Demographics

The Applicant did not perform an analysis of efficacy based on patient demographics.

In the studies reported in the literature, efficacy based on patient age was evaluated by several groups of investigators. Their findings are summarized below in section 6.1.7. 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 scores) of the patients although this information was generally captured. Most studies enrolled relatively healthy patients with ASA scores 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.

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.

6.1.4 Analysis of Primary Endpoint(s)

The Applicant did not perform an analysis of primary endpoints.

As indicated in section 6.1.1, reversal of neuromuscular blockade is most widely assessed, in both clinical practice and clinical research, by assessing the twitch response to a train of four (TOF) electrical impulses and comparing the ratio of the magnitude of the fourth twitch to that of the first. Furthermore, 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 $\geq 90\%$. 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%. In the literature, 11 articles described clinical studies assessed recovery to these higher TOF ratios. In the table below, the findings for those studies are summarized.

Table 6. Summary of the findings from the pivotal studies.

Source	NMBA Reversed	Dose of Neostigmine (mcg/kg)	Timing of Neostigmine Administration	Maximum TOF Reported (%)	Time to Maximum TOF (min)	Population
Abdulatif (63)	rocuronium	5	T ₁ = 10%	73	10	pediatric
		10	T ₁ = 10%	89	10	pediatric
		20	T ₁ = 10%	98	10	pediatric
		50	T ₁ = 10%	99	10	pediatric
		5	T ₁ = 10%	29	10	adults
		10	T ₁ = 10%	47	10	adults
		20	T ₁ = 10%	62	10	adults
Baurain (28)	rocuronium	40	T ₁ = 25%	90	15	adults
	vecuronium	40	T ₁ = 25%	88	15	adults
	atracurium	40	T ₁ = 25%	92	15	adults
	pancuronium	40	T ₁ = 25%	76	15	adults
Baurain (29)	vecuronium	20	T ₁ = 10%	76	15	adults
		20	T ₁ = 25%	85	15	adults
		20	T ₁ = 50%	92	15	adults
		40	T ₁ = 10%	86	15	adults
		40	T ₁ = 25%	86	15	adults
		40	T ₁ = 50%	94	15	adults
		80	T ₁ = 10%	80	15	adults
		80	T ₁ = 25%	88	15	adults
Bevan (41)	rocuronium	70	T ₁ = 1%	90	< 20	pediatric
		70	T ₁ = 10%	90	< 20	pediatric
		70	T ₁ = 25%	90	< 25	pediatric
		70	T ₁ = 1%	90	< 30	adults
		70	T ₁ = 10%	90	< 30	adults
		70	T ₁ = 25%	90	< 40	adults
	vecuronium	70	T ₁ = 1%	90	< 30	pediatric

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Source	NMBA Reversed	Dose of Neostigmine (mcg/kg)	Timing of Neostigmine Administration	Maximum TOF Reported (%)	Time to Maximum TOF (min)	Population
		70	T ₁ = 10%	90	< 30	pediatric
		70	T ₁ = 25%	90	< 30	pediatric
		70	T ₁ = 1%	90	< 40	adults
		70	T ₁ = 10%	90	< 40	adults
		70	T ₁ = 25%	90	< 40	adults
Caldwell (27)	vecuronium	40	TOF = 29%	86	10	adults
Goldhill (17)	atracurium	15	T ₁ = 6%	90	16	adults
		35	T ₁ = 12%	90	10	adults
		55	T ₁ = 15%	90	10	adults
		75	T ₁ = 9%	90	10	adults
Lederer (53)	rocuronium	30	5 min. after rocuronium	90	23	adults
		50	5 min. after rocuronium	90	19	adults
McCourt (37)	rapacurium boluses	50	T ₁ = 25%	80	10	adults
	rapacurium infusion	50	T ₁ = 25%	80	9	adults
	rocuronium	50	T ₁ = 25%	80	6	adults
Meistelman (58)	vecuronium	30	T ₁ = 1%	80	12	adults
		30	T ₁ = 10%	100	8	adults
		30	T ₁ = 25%	100	5	adults
Sacan (68)	rocuronium	70	T ₁ = 12%	90	17	adults
Schaller (52)	rocuronium	5	TOF = 50%	90	9	adults
		8	TOF = 50%	90	5	adults
		15	TOF = 50%	90	4	adults
		25	TOF = 50%	90	3	adults
		40	TOF = 50%	90	2	adults

6.1.5 Analysis of Secondary Endpoints(s)

The Applicant provided no analysis of secondary endpoints and offered no rationale as to why these endpoints were not relevant to the application.

In the literature, there were a number of studies in which TOF ratios of > 70% were evaluated as secondary endpoints. These endpoints were analyzed and discussed in the reviews of individual studies where they were used as endpoints. These reviews can be found in section 9.1 below.

6.1.6 Other Endpoints

No other endpoints were analyzed by the Applicant.

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

The Applicant conducted no analyses on patient sub populations.

The information below was derived from the literature submitted to the NDA regarding dosing requirements and efficacy of neostigmine in pediatric and geriatric patients.

Pediatric Patients

Neostigmine was evaluated for the reversal of a number of NMBAs in pediatric patients. The table below summarizes the data submitted by the Applicant for this patient population.

Table 7. Summary of efficacy data for neostigmine in pediatric patients

NMBA	Dose of Neostigmine (mcg/kg)	Number of Patients	Age Range (years)	When Administered	Efficacy Endpoints	Comments
Vecuronium (VCB)	31	24	2y - 8y	T ₁ had 1-25% recovery	Various TOF	Source: Meistelman et al. (58) TOF > 0.9 occurred at 10 min when neostigmine was given at T ₁ ≥ 0.1.
	70	40	2y - 6y	Spontaneous; 5 min after VCB; and T ₁ had 1-25% recovery	Various TOF	Source: Bevan et al. (41) Glycopyrrolate – 0.01 mg/kg TOF > 0.9 occurred at 30 min when neostigmine was given at T ₁ ≥ 0.1.

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NMBA	Dose of Neostigmine (mcg/kg)	Number of Patients	Age Range (years)	When Administered	Efficacy Endpoints	Comments
	30	8 10	3m – 10m 3y – 10y	$T_1 = 0.1$	Various TOF	Source: Debaene et al. (71) Atropine – 0.1 mg/kg TOF ≥ 0.9 occurred by 15 min.
Mivacurium	5 10 20 50	6 6 6 6	2y – 12y	$T_1 = 0.1$	T_1 and TOF	Source: Bevan et al. (64) Atropine - 2, 4, 8 or 20 mcg/kg TOF ≥ 0.75 occurred by 10 min for doses of neostigmine ≥ 10 mcg/kg, which was significantly faster than spontaneous recovery.

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NMBA	Dose of Neostigmine (mcg/kg)	Number of Patients	Age Range (years)	When Administered	Efficacy Endpoints	Comments
Atracurium	50	6	3y - 9y	PTC ₁ = 0.1	TOF _{0.8}	Source: Gwinnutt et al. (60) Atropine - 0.02 mg/kg TOF = 0.8 at 14 and 12 min after 50 and 10 mcg/kg neostigmine doses, respectively, at PTC ₁ = 0.1 and at 5 min after 50 mcg/kg ginve at T ₁ = 0.1
	10	6	1y - 8y	PTC ₁ = 0.1		
	50	6	1y - 7y	T ₁ = 0.1		
	50	40	0 - <16y	T ₁ = 0.1	T ₁ and TOF	Source: Kirkegaard-Nielson et al. (79) Atropine - 0.02 mg/kg <1y recovered fastest with TOF _{0.9} at 10 min. ≥2y had TOF _{0.9} at 15 min.

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NMBA	Dose of Neostigmine (mcg/kg)	Number of Patients	Age Range (years)	When Administered	Efficacy Endpoints	Comments
Rocuronium (RCB)	5 10 20 50	8 8 8 8	2y – 10y	T ₁ = 0.1	TOF	Source: Abdulatif et al. (63) Atropine - 5-20 mcg/kg TOF _{0.9} was < 10 min for the 2 highest doses; slightly > 10 min for the 0.1 dose and not reached by 10 min for the lowest dose of neostigmine.
	70	40	2y – 12y	Spontaneous; 5 min after RCB; and T ₁ had 1-25% recovery	TOF _{0.9}	Source: Bevan et al. (41) Glycopyrrolate - 0.1 mg/kg When neostigmine was administered at T ₁ =0.1, TOF _{0.9} was reached at 20 min.

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NMBA	Dose of Neostigmine (mcg/kg)	Number of Patients	Age Range (years)	When Administered	Efficacy Endpoints	Comments
Cis-atricurium						No pediatric information provided
d-Tubocurarine (dTc)	6.25 12.5 25 6.25 12.5 25	4 4 4 5 5 5	3 wk – 4 m 1y – 8y	Neostigmine was administered during dTc infusion after T ₁ was constant for 15 minutes. Infusion was continued after neostigmine was administered	Time to 70% of peak antagonism	Source: Fisher et al. (57) Atropine - 5, 10 or 20 mcg/kg for corresponding low to high doses of neostigmine For both age groups, the lower doses of neostigmine required 7-9 min for reversal; for the highest neostigmine dose, reversal required 5 min for both age groups.

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NMBA	Dose of Neostigmine (mcg/kg)	Number of Patients	Age Range (years)	When Administered	Efficacy Endpoints	Comments
Pancuronium						No pediatric information provided

Although there were no data to support the use of neostigmine in this patient population following the administration of pancuronium bromide or cisatracurium, the evidence for the other NMBAs strongly suggest that neostigmine would be effective at reversing these agents as well.

Geriatric Patients

Data from studies of geriatric patients indicate they have either a similar or greater dosing requirement than younger adults.

Koscielniak-Nielsen et al. (80) conducted a clinical study evaluating the dose-response relationships for doxacurium and neostigmine in 24 young (18-40 yr) and 24 elderly (70-85 yr) patients. At the end of surgery, neostigmine (5, 10, 20, or 40 mcg/kg) was injected at 25% recovery of the first twitch (T_1) in a TOF. Neuromuscular monitoring was continued for the next 10 minutes. Neostigmine-assisted recovery was not significantly different for the two age groups. The estimated doses of neostigmine to obtain $TOF_{0.7}$ after 10 min were also not significantly different: 54 ± 8 mcg/kg in the young and 42 ± 6 mcg/kg in the elderly.

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.

McCarthy et al. (20) examined the dose-response relationship for neostigmine in 36 adult (ages 18-50 yr) and 36 elderly (ages > 70 yr) patients presenting for elective ophthalmic surgery under general anesthesia. Neostigmine doses included 5, 15, 25, 35, and 45 mcg/kg. The TOF values at 1-minute intervals from 5 minutes post-study drug administration onwards were used to determine the dose-response relationships.

The difference in the time to spontaneous recovery of T_1 to 10% between the two treatment groups was significant: 24 minutes (SD = 6) and 33 minutes (SD = 8) for the younger and older adults, respectively.

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

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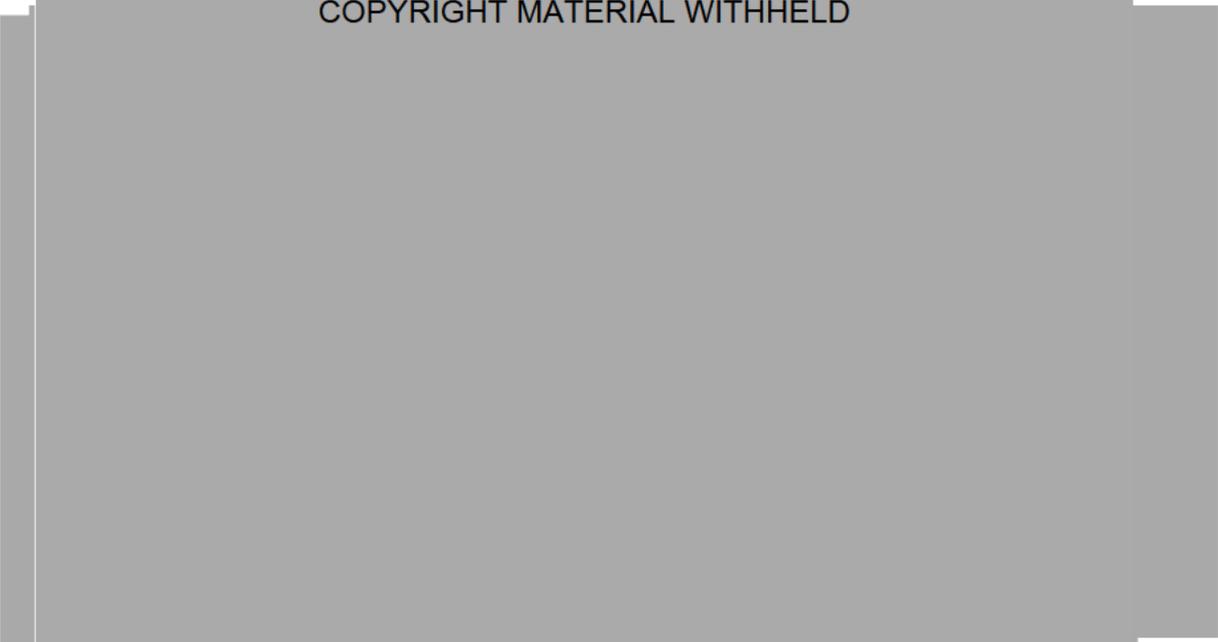


Figure 1. Dose-response curves for TOF ratios at 10 min after administration of neostigmine in adults and the elderly. Mean TOF ratios attained with each dose and the SD bars are shown. (Figure 1 on p. 282 of the article)

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, suggesting either a lesser relative potency or an increased dosing requirement of neostigmine by the elderly for antagonizing the neuromuscular blocking effects of vecuronium. Furthermore, the TOF ratios for the two treatment groups showed that increasing doses of neostigmine were associated with faster recovery in both adult and elderly groups; however, 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.

In summary, the results of this study indicated that the 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 and suggests that the elderly may require about twice the dose of neostigmine to achieve the same TOF ratio as younger adults at 10 minutes.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Applicant did not perform an analysis to identify specific dosing recommendations.

As indicated in section 6.1.1, reversal of neuromuscular blockade is most widely assessed, in both clinical practice and clinical research, by assessing the twitch response to a train of four (TOF) electrical impulses and comparing the ratio of the magnitude of the fourth twitch to that of the first. Furthermore, 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 $\geq 90\%$. 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%. In the literature, 11 articles described clinical studies assessed recovery to these higher TOF ratios. In the table 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 (63)	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 (28)	rocuronium	40	T ₁ = 25%	90	TOF ratio assessed at 15 min after T ₁ = 25%	adults
	vecuronium			88		
	atracurium			92		
	pancuronium			76		
Baurain (29)	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		
Bevan (41)	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	

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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 (41)	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 (27)	vecuronium	40	TOF = 29%	86	10	adults
Goldhill (17)	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 (53)	rocuronium	Spont. recovery	--	90	39	adults
		30	5 min. after rocuronium		23	
		50			19	
McCourt (37)	rapacurium boluses	Spont. recovery	--	80	72	adults
		50	T ₁ = 25%		10	
	rapacurium infusion	Spont. recovery	--		66	adults
		50	T ₁ = 25%		9	
	rocuronium	Spont. recovery	--		37	adults
50		T ₁ = 25%	6			
Meistelman (58)	vecuronium	30	T ₁ = 1%	80	12	adults
			T ₁ = 10%	100	8	adults
			T ₁ = 25%	100	5	adults

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Source	NMBA Reversed	Dose of Neostigmine (mcg/kg)	Timing of Neostigmine Administration	Maximum TOF Reported (%)	Time to TOF assessment or Maximum TOF (min)	Population
Sacan (68)	rocuronium	70	T ₁ = 12%	90	17	adults
Schaller (52)	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%	90	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 indicated that lower doses of neostigmine are adequate when more substantial levels of spontaneous recovery have occurred. Lastly, there is 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 NMBAs, 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 40 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 40 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

The Applicant provided no information addressing either of these issues.

Regarding persistence of efficacy, 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. With a half-life estimated to be between 77 and 113 minutes, the effects of neostigmine 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. 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; the interactions of other drug product that can affect the intensity or duration of neuromuscular blockade, e.g., volatile anesthetic agents and some antibiotics; and 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, its acute use in the perioperative and, occasionally, the intensive care unit settings limits the likelihood of this occurrence. 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.

6.1.10 Additional Efficacy Issues/Analyses

No additional efficacy issues were identified in the course of this review and no additional analyses were performed.

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.(81) The safety of 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 Adverse Event Reporting System, which was performed by 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 exerting its reversal 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 at the peripheral nervous system via the autonomic ganglia and adrenal medulla. However, the muscarinic side-effects of anticholinesterases tend to predominate and 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.(81) 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 in the practice of anesthesia. The Applicant has provided a substantial amount of clinical data that support the use of these two agents in this manner. 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.

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.

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; the review team from the Division of Pharmacovigilance II in the Office of Surveillance and Epidemiology performed the analysis of the AERS data and also conducted their own search and analysis of the published.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The literature provided by the Applicant that assessed the safety of neostigmine includes numerous clinical studies involving the drug administered in combination with varying doses of atropine or glycopyrrolate. The table below identifies the studies along with the doses of neostigmine and the anticholinergic evaluated.

Table 9. Clinical studies evaluating the safety of neostigmine in adults (based on Table 2.7.4-1 in the original NDA submission)

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., (1977)(1)	305	Safety assessment between atropine and glycopyrrolate	2.5 mg	atropine (1.0 mg) glycopyrrolate (0.5 mg)	d-tubocurarine or pancuronium
MIRAKHUR ET AL., (1977)(2)	40	Safety assessment between atropine and glycopyrrolate	2.5 mg	atropine (1.2 mg) glycopyrrolate (0.5 mg)	tubocurarine or pancuronium
BROCK-UTNE ET AL., (1978)(82)	20	Lower esophageal tone	2.5 mg 5.0 mg	glycopyrrolate (0.6 mg)	suxamethonium
SALEM ET AL., (1986)(7)	115	Postoperative heart rate and oral secretions	5 mg	atropine (1.2 or 1.8 mg); glycopyrrolate (0.6 mg or 0.9 mg)	pancuronium

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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
KING ET AL., (1988)(10)	19	Incidence of postoperative nausea and vomiting	2.5 mg	atropine (1.2 mg)	tubocurarine
GOLDHILL ET AL., (1988)(11)	51	Incidence of dysrhythmias, abnormal heart rate and BP	0.01 – 0.08 mg/kg	glycopyrrolate (0.2 mg)	pancuronium
JOHNSON ET AL., (1989)(12)	26	ECG, and arterial pressure	0.01 – 0.04 mg/kg	atropine (0.4 mg/1.0 mg neostigmine)	vecuronium
NAGIUB ET AL., (1989)(13)	70	Change in heart rate via ECG	0.04 – 0.06 mg/kg	atropine (0.014-0.04 mg/kg)	pancuronium
WETTERSLEV ET AL., (1991)(65)	55	Change in heart rate via ECG	0.035 mg/kg	atropine (8.0 µg/kg) glycopyrrolate (7.0 µg/kg)	gallamine
SURSESH ET AL., (1991)(18)	32	Dose response to cardiovascular changes	0.015 – 0.075 mg/kg	glycopyrrolate (3.0-15.0 µg/kg)	atracurium
VANDENBROEKE ET AL., (1994)(66)	40	Cardiovascular safety and rate of recovery from neuromuscular block	0.04 mg/kg	methyl-atropine (7.0µg/kg)	rocuronium
BOEKE ET AL., (1994)(23)	40	Incidence of postoperative nausea and vomiting	1.5 mg	atropine (0.5mg)	vecuronium
HARPER ET AL., (1994)(24)	57	Monitoring of vital signs, ECG, capnography and pulse oximetry	0.02 – 0.08 mg/kg	atropine (0.4mg/1mg neostigmine)	atracurium

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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
CALDWELL ET AL., (1995)(27)	60	Monitoring of ECG and non-invasive MAP	0.02 – 0.04 mg/kg	glycopyrrolate (4.0 or 8.0µg/kg)	vecuronium
DHONNEUR ET AL., (1996)(30)	80	Effect of renal failure on reversal from neuromuscular block	0.04 mg/kg	atropine (20µg/kg)	vecuronium
HOVORKA ET AL., (1997)(32)	80	Incidence of postoperative nausea and vomiting	2.0 mg	glycopyrrolate (0.4mg)	mivacurium
LESSARD ET AL., (1997)(33)	70	Monitoring of ECG, pulse oximetry and non-invasive MAP	0.010 – 0.04 mg/kg	glycopyrrolate (0.25, 0.5, or 1.0mg)	mivacurium
FUCHS-BUDER ET AL., (1999)(34)	24	Incidence of bradycardia	0.02 mg/kg	atropine (10µg/kg)	vecuronium
JOSHI ET AL., (1999)(36)	40	Incidence of postoperative nausea and vomiting	2.5 mg	glycopyrrolate (0.5mg)	mivacurium or rocuronium
MCCOURT ET AL., (1999)(37)	36	Monitoring of ECG, pulse oximetry and non-invasive MAP	0.05 mg/kg	glycopyrrolate (10µg/kg)	rapacuronium with and without rocuronium
MCCOURT ET AL., (1999)(38)	110	Incidence of emetic symptoms	0.02 – 0.05 mg/kg	glycopyrrolate (10µg/kg); atropine (20µg/kg)	rocuronium
PURDY ET AL., (1999)(40)	117	Postanesthetic AEs and SAEs	0.05 – 0.07 mg/kg	glycopyrrolate (0.01mg/kg)	rapacuronium

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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
BEVAN ET AL., (1999)(41)	80	Monitoring of ECG, pulse oximetry and non-invasive MAP	0.07 mg/kg	glycopyrrolate 0.01mg/kg; atropine (0.02 mg/kg)	rocuronium or vecuronium
HAYES ET AL., (2000)(43)	15	Monitoring of ECG, pulse oximetry and non-invasive MAP	0.05 mg/kg	Not reported	rapacuronium
LARIJANI ET AL., (2001)(44)	119	Heart rate and incidence of bronchospasm	0.05 mg/kg	glycopyrrolate (10mcg/kg)	rapacuronium
TRIBUDDHAR AT ET AL., (2008)(46)	46	Role of different doses of atropine on cardiovascular effects	2.5 mg	atropine (0.9 or 1.2 mg)	vecuronium

Table 10. Clinical studies evaluating the safety of neostigmine in pediatric patients (based on Table 2.7.4-3 in the original NDA submission)

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
SALEM ET AL., (1977)(56)	20	Hemodynamic response to atropine-neostigmine antagonism of neuromuscular block	0.05 mg/kg	atropine (20 µg/kg)	tubocurarine
DEBAENE ET AL. (1989)(71)	18	Monitoring of ECG, pulse oximetry and non-invasive MAP	0.03 mg/kg	atropine (10 µg/kg)	vecuronium
GWINNUTT ET AL., (1991)(60)	18	Monitoring of ECG, pulse oximetry and non-invasive MAP	0.05 – 0.10 mg/kg	atropine (20 µg/kg)	atracurium

7.1.2 Categorization of Adverse Events

The Applicant did not group or categorize adverse events. As the events were reported in the literature and the original data were not retrieved, the Applicant reported the events as described in the publications. No analyses of adverse events were performed by the Applicant, including summaries or incidence rates of the adverse events reported in the literature.

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

No attempt was made by the Applicant to pool data across studies or to estimate and compare incidence of adverse events. While such an analysis may be possible, the results would likely be difficult, if not impossible, to interpret due to the number of confounding factors affecting safety both within and among the studies, e.g., anesthetic agents, 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 Applicant did not analyze the available safety data to determine overall exposure, exposure at clinically relevant doses or the demographics of the exposed population. Based on Table 2.7.4-1 in the original NDA submission, 26 articles were identified by the Applicant as providing clinical safety information. These articles provided a database of 1,747 adult patients who were exposed to neostigmine in doses ranging from 10 mcg/kg to 80 mcg/kg. This population included a substantial numbers of both male and female patients as well as geriatric patients. Race of the patients was rarely reported. Similarly, Table 2.7.4-3 in the original NDA submission listed three studies in which clinical safety was assessed in a total of 56 pediatric patients.

7.2.2 Explorations for Dose Response

The Applicant did not conduct an exploration for dose responses of adverse events. Although such an exploration is possible, the data to do so are limited and confounded by a number of factors including the use of anticholinergic agents in various doses to mitigate or prevent the acetylcholine related adverse events and the concurrent use of anesthetic agents that have similar adverse event profiles.

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.

7.2.5 Metabolic, Clearance, and Interaction Workup

As noted in the Clinical Pharmacology review by Drs. Lee 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. (1979)(83), 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-life for normal, transplant and anephric patients were 80 ± 49 , 105 ± 64 and 181 ± 54 min (mean \pm SD), respectively. Clearances for normal, transplant and anephric patients were 17 ± 5 , 19 ± 6 and 8 ± 3 mL/min/kg (mean \pm 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, fasciculations.
Miscellaneous:	Increased urinary frequency and incontinence, diaphoresis.

7.3 Major Safety Results

7.3.1 Deaths

The Applicant reviewed historical reports in the literature dating back to 1949 and identified 3 reports of acute cardiac arrest and death in anaesthetized patients following the rapid intravenous administration of neostigmine. The etiologies of these deaths were attributed to the rapid administration of neostigmine leading to bradycardia or inappropriate timing of administration of an anticholinergic agent (atropine).

The table below presents a summary of the deaths. The Applicant did not attempt to secure access to the raw data from these reports; therefore, no case report forms (CRFs) or patient narratives were submitted.

Table 11. Summary of deaths reported in the literature (Table 2.7.4-7 from original NDA submission)

Author (Year) Reference	Age	Sex	Neostigmine Dose (mg)	Diagnosis	Cause of Death	Other Medications	Other Medical Conditions
Clutton-Brock (1949) (84)	62 years	Female	2.0 mg	Common bile duct obstruction	Cardiac arrest	Atropine (0.65mg)	Intra-operative cardiac "irregularities"
Hill (1949) (85)	7 months	Not reported	0.25 mg	Congenital atresia of the bile duct	Cardiac arrest	Atropine (0.22 mg)	Autopsy findings normal with exception of bile duct
Macintosh (1949) (86)	38 years	Male	2.5 mg	Acute surgical abdomen	Cardiac arrest	Atropine (0.65mg)	Cardiac hypertrophy and generalized peritonitis found at autopsy

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.

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 identify 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

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

Based on the literature submitted by the Applicant and the AERS database and literature review performed by DPV-2, the adverse events commonly reported for neostigmine were those related to its anticholinesterase activity and contained in the label for the currently marketed, unapproved product. These adverse events are identical to those proposed by the Applicant for inclusion if the product is approved, include those reported for uses of neostigmine outside the scope of the proposed indication, and are listed below:

- **Neurological:** Dizziness, weakness, convulsions, loss of consciousness, drowsiness, headache, dysarthria, miosis and visual changes
- **Cardiovascular:** Cardiac arrhythmias (including bradycardia, tachycardia, atrioventricular block and nodal rhythm) ^{(b) (4)}

- **Respiratory:** Increased oral, pharyngeal and bronchial secretions, dyspnea, respiratory depression, respiratory arrest and bronchospasm
- **Dermatologic:** Diaphoresis, flushing, rash and urticaria
- **Gastrointestinal:** Nausea, emesis, flatulence and increased peristalsis
- **Genitourinary:** Urinary frequency
- **Musculoskeletal:** Muscle cramps and spasm, arthralgia

In the only study that reported a detailed list of adverse events for neostigmine and a comparator, Schaller (2010)(52) evaluated the efficacy and safety of neostigmine in doses of 5, 8, 15, 25, or 40 mcg/kg in a mixture with 1 mcg glycopyrrolate/5 mcg neostigmine to sugammadex and saline. The adverse events for all doses of neostigmine were combined for tabular display in the article. The table below lists the findings for the neostigmine and placebo (normal saline) treatment arms of the study.

Table 12. Adverse events [n (%)] following neostigmine and placebo treatments (from Table 4 on p. 1059 of the article)

Adverse Event	Neostigmine (n = 51)	Placebo (n = 9)
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)
Oxygen desaturation < 90%	3 (7)	0
Paresthesia <i>nervus ulnaris</i>	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
At least 1 AE	28 (64)	4 (44)

* One patient developed acute lung failure 63 h 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 l, *i.e.*, 35% of normal) after bleomycine chemotherapy.

The unexpected finding of Schaller's study was the high incidence of postoperative shivering for neostigmine-treated patients. The authors reported that there were no dose-related responses to any of the adverse events. However, it should be noted that all but one of the neostigmine doses studied were less than 30 mcg/kg, and therefore, this study does not fully characterize its risk profile.

7.4.2 Laboratory Findings

Laboratory assessments were not generally conducted or reported following administration of neostigmine in the literature that serves as the basis for this NDA submission. Given the mechanism of action, the relatively short half-life, and the single-

dose exposures that are associated with neostigmine, it would not be expected to adversely affect hematological, coagulation, renal, hepatic, or serum chemistry profiles to a clinically significant degree. In addition, with greater than 50 years of clinical use and millions of patients exposed for the proposed indication, it is unlikely that a clinical laboratory parameter is being affected without the awareness of the medical community.

7.4.3 Vital Signs

The Applicant neither summarized nor analyzed the limited vital sign information provided in the literature. Based on the summaries of the adverse event reports, the most commonly reported vital sign abnormality following neostigmine administration was bradycardia. Tachycardia was reported in one publication. Clinically relevant changes in respiratory rate, blood pressure, core body temperature and oxygen saturation were not reported in the literature, according to the Applicant's table listing the studies of safety.

7.4.4 Electrocardiograms (ECGs)

The Applicant neither summarized nor analyzed the limited ECG information provided in the literature; however they included a list of the safety literature reviewed and the adverse events reported for each article (counts were not provided). 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. The following are the adverse events that were captured by the Applicant:

1. bradycardia
2. A-V dissociation
3. premature ventricular contraction
4. first degree heart block
5. ventricular extrasystoles
6. cardiac dysrhythmias (not otherwise specified)
7. cardiac arrest (from the list of reports of patient deaths)

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 Applicant made no assessment of the dose dependency of the adverse events reported in the literature or in their database. The variations in the methods used to conduct the clinical trials reported in the literature, e.g., anesthetic agents, surgical procedures, dose and type of anticholinergic agents, made a meaningful comparison of the doses of neostigmine and incidence of adverse events impossible.

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 or in their database. 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. 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.(83)

Patients with renal failure treated with vecuronium or reversed with neostigmine did not differ from those with normal renal function for either the rate or duration of the reversal effect.(30)

7.5.5 Drug-Drug Interactions

The Applicant provided the following information regarding drug-drug interactions for neostigmine:

1. Neostigmine should not be used to reverse the effects of depolarizing muscle relaxants such as succinylcholine or decamethonium, as it may prolong the phase-1 block.(87)
2. Certain antibiotics, particularly neomycin, streptomycin and kanamycin have nondepolarizing neuromuscular blocking action and therefore neostigmine dose adjustments may be required to reverse neuromuscular block in patients who have been taking these drugs.(88) Other antibiotics, including tobramycin, gentamicin and cefazolin, have no effect on the nondepolarizing neuromuscular blocking action of d-tubocurarine or its reversal by neostigmine and atropine.(89) Similarly, there was no effect on the nondepolarizing neuromuscular blocking action of rocuronium by cefuroxime, metronidazole, cefuroxime or metronidazole or its reversal by neostigmine.(90)

However, the literature included in the NDA submission describes several other key interactions that need to be considered in clinical practice and that should be included in product labeling. These are listed below:

1. Neostigmine-induced recovery is attenuated in patients treated with $MgSO_4$ due to the independent effects of $MgSO_4$ at the neuromuscular junction rather than a drug-induced decreased response to neostigmine.(34,91)
2. Volatile anesthetic agents may interfere with neostigmine-induced recovery from neuromuscular blockade if they are not discontinued prior to the administration of neostigmine.(4,42)

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

Neostigmine has not been reported to be associated with any abuse, withdrawal or rebound issues. 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

A 120-day safety update was not provided by the Applicant; however, the information contained in the supplemental review of the literature that was included in the submission dated June 15, 2012, did not reveal any safety issues not previously described in the literature or reported in the AERS database.

8 Postmarket Experience

Applicant Reported Findings

The Applicant reported that they have an established clinical safety database for neostigmine, and that 7 adverse drug events have been reported to the company since March 2003. Three events were considered non-serious; four were classified as serious adverse events (SAE). Each is described below.

Of the non-SAEs reported, two involved episodes of hypoventilation following drug administration and one involved an incident of decreased effect with no associated adverse events.

Of the 4 SAEs, two of the events were described by the Applicant as expected based on the product label of neostigmine. One of these involved a patient who experienced a decreased effect of neostigmine given for neuromuscular blockade reversal during eye surgery. The patient was hospitalized and recovered with no sequelae. The other event involved a patient with an extensive history of hypersensitivity who developed an anaphylactic reaction during an unspecified procedure in which she was administered an anesthetic that included propofol, vecuronium, midazolam, dexamethasone, cefazolin, and, at the end of the procedure, neostigmine to reverse the vecuronium. The patient was hospitalized for two days and recovered with no sequelae. The anesthesiologist suspected vecuronium as the most probable drug causing the event. The two remaining SAEs were reported in a literature article and were deemed unexpected based on the currently available (unapproved) product label. Both events were cases of non-cardiogenic pulmonary edema (NCPE) that began after administration of a combination of neostigmine and glycopyrrolate, which were used to reverse residual neuromuscular blockade. One of the patients was undergoing excision of a hemangioma on lower lip. Anesthesia was induced with thiopentone and suxamethonium. The patient was intubated and an oropharyngeal pack was inserted prior to the procedure. Anesthesia was maintained with propofol, N₂O:O₂ (50:50) and vecuronium. At the end of the procedure, after oropharyngeal suctioning and removal of oropharyngeal pack, the patient received neostigmine and glycopyrrolate. Shortly afterwards, the patient developed signs and symptoms of non-cardiogenic adult respiratory distress syndrome (ARDS). A chest x-ray was suggestive of pulmonary edema. The patient was mechanically ventilated overnight and was discharged after 2 days without complications. The second incident of NCPE after administration of neostigmine involved a pediatric patient who was undergoing corneal repair surgery. Anesthesia was induced with thiopentone and suxamethonium, and the patient was intubated. Anesthesia was maintained with propofol, N₂O:O₂ (50:50) and vecuronium. After the surgery the patient was extubated and administered neostigmine and glycopyrrolate. Shortly after extubation, the patient exhibited decreased oxygen saturation, crepitus sounds were heard during auscultation of the lungs, and frothy

secretions were observed on laryngoscopy. The patient was treated and transferred to the pediatric intensive care unit. The patient's outcome was not reported.

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 table below.

Table 13. 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

Labeled Adverse Events by Preferred Term	Adverse Event Count
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
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 14. 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)

SOC	Adverse Events (n ≥ 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)	Rhabdomyolysis-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)
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. They concluded that the analysis of all events reported in the case series did not find any new safety issue for which the proposed label can be strengthened or new events could be added.

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 2 cases in which the patient died. 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 five deaths that were included in the review, two of which involved the proposed indicated use. The first was reported by Middleton et al. (1957)(92) 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 than neuromuscular blockade and did not attribute the death to neostigmine. The second death was reported by Buzello et al. (1982)(93) 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.

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 (T_1) 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 $\geq 80\%$) 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 the table below).

Table 15. 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
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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 the table below). The ED_{50} values for adults were consistently higher than the ED_{50} and ED_{80} values in children.

Table 16 Calculated effective doses of neostigmine for 50% (ED₅₀) and 80% (ED₈₀) 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
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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 ED₅₀ or the ED₈₀ 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 T₁ 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 ED₈₀ 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.

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% 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 the table below.

Table 17. 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	COPYRIGHT MATERIAL WITHHELD				0.91 (0.01)	0.78 (0.01)
Vec	COPYRIGHT MATERIAL WITHHELD				0.88 (0.02)	0.79 (0.02)
Atr	COPYRIGHT MATERIAL WITHHELD				0.92 (0.01)	0.78 (0.01)
Pan	COPYRIGHT MATERIAL WITHHELD				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 N₂O/O₂. 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 the table and figure below.

Table 18. 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)
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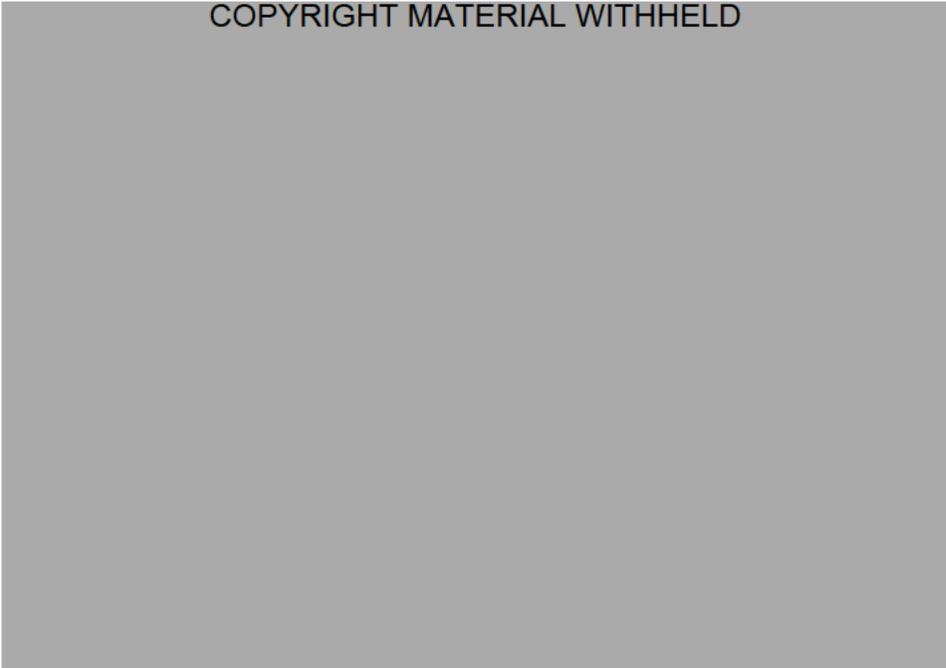


Figure 2. TOF recovery at 15 minutes (mean recovery, %) as a function of neostigmine dose (mcg/kg) and pre-reversal twitch height (% of control) [Figure 1 on p. 576 of article]

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 the table 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 19. 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)]			
	Roc	Vec	Roc	Vec	Rocuronium		Vecuronium	
					TOF _{0.7}	TOF _{0.9}	TOF _{0.7}	TOF _{0.9}
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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.

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

Table 20. 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 be 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.

The table 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 21. 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)] (%)
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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 pollicis 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% ($T_{10.75}$) and 90% ($T_{10.9}$) 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 T₁ twitch height was 18% ± 6% in NL patients and 19% ± 9% in patients with RF.

As indicated in the table 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 22. 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}
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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. (94) 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 m² 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 ($V_{d_{ss}}$)
- total plasma clearance (CI)

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 ED₅₀ values for the three age groups as:

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

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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 the table below.

Table 23. Time to various percentages of peak antagonism [mean \pm 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)
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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 a statistical preference for the three-compartment model. As indicated in the table 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 24. 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)
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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.

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 (ED₅₀) were determined from the dose-response curves using linear regression techniques. The table below summarizes the doses of neostigmine evaluated.

Table 25. 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-induced 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 CO₂ 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 pollicis 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 (T₁) 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 T₁ was 1-9% of the baseline/control level (very deep block), and for 3 patients, the neostigmine was administered when T₁ was 10-19% of control (deep block). Reversal from a moderate block, i.e., when T₁ 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 T₁ at reversal and the time to achieve a T₁ 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 mcg/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 the table below.

Table 26. 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		
	Low dose	Medium dose	High dose	Low dose	Medium dose	High dose
Neostigmine dose level						

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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 PaCO₂ 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 T₁ of the TOF when the TOF ratio was 0.9. Prior to the administration of neostigmine, T₁ was recorded and the T₁/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.

The table 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 27. 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)		
			$TOF_{0.5}$	$TOF_{0.75}$	$TOF_{0.9}$
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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 then 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 the table below.

Table 28. 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 the table 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 29. 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
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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/m², 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 normocarbida 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 the table below.

Table 30. 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)
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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 T₁ 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/O2 (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, were 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., $T_1/T_C \times 100$) 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 T_1 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 the table 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 31. Summary of findings for neuromuscular function recovery [mean (SD) or ration (%)] (Table 2 on p. 839 of the article)

Parameter	Control	Neostigmine 10 mca/ka	Neostigmine 20 mca/ka	Neostigmine 40 mca/ka
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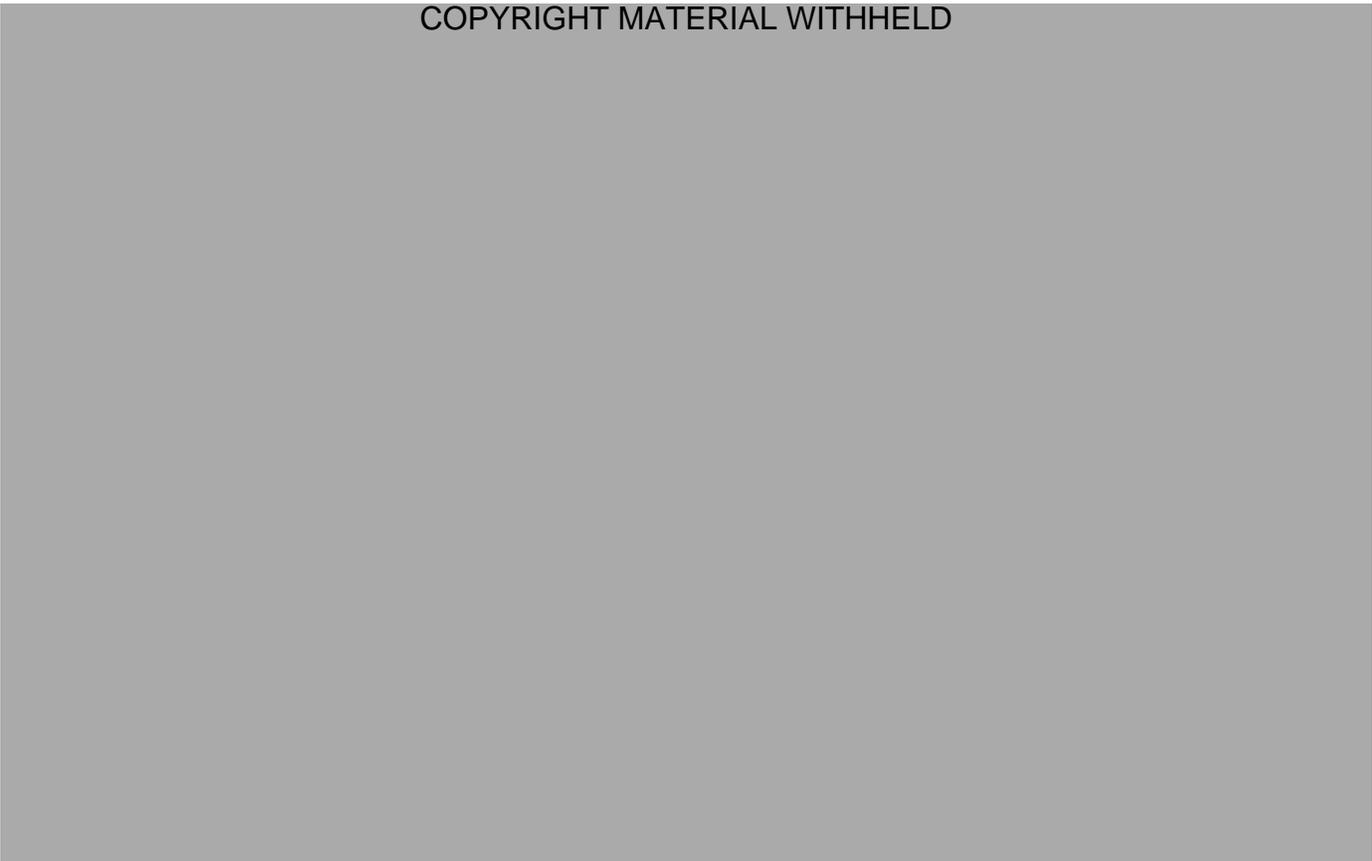


Figure 4. Recovery profile of TOF ratios for the 4 treatments over 20 minutes following study drug administration (Figure 2 from p. 839 of the article)

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 the table 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 32. Subject characteristics (Table 1 on p. 282 of article)

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

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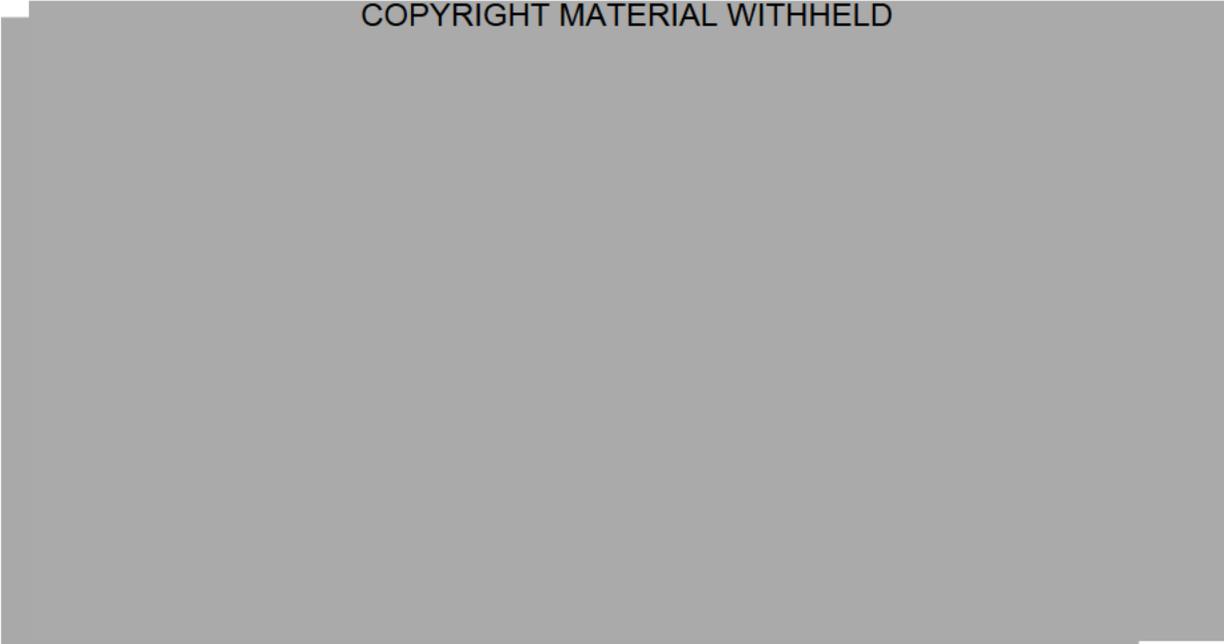


Figure 5. Dose-response curves for TOF ratios at 10 min after administration of neostigmine in adults and the elderly. Mean TOF ratios attained with each dose and the SD bars are shown. (Figure 1 on p. 282 of the article)

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 the table 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 33. 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

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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 $\geq 90\%$, 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 $90 \pm 10\%$ (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 the table 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 34. 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%)

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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 pediatric 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 $94 \pm 6\%$, $99 \pm$

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 \pm 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.

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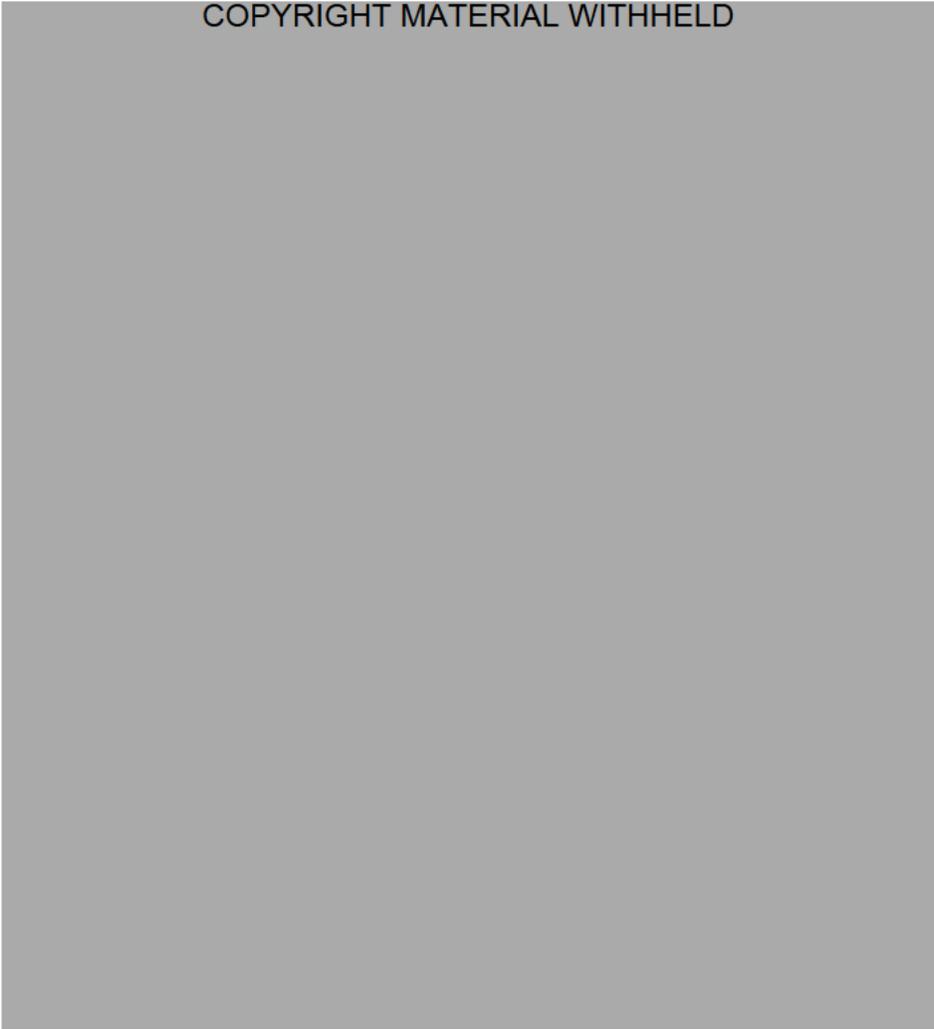


Figure 6. Recovery of the TOF ratio following reversal of vecuronium with neostigmine at three spontaneous recovery endpoints for T_1 of the TOF: 1%, 10% and 25% (Figure 2 on p. 98 of the article)

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 the table below.

Table 35. Recovery times of T₁ and TOF [mean ± SD] from T₁ 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)
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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 (T₁ of 1%) compared to later (T₁ 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 compatible 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 T₁ 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 isometric 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:

- $T_{10.75}$ 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 the table below.

Table 36. 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.)
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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 minutes 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 remifentanyl infusion set at 0.1 mcg/kg/min IV. The end-tidal concentration of desflurane ($4 \pm 1\%$) was maintained during the assessment of the study drugs. Ventilation was controlled to maintain the end-tidal CO₂ 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 below).

Table 37. 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)

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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 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 ratio 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 38. 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)
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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, remifentanyl, 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. The table below summarizes the findings for placebo and neostigmine treatments.

Table 39. 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)

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Based on the biexponential 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.

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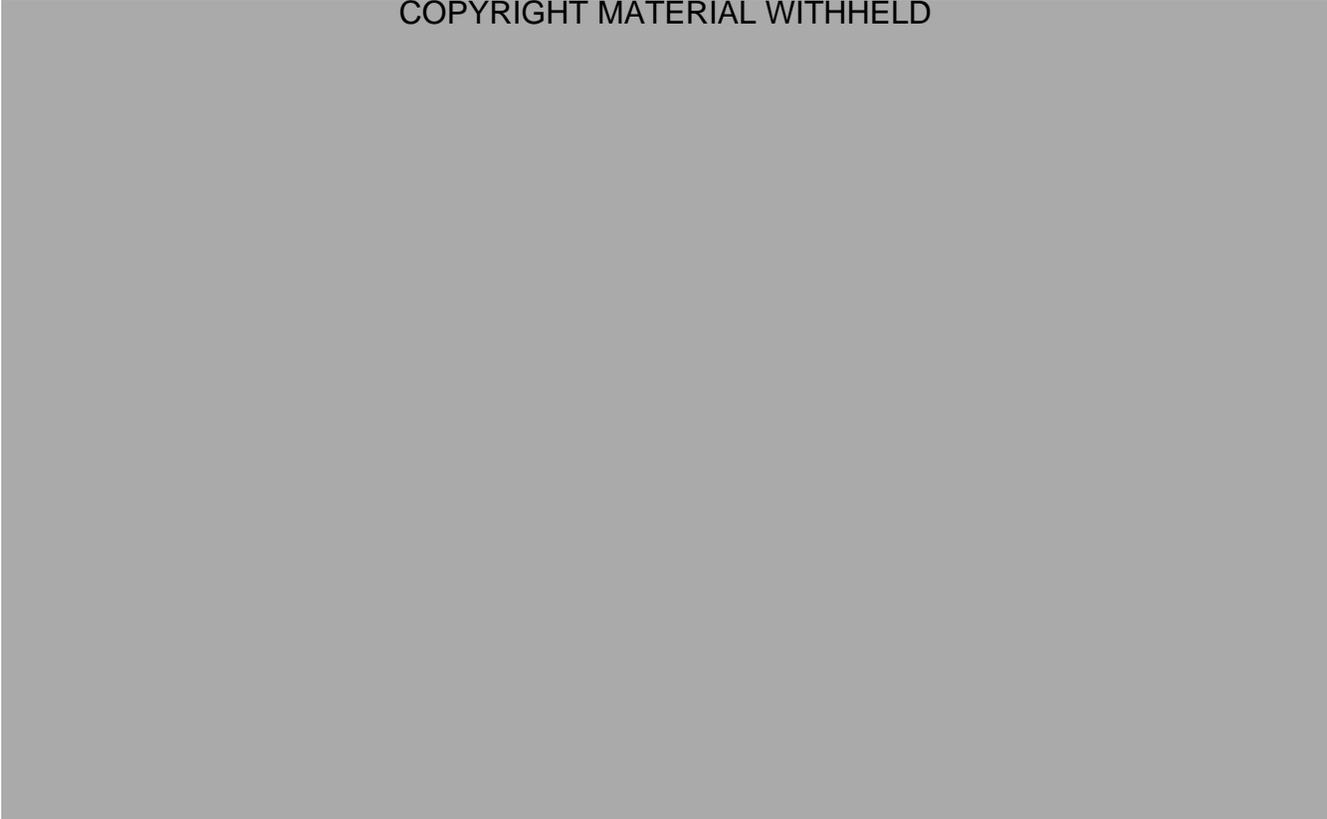


Figure 7. Estimate of mean dose-response, by dose, for the time between neostigmine administration to a TOF ratio of 0.9 (Figure 2 from the article)

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 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 40. 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 (%)
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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 then 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 the table below.

Table 41. 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.

9.2 Labeling Recommendations

The following is the package insert labeling proposed by the Applicant in their submission dated June 15, 2012. Comments and edits for consideration during labeling negotiations have been incorporated into the document.

13 Pages 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/

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