Neostigmine methylsulfate is a white crystalline powder and is very soluble in water and soluble in alcohol. Neostigmine Methylsulfate Injection, USP, is a sterile, pyrogen-free solution intended for intravenous use.

Each ml of the 0.5 mg/ml strength contains neostigmine methylsulfate 0.5 mg, phenol 4.5 mg (used as a preservative), and sodium acetate trihydrate 0.2 g, in water for injection. The pH is adjusted, when necessary, with acetic acid/sodium hydroxide to achieve a value of 5.5.

Neostigmine methylsulfate is a competitive cholinesterase inhibitor. By reducing the breakdown of acetylcholine, neostigmine methylsulfate increases an increase in acetylcholine in the synaptic cleft which contributes to the same binding site as non-depolarizing neuromuscular blocking agents, and reverses the neuromuscular blockade.

2.2. Pharmacodynamics

Neostigmine methylsulfate produced increases in acetylcholine levels results in the potentiation of both muscular and nicotinic cholinergic activity. The resulting elevation of acetylcholine competes with non-depolarizing neuromuscular blocking agents to reverse neuromuscular blockade. Neostigmine methylsulfate does not readily cross the blood-brain barrier and, therefore, does not significantly affect cholinergic function in the central nervous system.

2.3. Pharmacokinetics

Distribution: Following intravenous injection, the observed neostigmine methylsulfate volume of distribution is reported to be between 0.12 and 1.4 L/kg. Protein binding of neostigmine methylsulfate to human serum albumin ranges from 15% to 20%.

Metabolism: Neostigmine methylsulfate is metabolized by microsomal enzymes in the liver.

Elimination: Following intravenous administration, the reported elimination half-life of neostigmine methylsulfate is between 24 and 110 minutes. Total body clearance of neostigmine methylsulfate is reported between 1.1 and 16.7 mL/min/kg.

Renal Impairment: Elimination half-life of neostigmine methylsulfate was prolonged in aeophic patients compared to normal subjects; elimination half-life for normal, transplant and aeophic patients were 79.8 ± 46.6, 104.7 ± 64 and 181 ± 24 min (mean ± SD, respectively).

Hepatic Impairment: The pharmacokinetics of neostigmine methylsulfate in patients with hepatic impairment has not been studied.

Pediatrics: Elimination half-life of neostigmine methylsulfate is infants (1-10 months), children (1-6 years) and adults (19-48 years) were 39 ± 5, 46 ± 16, and 67 ± 8 min (mean ± SD), respectively. Observed neostigmine methylsulfate clearance for infants, children and adults were 14 ± 3, 11 ± 5 and 12 ± 6 mL/min/kg (mean ± SD, respectively).

Drug Interaction Studies: The pharmacokinetic interaction between neostigmine methylsulfate and other drugs has not been studied.

13. NONCLINICAL TOXICOLOGY

13.1. Carcinogenicity, Mutagenesis, Impairment of Fertility
Carcinogenesis: Long-term animal studies have not been performed to evaluate the carcinogenic potential of neostigmine.

Genotoxicity: Neostigmine methylsulfate was not mutagenic or clastogenic when evaluated in an in vitro bacterial reverse mutation assay (Ames test), in an in vitro Chinese hamster ovary cell chromosomal aberration assay, or in in vivo mouse bone marrow microsuspension assay.

Impairment of Fertility In fertile and early embryonic development study in rats, male rats were treated for 28 days prior to mating and female rats were treated for 14 days prior to mating with intravenous neostigmine methylsulfate. (human equivalent dose of 1.6, 4, and 8 mg/kg/day, based on body surface area). No adverse effects were reported at any dose (up to 0.5-times the MRHD of 5 mg/kg/person based on a body surface area comparison).

14. CLINICAL STUDIES

The evidence for the efficacy of neostigmine methylsulfate for the reversal of the effects of non-depolarizing neuromuscular blocking agents after surgery is derived from the published literature. Randomized, double-blind, placebo-controlled or parallel-design studies using similar efficacy endpoints evaluated a total of 404 adult and 80 pediatric patients undergoing various surgical procedures. Patients had reductions in their recovery time from neuromuscular blockade post-neostigmine methylsulfate treatment compared to spontaneous recovery.

16. HOW SUPPLIED/STORAGE AND HANDLING

Neostigmine Methylsulfate Injection, USP is a clear, colorless, sterile solution available in the following:

NDC No. Strength Vial Size
0641-6105-10 0.5 mg/ml 10 ml mult-dose vial supplied in packages of 10
0641-6105-20 0.5 mg/ml 10 ml mult-dose vial supplied in packages of 25
0641-6148-10 1 mg/ml 10 ml mult-dose vial supplied in packages of 10
0641-6148-20 1 mg/ml 10 ml mult-dose vial supplied in packages of 25
0641-6149-20 5 mg/ml 10 ml mult-dose vial supplied in packages of 25

The skel stopper is not made with natural rubber latex.

Neostigmine Methylsulfate Injection, USP should be stored at 25°C to 30°C (77°F to 86°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (See USP General Notices and Procedures, Carbohydrate Controls). Protect from light. Store in carton until time of use.


Neostigmine Methylsulfate Injection, USP is a cholinesterase inhibitor indicated for the reversal of the effects of non-depolarizing neuromuscular blocking agents after surgery.

2.2. Dosage in Adults

a. Peripheral nerve stimulation devices capable of delivering a train-of-four (TOF) stimulus are essential to effectively using Neostigmine Methylsulfate Injection, USP.

b. There must be a useful response to the first stimulus in the TOF at a dosage of at least 10% of the baseline level, i.e., the response prior to NMBA administration, prior to the administration of Neostigmine Methylsulfate Injection, USP.

c. Prior to administration, visually inspect Neostigmine Methylsulfate Injection, USP for particulate matter and discoloration.

2.2.1. Dose in Adults

a. Parenteral nerve stimulation devices capable of delivering a train-of-four (TOF) stimulus are essential to effectively using Neostigmine Methylsulfate Injection, USP.

b. There must be a useful response to the first stimulus in the TOF at a dosage of at least 10% of the baseline level, i.e., the response prior to NMBA administration, prior to the administration of Neostigmine Methylsulfate Injection, USP.

c. Prior to administration, visually inspect Neostigmine Methylsulfate Injection, USP for particulate matter and discoloration.

2.2.2. Dose in Adults

Dose and route: Neostigmine methylsulfate injection should be injected slowly over a period of at least 1 minute.
Cardiovascular Disorders
- cardiac arrest, cardiac arrhythmias (A-V block, nodal rhythm), hypertension, nonspecific ECG changes, syncope
Respiratory, Thoracic and Mediastinal Disorders
- hyperventilation, cough, photophobia, lacrimation, conjunctival injection, sneezing
Skins and Subcutaneous Tissue Disorders
- dry mouth, nausea, post-procedural nausea, vomiting
Gastrointestinal Disorders
- bowel cramps, diarrhea, flatulence, increased peristalsis
Renal and Urinary Disorders
- urinary frequency
Neuromuscular and Connective Tissue Disorders
- arthralgia, muscle cramps, spasm, weakness
Musculoskeletal and Connective Tissue Disorders
- myalgia, joint pain

7. DRUG INTERACTIONS
The pharmacokinetic interaction between neostigmine methylsulfate and other drugs has not been studied. Neostigmine methylsulfate is metabolized by microbial enzymes in the liver. Use with caution when using Neostigmine Methylsulfate Injection, USP with other drugs which may alter the activity of metabolizing enzymes or transporters.

8. USE IN SPECIFIC POPULATIONS
8.1. Pregnancy
Risk Category B
There are no adequate or well-controlled studies of Neostigmine Methylsulfate Injection, USP in pregnant women. It is not known whether Neostigmine Methylsulfate Injection, USP can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. The incidence of malformations in human pregnancies has not been established for neostigmine as the data are limited. All pregnancies, regardless of drug exposure, have a background risk of 2 to 4% for major birth defects and 10 to 20% for pregnancy loss. No adverse effects were noted in rats or rabbits treated with human equivalent doses of neostigmine methylsulfate doses up to 8.1 and 13 mcg/kg/day, respectively, during organogenesis (0.1 to 0.2 times the maximum recommended human dose of 5 mg/kg per os/day based on body surface area comparisons). Cholinesterase drugs, including neostigmine, may cause uterine irritability and induce premature labor when administered to pregnant women near term. Neostigmine Methylsulfate Injection, USP should be given to a pregnant woman only if clearly needed.

Data
Animal Data
In preclinical developmental studies, rats and rabbits were administered neostigmine methylsulfate at human equivalent doses (HED), on a mg/m^2 basis, of 1.6, 4 and 8.1 mcg/kg/day and 3.2, 8.1, and 13 mg/kg/day, respectively, during the period of organogenesis. (Rat and Rabbit Days 6 through 17 for rats and Gestation Days 24 through 30 for rabbits.) There was no evidence for a teratogenic effect in rats and rabbits up to HED 8.1 and 13 mcg/kg/day, which are approximately 0.057 times and 0.1 times the HMRD of 5 mg/kg, respectively. In the presence of minimal maternal toxicity (fetuses, alvei, and interstitial pneumonia), the studies resulted in exposures in the animals well below predicted exposures in humans.

In a pre- and postnatal development study in rats, neostigmine methylsulfate was administered to pregnant female rats at human equivalent doses (HED) of 1.6, 4 and 8.1 mcg/kg/day from Day 6 of gestation through Day 21 of lactation, with mating on Day 14. No adverse effects on physical development, locomotor activity, learning ability, or fertility in the offspring occurring at HED doses up to 1.6 mcg/kg/day which is 0.057-times the HMRD of 5 mg/kg on a mg/m^2 basis in the presence of minimal maternal toxicity (fetuses, alvei, and interstitial pneumonia). The studies resulted in exposures in the animals well below predicted exposures in humans.

8.2. Labor and Delivery
The effect of Neostigmine Methylsulfate Injection, USP on the mother and fetus with regard to labor, delivery, the newborn and its delivery or other intervention or resuscitation of the newborn, is not known.

Cholinesterase inhibitor drugs may induce premature labor when given intraoperatively to pregnant women near term.

8.3. Nursing Mothers
It is not known whether neostigmine methylsulfate is excreted in human milk. Caution should be exercised when Neostigmine Methylsulfate Injection, USP is administered to a nursing woman.

8.4. Pediatric Use
Neostigmine Methylsulfate Injection, USP is approved for the reversal of the effects of non-depolarizing neuromuscular blocking agents after surgery in pediatric patients of all ages.

Recovery of neuromuscular activity occurs more rapidly with smaller doses of cholinesterase inhibitors in infants and children than in adults. However, infants and small children may be at greater risk of complications from incomplete reversal of neuromuscular blockade due to decreased respiratory reserve. The risks associated with incomplete reversal outweigh any risk from giving higher doses of Neostigmine Methylsulfate Injection, USP up to 0.07 mg/kg or up to a total of 1 mg/kg over 1 hour.

The dose of Neostigmine Methylsulfate Injection, USP required to reverse neuromuscular blockade in children varies between 0.03 mg - 0.07 mg/kg, the same dose range shown to be effective in adults, and should be selected using the criteria used as for adult patients (see Clinical Pharmacology (12.3)).

Since the blood pressure in pediatric patients, particularly infants and neonates, is sensitive to changes in heart rate, the effects of an anticholinergic agent (e.g., atropine) should be observed prior to administration of neostigmine to lessen the probability of bradycardia and hypotension.

8.5. Geriatric Use
Because elderly patients are more likely to have decreased renal function, Neostigmine Methylsulfate Injection, USP should be used with caution and monitored for a longer period in elderly patients. The duration of action of neostigmine methylsulfate is prolonged in the elderly; however, elderly patients also experience slower spontaneous recovery from neuromuscular blocking agents. Therefore, dosage adjustments are not generally needed in geriatric patients; however, these patients should be monitored for longer periods than younger adults to assure additional doses of Neostigmine Methylsulfate Injection, USP are not required. The duration of monitoring should be extended on the anticipated duration of action for the NMMA used on the patient (see Dosage and Administration (2.4)).

8.6. Renal Impairment
Elimination half-life of neostigmine methylsulfate was prolonged in anephric patients compared to normal subjects. Although no adjustments to Neostigmine Methylsulfate Injection, USP dosing appear to be warranted to a larger extent, renal function should be checked to determine whether, and to what extent, post-operative monitoring needs to be extended.

8.7. Hepatic Impairment
The pharmacokinetics of neostigmine methylsulfate in patients with hepatic impairment have not been studied. Neostigmine methylsulfate is metabolized by microsomal enzymes in the liver. No adjustments to the dosing of Neostigmine Methylsulfate Injection, USP appear to be warranted to a larger extent, renal function should be checked to determine whether, and to what extent, post-operative monitoring needs to be extended.

9. OVERDOSAGE
Muscarinic symptoms (nausea, vomiting, diarrhea, sweating, increased bronchial and salivary secretions, and bradycardia) may appear with overdose of Neostigmine Methylsulfate Injection, USP (cholinergic crisis). This can be managed by the use of additional atropine or glycopyrrolate. The possibility of iatrogenic overdose can be limited by carefully monitoring the muscle twitch response to peripheral nerve stimulation. Should overdose occur, ventilation should be supported by artificial means until the adequacy of spontaneous respiration is assured, and cardiac function should be monitored.

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