

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation
CLINICAL STUDIES

NDA: 203-629

Name of drug: Neostigmine

Indication: Reversal of non-depolarizing neuromuscular blocking agents

Applicant: APP Pharmaceuticals

Date(s): Submitted: December 28, 2011

PDUFA: September 28, 2012

Review Priority: Standard

Biometrics Division: Division of Biometrics II

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Medical Division: Division of Anesthesia, Analgesia, and Rheumatology

Clinical Team: Medical Officer: Arthur Simone, M.D.

Medical Team Leader: Chris Breder, M.D., Ph.D.

Biometrics division director: Thomas Permutt, Ph.D.

Project Manager: Allison Meyer

Keywords: NDA review

1 BACKGROUND

APP Pharmaceuticals is seeking approval of neostigmine, a marketed unapproved drug, for reversal of neuromuscular blocking agents. The applicant is relying solely on published literature to establish the efficacy of neostigmine.

2 REVIEW

Of the 42 published articles submitted to support the efficacy of neostigmine, my review focused on one study, Schaller et al., 2010¹. The medical officer considered this to be one of the best designed studies, and the article included some data.

2.1 SCHALLER ET AL., 2010

This article described a single center, randomized, double-blind, study that was conducted in Munich, Germany. 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 µg/kg), or placebo (saline). Patients were anesthetized with propofol and fentanyl and maintained with propofol and remifentanyl according to clinical need and anesthesiologist preference. A neuromuscular block was applied 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. According to the authors the primary aim of this study was to determine the dose of neostigmine and sugammadex which reversed a shallow residual neuromuscular block from a train-of-four (TOF) ratio of 0.5 to a TOF ratio ≥ 0.9 . 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 medical officer requested I conduct an analysis 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 included in my review.

¹ Schaller SJ, Fink H, Ulm K, Blobner M: Sugammadex and neostigmine dose-finding study for reversal of shallow residual neuromuscular block. *Anesthesiology* 2010; 113:1054-60

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 µg/kg neostigmine.

Figure 1. Dose response curve for neostigmine
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Source: Figure 2 from Schaller, et al., 2010

Since the minimum, median, and maximum times were known, I approximated the values that were above and below the median but within the reported range. I did this by visual examination of Figure 1. My approximations along with the known values are shown in Table 1.

Table 1. Time (minutes) for reversal of neuromuscular block to TOF ratio ≥ 0.9

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

Source: Reviewer

I compared each dose of neostigmine to placebo using a log-rank test. To account for multiple comparisons and maintain the overall Type 1 error at 0.05, I utilized a Sidak adjustment. Results are shown in Table 2.

Table 2. Comparison of time to TOF ratio ≥ 0.9

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

3 CONCLUSION

Based on my analysis of data provided in Schaller et al, I find that neostigmine reduces the recovery time required to reach TOF ratio ≥ 0.9 when administered at a TOF ratio of 0.5. Thus, there is evidence to support the use of neostigmine to reverse neuromuscular blocks. This finding of efficacy is further supported by additional literature articles reviewed by Dr. Art Simone.

4 LABEL REVIEW

The applicant does not propose to include a clinical studies section in the label.

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/s/

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