Anesthesiology 2010; 112:16–8


# Neostigmine: How Much Is Necessary for Patients Who Receive a Nondepolarizing Neuromuscular Blocking Agent?

FORTY-FIVE years after Beecher and Todd[1] first described an increase in mortality associated with the use of D-tubocurarine, anesthesiologists are still learning how best to use neuromuscular blocking agents (NMBAs) and their antagonists. Practices regarding antagonism of residual neuromuscular block vary based on the country of practice,[2] type of anesthetic practice,[3] and individual clinician preference. These disparate practices developed in part because of concern of adverse effects, such as arrhythmias, nausea, and vomiting, resulting from anticholinesterase administration as well as an inability to reliably detect the presence of residual neuromuscular block. Although a patient with four equal responses to train-of-four (TOF) stimulation, on either visual or tactile assessment, might be completely recovered from neuromuscular blockade, the TOF ratio (TOFR) could be as low as 0.4.[4] Subjective detection of fade is improved by monitoring the response to double-burst stimulation that allows detection of 40% fade in the response.[5] However, satisfactory recovery of neuromuscular function is defined as a TOFR $\geq$ 0.9. In the absence of subjective fade on double burst or TOF stimulation, the clinician cannot distinguish a TOFR = 0.9 from 0.6 and, hence, cannot be certain whether neostigmine is indicated. Although not administering an anticholinesterase increases the risk of residual neuromuscular blockade,[6] unwarranted administration of neostigmine (at a TOFR $\geq$ 0.9) can exacerbate weakness.[7] Herein lies the quandary for the practicing clinician—whether to administer an anticholinesterase and if so, how much? The article by Fuchs-Buder *et al.*[8] in this month's ANESTHESIOLOGY provides new insight into this increasingly complex topic by addressing the appropriate dosing of anticholinesterase when subjective fade to double burst or TOF stimulation cannot be detected.

Fuchs-Buder *et al.* administered neostigmine when patients had spontaneously recovered to a TOFR = 0.4 or 0.6 after administration of atracurium. Patients received 10, 20, or 30 $\mu$g/kg of neostigmine, and recovery to TOFR = 0.9 and 1.0 was monitored with an acceleromyograph. Doses of 40 $\mu$g/kg or less of neostigmine have been found effective for reversing 90% neuromuscular block when monitoring for recovery to a TOFR = 0.7.[9–12] No study, however, has looked at the effect of administration of these small doses of neostigmine on the time required for complete recovery of neuromuscular function.

Depth of neuromuscular block depends on the balance of the NMBA and acetylcholine at the neuromuscular junction, and recovery depends on increasing acetylcholine concentration relative to the NMBA. This can occur in one of the two ways: ongoing elimination of the NMBA from the plasma and inhibition of acetylcholinesterase with administration of an anticholinesterase, such as neostigmine. The potential for neostigmine to rapidly restore neuromuscular function is limited. It will not effectively antagonize 100% neuromuscular block, and requiring 10 min to peak effect, it cannot instantaneously restore neuromuscular function. Fortunately, there is a remarkable amount of redundancy built into the anatomic and physiologic processes of neuromuscular transmission. Even when the TOFR has recovered to unity, the majority of acetylcholine receptors may still be occupied by NMBA—potentially rendering a patient susceptible to failure of muscle strength with a physiologic change, such as decrease in temperature or respiratory acidosis. Fade in the twitch response occurs after tetanic stimulation of a neuromuscular unit that has recovered after vecuronium-induced neuromuscular blockade.[13] This observation supports the notion that even recovery to a TOFR = 1.0 is not a true baseline, and all patients who receive an NMBA should receive an anticholinesterase.

However, administering an anticholinesterase does not facilitate elimination of the NMBA from the body, and administration of neostigmine is not without adverse effects. Neostigmine directly blocks acetylcholine receptors,[14] and excessive acetylcholine can cause both a depolarizing block and an open-channel block.[15,16] Potentiation of, rather than recovery from, neuromuscular block has been demonstrated when 40 $\mu$g/kg of neostigmine is administered after recovery to a TOFR $\geq$ 0.9 after administration of 0.1 mg/kg of vecu-

◆ This Editorial View accompanies the following article: Fuchs-Buder T, Meistelman C, Alla F, Grandjean A, Wuthrich Y, Donati F: Antagonism of low degrees of atracurium-induced neuromuscular blockade: Dose—effect relationship for neostigmine ANESTHESIOLOGY 2010; 112:34–40.

Accepted for publication September 16, 2009. The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

ronium 2, 3, or 4 h earlier.[17] In patients receiving two doses of neostigmine separated by 5 min after recovery of the TOFR to 0.9, the second dose of 2.5 mg neostigmine causes an increase in the TOF fade ratio and a decrease in response to tetanic stimulation.[18] Neostigmine administered to rats after complete recovery of neuromuscular function (TOFR = 1.0) from vecuronium-induced neuromuscular block reduces muscle strength and respiratory function.[7] If patients have completely recovered from neuromuscular block, they do not need neostigmine, and its administration can be detrimental.

Fuchs-Buder *et al.*[8] attempt to define a dose–response relationship for neostigmine from lesser degrees of neuromuscular block (TOFR = 0.4 or 0.6). Recovery to a TOFR ≥ 0.9 occurs more quickly than return to a TOFR = 1.0 when neostigmine is administered at a TOFR = 0.4 or 0.6. Administration of 10, 20, or 30 μg/kg of neostigmine shortens recovery when compared with placebo. Increasing the dose of neostigmine from 10 to 30 μg/kg decreases recovery from a TOFR of 0.4 to 0.9 or 1.0. Surprisingly, however, there is no such dose–response relationship when antagonizing block from a TOFR = 0.6. The authors seem to have identified the limit at which the response to neostigmine can be measured. If complete spontaneous recovery occurs within approximately 15 min from 60% neuromuscular block, and the peak measurable effect of neostigmine occurs 10 min after its administration, recovery can be shortened to 5 min with the administration of the anticholinesterase. Additional increases in dose to attempt to further shorten recovery are likely to be ineffective, if not counter productive.[18]

The authors found that administration of 30 μg/kg of neostigmine at a TOFR = 0.6 resulted in complete recovery of neuromuscular function (TOFR = 1.0) within 7 min and to a TOFR = 0.9 within 6 min. When administered at a TOFR = 0.4, all patients recovered to a TOFR = 1.0 within 11 min and to a TOFR = 0.9 within 6 min. Importantly, no patient developed weakness after administration of anticholinesterase. These results are applicable only to patients who received the NMBA atracurium and are receiving nitrous oxide throughout recovery. Nitrous oxide potentiates nondepolarizing neuromuscular blockers.[19,20] In its absence, would the administration of neostigmine have increased fade in the TOF? In addition, applicability of these results to the operating room is not apparent as the use of quantitative monitors (monitors that report the TOFR) of neuromuscular blockade is not routine.[21] What happens when small doses of neostigmine are administered at a TOFR = 0.7, 0.8, 0.9, or 1.0 remains to be determined as these different degrees of recovery cannot be distinguished using standard twitch monitors. On the basis of the results of this study, however, clinicians can be reassured that administration of 50 μg/kg of neostigmine is not necessary if a patient has four equal responses to TOF stimulation and that a dose of 30 μg/kg will be sufficient. Routine use of even smaller doses of anticholinesterases when no fade is appreciable in the TOFR requires that quantitative monitors be available to document the depth of block being antagonized as well as the time to complete recovery of neuromuscular function. Even once optimal dosing of neostigmine at all levels of neuromuscular block has not been defined, true safety in the use of NMBAs will be improved only by decreasing the occupancy of acetylcholine receptors by NMBAs. This will require the use of NMBAs that are rapidly broken down in the plasma or reversal agents that render the NMBA unable to bind to acetylcholine receptors.

**Cynthia A. Lien, M.D.,** Department of Anesthesiology, Weill Cornell Medical College, New York Presbyterian Hospital, New York, New York. calien@med.cornell.edu

## References

1. Beecher HK, Todd DP: A study of the deaths associated with anesthesia and surgery. Ann Surg 1954; 140:2–34
2. Debaene B, Plaud B, Dilly MP, Donati F: Residual paralysis in the PACU after a single intubating dose of nondepolarizing muscle relaxant with an intermediate duration of action. Anesthesiology 2003; 98:1042–8
3. Gray TC: D-Tubocurarine chloride. Proc R Soc Med 1948; 41:559–68
4. Viby-Mogensen J, Jensen NH, Engbaek J, Ording H, Skovgaard LT, Chraemmer-Jørgensen B: Tactile and visual evaluation of the response to train-of-four nerve stimulation. Anesthesiology 1985; 63:440–3
5. Fruergaard K, Viby-Mogensen J, Berg H, el-Mahdy AM: Tactile response of the response to double burst stimulation decreases, but does not eliminate, the problem of postoperative residual paralysis. Acta Anaesthesiol Scand 1998; 42:1168–74
6. Tramer MR, Fuchs-Buder T: Omitting antagonism of neuromuscular block: Effect on postoperative nausea and vomiting and risk of residual paralysis: A systematic review. Br J Anaesth 1999; 82:379–86
7. Eikermann M, Fassbender P, Malhotra A, Takahashi M, Kubo S, Jordan AS, Gautam S, White DP, Chamberlin NL: Unwarranted administration of acetylcholinesterase inhibitors can impair genioglossus and diaphragm muscle function. Anesthesiology 2007; 107:621–9
8. Fuchs-Buder T, Meistelman C, Alla F, Grandjean A, Wuthrich Y, Donati F: Dose-effect relationship for neostigmine to antagonize low degrees of atracurium-induced neuromuscular blockade. Anesthesiology 2010; 112:34–40
9. McCourt KC, Mirakhur RK, Kerr CM: Dosage of neostigmine for reversal of rocuronium block from two levels of spontaneous recovery. Anaesthesia 1999; 54:651–5
10. Harper NJ, Wallace M, Hall IA: Optimum dose of neostigmine at two levels of atracurium-induced neuromuscular block. Br J Anaesth 1994; 72:82–5
11. Jones JE, Parker CJ, Hunter JM: Antagonism of blockade produced by atracurium or vecuronium with low doses of neostigmine. Br J Anaesth 1988; 61:560–4
12. Johnson RA, Harper NJ: Antagonism of moderate degrees of vecuronium-induced neuromuscular block by small doses of neostigmine. Br J Anaesth 1989; 62:483–7
13. Eikermann M, Gerwig M, Hasselmann C, Fiedler G, Peters J: Impaired neuromuscular transmission after recovery of the train-of-four ratio. Acta Anaesthesiol Scand 2007; 51:226–34
14. Nagata K, Huang CS, Song JH, Narahashi T: Direct actions of anticholinesterases on the neuronal nicotinic acetylcholine receptor channels. Brain Res 1997; 769:211–8
15. Legendre P, Ali DW, Drapeau P: Recovery from open

channel block by acetylcholine during neuromuscular transmission in zebra fish. J Neurosci 2000; 20:140–8
16. Drapeau P, Legendre P: Neuromuscular transmission on the rebound. Receptors Channels 2001; 7:491–6
17. 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
18. Goldhill DR, Wainwright AP, Stuart CS, Flynn PJ: Neostigmine after spontaneous recovery from neuromuscular blockade. Anaesthesia 1989; 44:293–9
19. Kopman AF, Chin W, Moe J, Malik R: The effect of nitrous oxide on the dose–response relationship of rocuronium. Anesth Analg 2005; 100:1343–7
20. Illman H, Heikki A, Olkkola K: Quantitation of the effect of nitrous oxide on rocuronium infusion requirements using closed-loop feedback control. ANESTHESIOLOGY 2008; 108: 388–91
21. Naguib M, Kopman AF, Lien CA, Hunter JM, Lopez A, Brull SJ: A survey of current neuromuscular practice in the United States and Europe. Anesth Analg (in press)

## ANESTHESIOLOGY REFLECTIONS

# Laënnec's 1819 Stethoscope

An asthmatic "consumptive" with a keen sense of musical pitch, French physician René Théophile Hyacinthe Laënnec (1781–1826) enjoyed watching children play near the Louvre as they listened to the scratching of pins from the opposite end of a long stick. To think that such play would later inspire Laënnec (by 1816) to invent the stethoscope! Both a flautist and a woodturner, Laënnec soon found himself turning walnut-wood cylinders into shorter, wider versions of flutes *sans* finger holes—stethoscopes. Finally, physicians could abandon direct "ear-on-chest" auscultation in favor of the stethoscope, an innovation which preserved (particularly female) patients' modesty and physicians' professional distance. In 1819 Laënnec handcrafted a stethoscope (*see above, courtesy of the Wood Library-Museum*) for a Strasbourg colleague. That Laënnec creation was acquired by telephone auction in 1991 by a quick-dialing curator. (Copyright © the American Society of Anesthesiologists, Inc. This image appears in color in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

*George S. Bause, M.D., M.P.H., Honorary Curator, ASA's Wood Library-Museum of Anesthesiology, Park Ridge, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.*