

# Neostigmine versus Sugammadex

## Which, When, and How Much?

THERE is convincing evidence that, when reversal of rocuronium-induced neuromuscular paralysis is attempted during deep levels of blockade (posttetanic counts of 1 or 2), sugammadex given in the appropriate dose is a more rapid-acting and reliable antagonist of residual weakness than is neostigmine.<sup>1</sup> The same effect is true at more moderate levels of block (a train-of-four [TOF] count of 1–2) for rocuronium<sup>2</sup> and vecuronium<sup>3</sup> and for rocuronium compared with neostigmine reversal of cisatracurium.<sup>4</sup> The doses of sugammadex required for prompt and effective antagonism of a rocuronium- or vecuronium-induced block at these markers are now well established. However, there is almost no information available regarding how much sugammadex is needed when the level of block is more modest. In this issue of ANESTHESIOLOGY, Schaller *et al.*<sup>5</sup> provide dosage suggestions for neostigmine and sugammadex when TOF ratio has recovered spontaneously to a value of 0.50 after the administration of rocuronium.

A TOF ratio of 0.50 is an important marker in the recovery process for several reasons. Once a value of 0.50 is reached, subjective (tactile or visual) appreciation that fade exists at all is highly uncertain.<sup>6</sup> Unfortunately, the great majority of anesthesiologists still do not have access to neuromuscular monitors that can quantify the evoked response to TOF stimulation. Thus, this level of residual block is easily missed by clinicians. This state of affairs is of concern because a TOF ratio of 0.50 is associated with clear signs of inadequate clinical recovery<sup>7</sup>—and potential for adverse clinical consequences.<sup>8,9</sup> It is for this reason that, in the absence of some way of quantifying TOF ratio at the end of surgery, routine reversal of residual block has been advocated.<sup>10</sup>

The clinician who cannot detect fade on TOF stimulation after spontaneous recovery from a nondepolarizing block has a dilemma. Is a fully effective dose of neostigmine (50–70  $\mu\text{g}/\text{kg}$ ) still required if recovery to a TOF value of 0.90 within 5–10 min is desired? Recent evidence suggests that this intervention is not necessary. Under these conditions, Fuchs-Buder *et al.*<sup>11</sup> predicted that as little as 20  $\mu\text{g}/\text{kg}$  neostigmine would be 100% effective within 10 min, a conclusion given credence by Schaller *et al.*<sup>5</sup> On the basis of a biexponential model, they calculated that 34  $\mu\text{g}/\text{kg}$  neostig-

mine was required for recovery within 5 min in 95% of patients, but only 10  $\mu\text{g}/\text{kg}$  would be required for the average patient if a 10-min reversal interval was deemed acceptable. However, a caveat is in order. The conclusions by Schaller *et al.*<sup>5</sup> do not apply to a TOF count of 4 with detectable fade. When the fourth response to TOF stimulation first becomes detectable, even a 70  $\mu\text{g}/\text{kg}$  dose of neostigmine cannot guarantee recovery to a TOF ratio of 0.90 with 10 min.<sup>12</sup>

Because a TOF count of 1–2 is obviously associated with a higher plasma level ( $C_p$ ) of blocker than would be found when the TOF count is 4 with minimal fade, it seems only logical that the sugammadex dose requirements usually cited should be less as recovery spontaneously progresses. How much lower is the  $C_p$  when the TOF ratio is 0.40–0.50 compared with values at a TOF count of 1–2? It is possible to make some predictions. Tactile appreciation of the first twitch ( $T_1$ ) to TOF stimulation usually occurs at a  $T_1$  value of approximately 5% of control.<sup>13</sup> By the time the TOF ratio has recovered to 0.40–0.50,  $T_1$  is usually 75% of control.<sup>14</sup> Using a pharmacokinetic/pharmacodynamic model for vecuronium,<sup>15</sup> this degree of recovery ( $T_1$  at 5–75% of control) is associated with a more than 50% decline in the  $C_p$  of the drug. The manufacturer suggested dose of sugammadex for rocuronium (2 mg/kg at a TOF count of 2) is very conservative. It was designed to assure adequate reversal of vecuronium as well as rocuronium. However, dose requirements for the latter drug are only half that required for vecuronium. Thus, antagonism of residual rocuronium block at a TOF ratio of 0.50 is unlikely to require doses in excess of 0.50 mg/kg, and perhaps significantly less may prove satisfactory. This is exactly what Schaller *et al.*<sup>5</sup> observed. They calculated that as little as 0.22 mg/kg was necessary to achieve a TOF ratio of 0.90 within 5 min for 95% of their subjects.

This paper by Schaller *et al.*<sup>5</sup> paper highlights an important gap in our knowledge about how to dose sugammadex. There is little if any information on how to proceed when the TOF count is 4 but there is subjective tactile or visual TOF fade (a ratio of 0.10–0.40). It would not be surprising if a dose of only 1.0 mg/kg proved to provide adequate antago-

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nism of both vecuronium and rocuronium at this level of block, but data to support this supposition are lacking. At the moment, this topic is perhaps of academic interest only as the drug is available only in single-dose vials of 200 or 500 mg. Thus, there is no incentive for showing restraint in the dose of sugammadex administered. Nevertheless, this is a clearly an area that deserves further research.

The authors make one comment that is controversial. Even at a TOF ratio of 0.50, they state that quantitative monitoring of neuromuscular recovery is mandatory to ensure adequate recovery. I'm not so sure. One of the potential advantages of sugammadex *versus* neostigmine is that the evoked response from conventional peripheral nerve stimulators gives the clinician adequate information on which to base dosage decisions. We know the dose of sugammadex to administer at a posttetanic count of 1–2 (4 mg/kg) and at a TOF count of 2 (2 mg/kg). Undoubtedly, additional studies will elucidate the required dose when the fourth response to TOF stimulation first becomes subjectively apparent and when fade on TOF stimulation can no longer be detected.

Anesthetists fortunate enough to have access to both sugammadex and neostigmine must make a decision. Which neuromuscular antagonist should they administer when they cannot discern tactile fade at the thumb? In an ideal world with unlimited resources, perhaps a case can be made for abandoning the use of anticholinesterase antagonists even when residual neuromuscular block is minimal. However, as Schaller *et al.*<sup>5</sup> point out, the smallest vial of sugammadex costs €78 in Europe (approximately \$100 U.S.). A 10-ml vial of neostigmine may be purchased in the United States for between \$0.20 and \$1.00 per milligram. Even after the price of glycopyrrolate is factored in, the price of anticholinesterase antagonism is unlikely to exceed \$4.00 per patient. Although antagonism of mild residual block with low-dose neostigmine is not quite as prompt as seen with sugammadex, in the day-to-day practice of anesthesia, it is probably fast enough. In the present economic environment, I have difficulty imagining a clinical circumstance (perhaps a patient with myasthenia gravis) in which one would administer sugammadex in preference to neostigmine or edrophonium when rocuronium- or vecuronium-induced neuromuscular recovery has progressed to the point that fade on TOF stimulation can no longer be subjectively detected.

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