

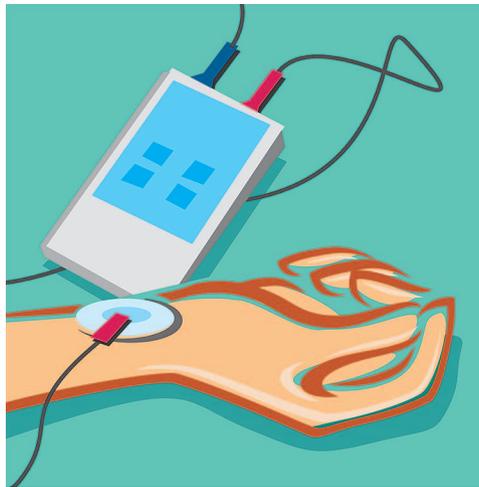
# Low-dose Sugammadex Reversal

## *There Is No Such Thing as a Free Lunch*

“At The Crescent...  
Can be found the choicest of  
Segars, wines and liquors...  
N. B.—A free lunch every day  
at 11 o'clock will be served up.”  
(*The Commercial Advertiser*  
notice, June 1850, Milwaukee)

**T**HIS issue of ANESTHESIOLOGY contains a clinical study that has important implications regarding how best to manage residual neuromuscular block once the train-of-four (TOF) count at the adductor pollicis muscle has returned spontaneously to four detectable responses, but when tactile or visual fade to TOF stimulation is still present.<sup>1</sup> The article makes two important contributions. First, contrary to “common wisdom,” it confirms that neostigmine cannot be relied on to produce prompt and adequate recovery of neuromuscular function, even when administered at a threshold TOF-count of four. Second, it fills an important gap in our knowledge: what is the recommended dosage of sugammadex for reversal of rocuronium at this modest level of neuromuscular block?

In 1995, Beemer<sup>2</sup> wrote, “In practical terms, the maximum depth of block that can be [promptly] antagonized [by anticholinesterases] approximately corresponds to the reappearance of the fourth response to TOF stimulation.” However, in that era, a TOF ratio of 0.70 was accepted as indicating satisfactory neuromuscular recovery. The current definition of adequate recovery from nondepolarizing block necessitates return of the TOF ratio to a value of 0.90 or greater.<sup>3,4</sup> A few years later, Kirkegaard *et al.*<sup>5</sup> reexamined neostigmine dosage requirements at a threshold TOF-count of four, and their observations were disquieting. The average time to



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achieve a TOF ratio of 0.90 was 17 min, but they also noted that it was “not possible within 30 min to achieve a TOF ratio of 0.9 in all patients, regardless of the number of tactile responses present at neostigmine administration.” In other words, even when neostigmine is administered for reversal of neuromuscular block at a very shallow block (at a threshold TOF-count of four), some patients will require more than 30 min to achieve an adequate recovery of neuromuscular function. The current study by Pongrácz *et al.* confirms these observations. The authors’ report for the subjects in the neostigmine group (0.05 mg/kg) is that the median time to recover to a nonnormalized accelerographic TOF ratio of 1.0 was 8.7 min, with a (truncated) maximum value of 15 min. Unfortunately, the authors chose to exclude four subjects (representing 20% of those initially recruited) because *the TOF ratios in this subgroup did not return to a TOF value of 1.0 within 15 min*—at which point, the authors decided to discontinue measuring the recovery

times. Thus, the average and maximum values noted above for the neostigmine group (N = 16) are, necessarily, unrealistically optimistic. This wide variability in recovery times, however, was in marked contrast to what was observed after the administration of sugammadex 1.0 mg/kg (median 1.9; range 1.2–4.5 min).

There is abundant evidence after rocuronium administration, once the TOF-count has spontaneously returned to a value of two, that sugammadex 2.0 mg/kg assures prompt (<3.0 min) return to a TOF value of 0.90 or more.<sup>6,7</sup> We also know, once the TOF ratio has recovered to a value of 0.40 or greater (a TOF-count of four at which tactile or visual fade usually goes undetected), that doses of

Image: A. Johnson.

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◆ This Editorial View accompanies the following article: Pongrácz A, Szatmári S, Nemes R, Fülesdi B, Tassonyi E: Reversal of neuromuscular blockade with sugammadex at the reappearance of four twitches to train-of-four stimulation. ANESTHESIOLOGY 2013; 119:36–42.

sugammadex as low as 0.25 mg/kg will, within 5 min, result in 95% of patients recovering to a TOF value 0.90 or greater.<sup>8</sup> Before the current report of Pongrácz *et al.*,<sup>1</sup> no data were available regarding sugammadex requirements at a threshold TOF-count of four, although a recent editorial in this journal speculated that at this level of neuromuscular recovery a dose of 1.0 mg/kg should produce satisfactory recovery.<sup>9</sup> This is precisely what Pongrácz *et al.* observed. The authors report that once the fourth response to TOF stimulation is first detected after spontaneous recovery from rocuronium-induced block, a 1.0 mg/kg dose of sugammadex returns the TOF ratio to 1.0 in 2 min on average, with a maximum time of 4.5 min; furthermore, a dose as low as 0.50 mg/kg was clearly superior to neostigmine 0.05 mg/kg.

The results of Pongrácz *et al.* lead to an inescapable conclusion. During recovery from rocuronium-induced block, if any fade is detectable at a TOF-count of four, a low-dose (0.50–1.0 mg/kg) sugammadex administration will result in faster and more reliable antagonism (and with potentially fewer side effects) than can be achieved with conventional doses of neostigmine. However, there is no “free lunch.” The current cost of a 200-mg vial sugammadex (the smallest unit dose currently available outside the United States) is in excess of \$90. Thus, a dilemma is facing the clinicians: at what acquisition price does sugammadex’s greater efficacy translate into added clinical value?

In a comparison of sugammadex 2.0 mg/kg with neostigmine 0.05 mg/kg administered at a TOF-count of two, Khuenl-Brady *et al.*<sup>10</sup> reported mean times of recovery (return to a TOF ratio equal to 0.90) of 2.7 and 17.9 min for sugammadex *versus* neostigmine, respectively. *Of perhaps greater significance from a patient safety perspective were the outliers: the 95th percentile times to recovery to TOF ratio of 0.90 were 7 and 76 min, respectively.* Thus, a reasonable case can be made that when antagonizing block of even moderate depth, sugammadex potentially can be cost-effective, provided that the time savings observed can be translated into productive use such as increased operating room and postanesthesia care unit utilization.<sup>11</sup> Butterly *et al.*<sup>12</sup> provided convincing evidence that a TOF ratio less than 0.90 on arrival in the postanesthesia care unit is associated with clinically significant delays in discharge from the unit. Such delays may result in significant disturbances in surgical patient flow and efficiency because patients from the operating room may be delayed from entering the postanesthesia care unit.

Because sugammadex-initiated antagonism of residual block at a threshold TOF-count of four is unlikely to result in time savings of the magnitude noted above, can its use still be justified when all four evoked responses to TOF stimulation are present? We suggest that we may not yet have sufficient information for a definitive answer. The aforementioned economic analysis ignores the issue of patient safety. There is little question that undetected block upon arrival in the postanesthesia care unit is associated with a small, but nonetheless real, incidence of critical adverse respiratory

events.<sup>13</sup> We also know that in patients without obvious pulmonary risk factors, even minor degrees of residual block are associated with reductions in forced vital capacity and peak expiratory flow in the immediate postoperative period, indicating impaired respiratory muscle function.<sup>14</sup> How then do we manage patients with potential or real reductions in pulmonary reserve such as those with sleep apnea, chronic obstructive pulmonary disease, morbid obesity, multiple sclerosis, or one of many possible myopathies? A reasonable case can be made that in patients at risk of pulmonary complications, the added cost of sugammadex administration is justified and defensible. The argument for sugammadex in preference to neostigmine in these patients would of course be strengthened if the acquisition price of sugammadex were less formidable. Reducing the drug’s acquisition cost does not necessarily mandate a reduction in the price per milligram of the drug. Availability of 50 or 100 mg vials (with a commensurate reduction in price) in addition to the drug’s current packaging (2 and 5 ml vials of sugammadex 100 mg/ml) would be a very useful first step.

We know that pharmacologic reversal of deep block (*i.e.*, TOF-count of one or less) with traditional anticholinesterases (neostigmine) is ineffective. At the other end of the neuromuscular block spectrum, pharmacologic reversal using neostigmine when the spontaneous recovery is almost complete (*i.e.*, when the TOF ratio is close to 1.0) can also present clinical problems. There are multiple studies regarding neuromuscular weakness induced by the administration of neostigmine after spontaneous recovery, and the mechanism for this paradoxical effect has been elucidated: impairment of airway musculature (genioglossus) and the diaphragm.<sup>15,16</sup> The neostigmine pharmacologic reversal, when spontaneous recovery is almost complete, thus introduces yet another potential patient safety risk. It is this indiscriminate clinical practice (read, without objective assessment) that might explain why neostigmine was recently reported to INCREASE the risk of postoperative desaturation by 32%, and the need for tracheal reintubation by 76%.<sup>17</sup> Based on this information, it may well appear that the cost we may need to pay for our (or our patients’) lunch will be worth it. We would, however, add two caveats: first, administration of a 1 mg/kg (or lower) dose for the reversal of rocuronium-induced block presupposes that the clinician has determined that the TOF-count has returned to four palpable responses at the adductor pollicis muscle, and not at other muscle groups such as the facial muscles.<sup>18</sup> The rational use of sugammadex still requires intraoperative monitoring of neuromuscular function at the appropriate site. Second, the suitability of low-dose sugammadex for the antagonism of vecuronium at a threshold TOF-count of four has yet to be demonstrated.

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