

## ◆ EDITORIAL VIEWS

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### ***Surrogate Endpoints and Neuromuscular Recovery***

IN this issue of ANESTHESIOLOGY, Eriksson *et al.*<sup>1</sup> present data that add to a growing body of information suggesting that our definition of what constitutes adequate recovery of neuromuscular function after administration of nondepolarizing relaxants needs to be reexamined. Most anesthesiologists have come to consider recovery of the train-of-four (TOF) ratio  $> 0.70$  as synonymous with adequate return of neuromuscular function. Eriksson *et al.* show that at a TOF  $< 0.90$  (measured at the adductor pollicis) resting upper esophageal muscle tone is significantly decreased, and the coordination required between esophageal sphincter relaxation and contraction of the pharyngeal constrictor muscles necessary for deglutition becomes dysfunctional. Persons studied showed misdirected swallowing with increasingly frequent episodes of aspiration (penetration of contrast media into the laryngeal vestibule to the level of the vocal cords) as the level of neuromuscular block intensified (8%, 25%, and 33% at TOF ratios of 0.80, 0.70, and 0.60, respectively).

Eriksson *et al.*'s findings correspond with other recent observations that potentially consequential signs and symptoms of residual block may persist until the TOF ratio exceeds a value of 0.90. There is convincing evidence that even partial neuromuscular block (TOF = 0.70) impairs the ventilatory response to hypoxia, suggesting an effect of nondepolarizing relaxants on carotid body hypoxic chemosensitivity.<sup>2</sup> Another recent study in awake volunteers found that although symptoms varied among them, TOF values in the range of 0.70-0.75 were associated with all of the following

symptoms: diplopia and difficulty in tracking moving objects, decreased grip strength, inability to maintain incisor teeth apposition, inability to sit up without assistance, severe facial weakness, and a profound sense of generalized fatigue.<sup>3</sup> Eriksson *et al.* conclude that patients with a TOF ratio  $< 0.90$  are at increased risk for passive regurgitation and aspiration.

The authors' data are disquieting. After administration of blockers of intermediate duration, it appears that at least 5-10% of patients arriving in the postanesthesia care unit will have TOF ratios  $< 0.70$ .<sup>4</sup> This frequency may reach 20% when these drugs are administered by infusion<sup>5</sup> and exceed 40% when traditional long-acting relaxants are used.<sup>6</sup> Prompt recovery to a TOF ratio of  $> 0.90$  is even less common. A recent study in which pancuronium was administered according to rigid clinical guidelines demonstrated this dictum.<sup>7</sup> After spontaneous recovery to a tactile TOF count of 2, residual block was antagonized with 0.05 mg/kg neostigmine. Thirty minutes later, 37 of 56 (66%) patients classified as American Society of Anesthesiologists (ASA) physical status I or II still had TOF ratios  $< 0.90$ , and 8 of these patients (14%) failed to achieve this benchmark 90 min after reversal. All available data suggest that patients receiving newer (and more expensive) nondepolarizing relaxants of short to intermediate duration have a lower incidence of residual block in the immediate postoperative period compared with those to whom long-acting blockers were administered. A 1989 editorial in this journal argued that "... even one case of severe, undetected respiratory depression and hypoxia in the postanesthesia care unit resulting in adverse effect is unacceptable ...".<sup>8</sup> Thus we can logically assert that the use of such traditional drugs as pancuronium should be discouraged.

Nevertheless, despite the high incidence of residual paresis found in routine clinical practice, there are remarkably few outcome data to suggest that this represents a frequent cause of major complications or death. In none of Eriksson's patients did tracheal aspiration occur, and the ability to cough was probably well maintained at the levels of neuromuscular block achieved. Thus a recently published set of practice guidelines from Duke University aimed at minimizing drug acquisition costs mandates succinylcholine and pancuronium as the default muscle relaxants to be used for any procedure that requires muscle relaxation. According to these guidelines, drugs of inter-

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mediate duration may be considered for procedures < 90 min long, but are permissible in longer cases only when control of the heart rate is extremely important.<sup>9</sup> The authors of the Duke protocol could not identify significant differences for any physiologic variable in sample populations studied before rather than after instituting practice guidelines. Their data showed that only 1 patient of 966 required unplanned mechanical ventilation because of an inability to reverse the effects of pancuronium. The extent to which equivalent drug administration policies are in place throughout North America is unclear, but departments adopting similar philosophies are certainly not rare.

It is difficult to reconcile Eriksson's conclusion that patients with TOF ratios < 0.90 have an increased susceptibility to aspiration with the Duke practice guidelines. In large part, we are hampered by insufficient information. The incidence of serious perioperative adverse events associated with the administration of muscle relaxants is unknown but probably small. How, then, do we determine if consequential differences in outcome exist between various relaxant regimens? In practice it may not be possible to do so. For example, assume that drug X has a true adverse effect rate of 1 in 500, whereas for drug Y this frequency is 1 in 1,500. Over 10,000 persons would have to be studied to show that this difference was significant. However, studies of this magnitude are rarely performed.

Often we are forced to accept surrogate measures as a substitute for true outcomes.<sup>10</sup> The TOF ratio is one such surrogate. There are no outcome data to substantiate the position that patients who arrive in the postanesthesia care unit with TOF ratios of 0.50 experience more adverse events than did those who have recovered to values > 0.80–0.90. Nevertheless, there is convincing experimental evidence to show that persons with the lower values have measurable decreases in mechanical respiratory reserve,<sup>11</sup> decreased ventilatory response to hypoxia,<sup>2</sup> an impaired ability to swallow and protect the upper airway from aspiration,<sup>1,12</sup> and many subjective discomforts.<sup>3</sup> It is difficult to accept the position that none of this matters.

The degree of neuromuscular recovery that can be achieved at the end of surgery is determined by two processes: direct antagonism by the anticholinesterase and spontaneous recovery by the neuromuscular blocking agent, with the latter becoming the major determinant at deeper levels of neuromuscular block.<sup>13</sup> Expressed somewhat differently, anticholinesterases have a "ceiling" to the extent of the block that can be

completely antagonized. When reversal of neuromuscular block greater than this ceiling is attempted, the peak effect of the antagonist is followed by a slow plateau phase that represents the balance between decreasing anticholinesterase activity and spontaneous reduction in the blood level of the blocking drug. Thus moderate levels of pancuronium-induced neuromuscular block (tactile TOF counts of 3 or 4) can, as a rule, be reversed rather promptly, whereas a more intense block may be difficult to antagonize. This is particularly true in infants and in the elderly population, and in persons with reduced renal and hepatic function. It is not surprising, therefore, that residual neuromuscular weakness in the postanesthesia care unit (as measured by the TOF ratio) is found more frequently in patients receiving traditional long-acting relaxants than in patients recovering from shorter-acting drugs, which are cleared more rapidly from plasma.

How is the clinician to proceed? To quote a recent letter to this journal:

"... we have always extrapolated the results regarding surrogate endpoints into our practice. The alternative is to ignore the surrogate measures and do nothing for our patients. I hope we will continue to use an amalgamation of surrogate endpoints, *i.e.*, our overall knowledge, logic, intelligence, and passion until 'true outcomes' are available."<sup>14</sup>

Available evidence suggests that the margin of postoperative neuromuscular safety afforded by blocking drugs of long duration is not as great as that provided by newer agents of short-to-intermediate duration. The suggested return to longer-acting but less expensive agents needs to be approached with great caution.

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## Application of Practice Guidelines to Anesthesiology

FOUR recent studies in the anesthesia literature have reported successful and similar programs to change anesthesiologists' practice patterns.<sup>1-4</sup> This issue of *ANESTHESIOLOGY* contains one such report.<sup>1</sup> Two studies (by Freund *et al.*<sup>1</sup> and Lubarsky *et al.*<sup>2</sup>) tested the success of their efforts to change practice patterns by comparing drug use during a historical control period to that in a later intervention period at single hospitals. The other two studies (by Cohen *et al.*<sup>3</sup> and Rose *et al.*<sup>4</sup>) performed such an analysis at a control and a study hospital. Increases in the proportion of patients treated using the practice guidelines were then compared between the two hospitals. All four studies simultaneously monitored changes in patient demographics and outcomes. The studies examined practice guidelines for

neuromuscular blocking drugs,<sup>1</sup> expensive anesthetic drugs,<sup>2</sup> prevention of nausea,<sup>3</sup> and management of postoperative pain.<sup>4</sup>

Comparison of how these groups achieved changes in anesthesiologists' practice patterns are important. Two studies<sup>1,2</sup> succeeded at changing anesthesiologists' practice patterns by combining education, practice guidelines, and paper barriers. Completion of a form at an operating room pharmacy<sup>1</sup> or advance approval of the attending anesthesiologist<sup>2</sup> was required to obtain the more expensive drugs. The former study<sup>1</sup> showed that the paper barriers produced changes that were maintained for 2 yr. The latter study<sup>2</sup> discussed that maintenance of the changed behavior was achieved, in part, by providing anesthesiologists with individualized feedback on their (1) deviation from the practice guidelines and (2) drug administration compared with their peers. The other two studies<sup>3,4</sup> succeeded at changing practice patterns by combining education, practice guidelines, and individualized feedback. The individualized feedback included the number of patients cared for during the promoted measures.

Together, the results of these<sup>1-4</sup> studies stand in contrast to some previous studies in anesthesiology that failed to show that education and practice guidelines change physicians' practice patterns. Anesthesiologists'

This Editorial View accompanies the following article:  
Freund PR, Bowdle TA, Posner KL, Kharasch ED, Burkhart VD: Cost-effectiveness reduction of neuromuscular-blocking drug expenditures. *ANESTHESIOLOGY* 1997; 87:1044-9.

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