In Reply.—We appreciate Drs. Fisher’s and Shafer’s interest in our work.1 We agree with their view that our model did not optimally fit all data points. There is a large variation in the placebo and 2.0 mg/kg group, and it was difficult to define a model that optimally fits these data points. For higher doses of sugammadex, the model fits the data very well.

We have conducted a Phase 2 clinical trial. Those studies attempt to learn what is a good (if not optimal) drug regimen to achieve useful clinical value (acceptable benefit/risk). In contrast to the confirming phases of drug development, the learning phases entail so-called explanatory analyses; i.e., analyses that estimate the quantitative relationship between inputs and outcomes according to some mechanistic view of the relationship.2 In a Phase 2 study, a nominal design, including all ostensibly controllable factors affecting the conduct of the trial, is an abstract ideal. In fact, in any real study, deviations from nominal design are inevitable.3 We decided to apply the model to our data which has been defined a priori, and has been used for several data sets on sugammadex which already have been published.3–5 We did not want to retrospectively change the predefined approach of our statistical analysis. In future confirmatory studies on sugammadex it will be possible to develop and apply a more sophisticated model. The suggestions of Drs. Fisher and Shafer will be very useful in that context.

To the Editor.—In the September issue of ANESTHESIOLOGY, Murphy et al.1 demonstrated that residual neuromuscular blockade may produce adverse respiratory outcomes. We believe that the methodology used in their study is significantly flawed, and that their conclusions comparing qualitative (conventional nerve stimulators) and quantitative (acceleromyography) monitoring are not supported by their results. In our opinion, their study failed to demonstrate that quantitative monitoring is superior to qualitative monitoring in reducing the incidence of adverse respiratory events in the perioperative period.

Naguib et al.2 have written: “In neuromuscular blockade studies, nuance in protocol and apparently ‘minor’ variations in methodology may markedly affect outcome.” We find three types of faults with the present methodology. First, they used visual rather than tactile evaluation of train-of-four (TOF) responses. The present study, involving 20 faculty and 50 residents and nurse anesthetists, and similar papers from the same institution3–4 indicate that they routinely produce a level of blockade which results in two to three visual TOF responses. This practice is based upon an early study comparing electromyogram findings with a single surgeon’s subjective evaluation of abdominal relaxation.5–6 We believe that evaluating visual as compared to tactile TOF responses tends to underestimate the level of blockade and overestimate the amount of recovery. We have observed patients with 4/4 visual and simultaneous 0/4 tactile TOF responses. Others6–7 have noted that visual TOF tends to overestimate the return of neuromuscular function, as compared with tactile monitoring. Furthermore, we are not aware of any studies that support the use of visual TOF monitoring or maintaining two to three visual TOF responses to attain satisfactory surgical relaxation. There are numerous studies8–10 that rely upon tactile TOF monitoring, a clinical simplification of the original investigations of TOF using mechanomyography.

Secondly, we do not believe that the present study truly compared one group of patients who were managed with conventional neuromuscular monitoring with another group who were managed with quantitative monitoring. Both groups of patients received conventional TOF monitoring to maintain two to three visual TOF responses and guide the administration of additional doses of rocuronium. Acceleromyography was not used in the quantitative group until after administration of the last dose of rocuronium to assure that a TOF ratio of > 0.8 was reached before tracheal extubation. The conventional group underwent tracheal extubation after a conventional nerve stimulator demonstrated the loss of visual TOF fade, an inaccurate indicator of TOF ratio.7

Thirdly, the authors did not follow common practices of neuromuscular monitoring and management of extubation when using a conventional monitor. It has been demonstrated that using intermediate neuromuscular blockers and waiting until the appearance of 2 or 3–4 tactile TOF responses before the administration of neostigmine markedly increases the likelihood of adequate (TOF ratio of > 0.8) recovery within 20–30 min, at which time the trachea can be safely extubated.11–12 It is predictable from the present study design that patients in the quantitative group who are extubated with a TOF ratio of > 0.8 will not have residual blockade in the postanesthesia care unit, while those in the conventional group whose tracheas are extubated on the basis of loss of visual TOF fade will have a deeper level of blockade and more likely demonstrate residual blockade.

While Murphy et al. have alerted us to the relationship between residual neuromuscular blockade in the setting and practices described in the article, they have failed to support the editorial opinion that acceleromyography should be available in every operating room where neuromuscular blockers are administered.11–12 Instead, they have demonstrated that acceleromyography reduces the risk of residual neuromuscular blockade in a setting where evidence based standards for conventional monitoring are not routinely followed. We agree with Naguib et al.: “What makes the difference in the incidence of residual

References


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blockade is not the monitor but the anesthetist.” To reduce the incidence of residual blockade and adverse respiratory events in Evan-
ston, we recommend that these authors and practitioners more care-
fully evaluate the degree of neuromuscular blockade required for their surgical patients, and either follow the recommendations above for using conventional nerve stimulators or use acceleromyography to guide the timing of tracheal extubation.

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(accepted for publication January 6, 2009.)

In Reply.—We thank Dr. Horowitz for his comments on our study.1 We welcome the opportunity to address his criticisms of the method-
ology used in our investigation and of our conclusions related to the effect of acceleromyography monitoring on residual neuromuscular blockade and adverse postoperative respiratory events.

First, we agree with the statement that nuances in neuromuscular management protocols may affect outcomes. Practices related to dos-
ing, monitoring, and reversal of neuromuscular blocking agents may vary widely between institutions. The protocol used in our control group (conventional qualitative train-of-four [TOF] monitoring) was designed to reflect “optimal” neuromuscular management, as defined by Kopman et al. (use of intermediate-acting muscle relaxants, avoid-
ance of total twitch suppression, anticholinesterase reversal of block-
ade at a TOF count of 3–4).2 These techniques, which may reduce the incidence of residual paresis in the postanesthesia care unit, are routinely used at our institution in surgical patients requiring muscle relaxation. Dr. Horowitz suggests that the methodology of neu-
romuscular monitoring used in the conventional TOF group was flawed, because use of visual evaluation of TOF responses may result in an underestimation of the level of the blockade and an overestimation of neuromuscular recovery. Available evidence does not support this hypothesis. Two studies specifically comparing visual versus tactile assessment of fade concluded that the ability of both techniques to detect fade was comparable at TOF ratios below 0.4 and between 0.4–0.7.3,4 The sensitivity in detecting fade was poor with both methods at all TOF ratios >0.4, and no statistically or clinically significant differences were observed when either vi-
sual or tactile assessments were evaluated.3,4 Therefore, we do not believe that using tactile instead of visual evaluations of TOF re-
sponses would have influenced our findings in the conventional TOF group. In addition, there are no clinical studies demonstrating that the use of tactile assessments of TOF responses results in a reduced incidence of postoperative residual blockade when com-
pared to visual evaluations.

Second, Dr. Horowitz questions our use of interoperative acceler-
omyography monitoring in our study group. We agree that quantitative neuromuscular monitoring does not provide any additional informa-
tion over standard peripheral nerve monitoring during moderate levels of neuromuscular blockade (TOF count of 2–5) required for surgical relaxation. As described in our article, the value of acceleromyography monitoring is primarily during neuromuscular recovery. Our data sug-
gests that acceleromyography monitoring allows for more rational and
precise neuromuscular management during the last 45–60 minutes of the anesthetic.

Third, Dr. Horowitz states that we “did not follow common practices of neuromuscular monitoring and management of extubation when using a conventional monitor.” Dr. Horowitz does not define what these “com-
mon practices” are. Current evidence suggests that “common practices of neuromuscular monitoring” are not evidence-based, and techniques proven to reduce the incidence of residual neuromuscular blockade are infrequently applied by clinicians. Surveys from Germany, Denmark, France, and Great Britain all indicate that quantitative and qualitative monitoring is rarely used in daily clinical practice.5–7 In addition, know-
ledge about appropriate neuromuscular and clinical criteria required to exclude residual paresis before tracheal extubation is lacking.5–7 Although we did not follow “common practices of neuromuscular man-
agement” (which would have increased the incidence of residual neuro-
muscular blockade in the conventional TOF group), we believe that our neuromuscular management protocol represented the best available evidence. In fact, the two previous randomized acceleromyography trials compared a group of patients monitored with acceleromyogra-
phy with a control group receiving no neuromuscular monitoring (the more “common clinical practice of neuromuscular monitoring” re-
f ered to by Dr. Horowitz).9,9 Of interest, the incidence of residual paresis was significantly reduced by acceleromyography monitoring in all three randomized trials. Furthermore, neuromuscular blockade was reversed at a mean visual TOF count of 4 in both groups, which represents good “evidence-based” practice.

Methods proven to reduce the incidence of postoperative residual blockade (use of intermediate-acting neuromuscular blocking agents, avoidance of total twitch suppression, anticholinesterase reversal of blockade at a TOF count of 3–4) should be adopted by clinicians. However, current data does not support the belief expressed by Dr. Horowitz that use of tactile assessment of TOF responses is supe-
rior to visual evaluation in reducing the risk of residual neuromuscular blockade and adverse postoperative outcomes. At the present time, “evidence-based standards for conventional monitoring” as described by Dr. Horowitz do not exist. Such guidelines would likely result in increased routine use of neuromuscular monitoring and anticholinesterase agents, and reduced complications related to incomplete neu-
romuscular recovery in the postoperative period.