

form of headache was noted in only one *versus* six patients in the 29- and 26-G groups, respectively.

The difference between minimal to mild headache ( $P < 0.05$ ) and moderate headache ( $P < 0.01$ ) was statistically significant, but there was not significant difference between mild and moderate headache ( $P < 0.14$ , exact Fisher test). The technique of spinal anesthesia with 29-G needles is readily learned, requires only little increased time and no more effort to complete, and is as successful as spinal anesthesia with larger 26-G needles in the routine practice. We recommend the use of 29-G needles for use in younger patients at risk for headache. With the increasing number of patients presenting for ambulatory surgical procedures, these thin needles may prove to be especially beneficial in precluding headache.

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## Dose-Response Relationship to Mivacurium in Humans

*To the Editor:*—We would like to make a correction and comment regarding the recent paper describing the dose-response relationship of mivacurium chloride in humans.<sup>1</sup> Weber *et al.*<sup>2</sup> did not use a single twitch mode of nerve stimulation in their study of the dose-response relationship of mivacurium. We used a stimulation pattern of 2 Hz for 2 s at 10-s intervals.

Because of recent discussion about the methods of calculation of the dose-response relationship for mivacurium,<sup>3</sup> we would like to offer reanalysis of our dose-response data for mivacurium. Similar questions could be asked of Caldwell *et al.*<sup>1</sup> The ED<sub>50</sub> reported by Weber *et al.*<sup>2</sup> was calculated from observations of 26 patients with normal pseudocholinesterase activity who each received a single dose of either 30, 40, or 50 µg/kg of mivacurium. If we add an additional nine adult patients who received 60 µg/kg of mivacurium to the calculation of the dose-response relationship, then the ED<sub>50</sub> is 43 µg/kg and the ED<sub>95</sub> is 70 µg/kg.<sup>4</sup> This is in contrast to the ED<sub>50</sub> of 41 µg/kg and ED<sub>95</sub> of 58 µg/kg calculated from the observation of 26 patients.<sup>2</sup> Not all of the nine adults receiving 60 µg/kg developed 100% neuromuscular blockade. The patients who developed 100% neuromuscular blockade in this group were assigned a probit of eight. We would expect, as do others,<sup>3</sup> that adding patients with 100% neuromuscular blockade to the calculation of a dose-response relationship might increase the slope of the regression line. It is our preference to present dose-response data based on the responses of patients who have received doses between the ED<sub>20</sub> and ED<sub>80</sub>, because this is expected to be the linear portion of the dose-response relationship and linear regression is employed to estimate the relationship.

These arguments are somewhat specious in that adding nine patients who received 60 µg/kg of mivacurium to our calculations of the dose-response relationship produced no statistically significant change in the slope or intercept of the regression line. Individual patient variability in response appears to be more important than these small differences in methods in the determination of the dose-response relationship for mivacurium.

Variation in pseudocholinesterase activity may contribute to interpatient variability in response to mivacurium. We find it interesting

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3. Tourtellotte WW, Henderson WG, Tucker RP, Gilland O, Walker JE, Kokman E: A randomized double-blind clinical trial comparing the 22 versus 26 gauge needle in the production of the postlumbar puncture syndrome in normal individuals. *Headache* 12:73, 1972

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that Caldwell *et al.*<sup>1</sup> noted aberrant response to mivacurium in patients with slightly abnormal pseudocholinesterase activity. Perhaps the patient who was sensitive to mivacurium and had pseudocholinesterase activity at the low end of the normal range and 85% inhibition by dibucaine is a homozygous normal patient as determined by response to dibucaine and the substrate used by Smith Kline Bioscience Laboratories, Van Nuys, California. (Could there be a significant difference between 84 and 86% inhibition?) Undoubtedly, there is a difference between the effects of pseudocholinesterase on mivacurium and on the substrate employed to assay pseudocholinesterase in this study. All patients with "normal pseudocholinesterase activity" may not metabolize mivacurium at the same rate. The characterizations of pseudocholinesterase activity that were useful guides for the administration of succinylcholine may not be as useful in the description of the effects of mivacurium. To improve our understanding of this area, the substrate used to assess pseudocholinesterase activity should be reported.

In the study of Weber *et al.*,<sup>2</sup> the substrate used was acetylthiocholine iodide.

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2. Weber S, Brandom BW, Powers DM, Sarner JB, Woelfel SK, Cook DR, Foster VJ, McNulty BF, Weakly JN: Mivacurium chloride (BW B1090U)-induced neuromuscular blockade during nitrous oxide-isoflurane and nitrous oxide-narcotic anesthesia in adult surgical patients. Anesth Analg 67:495-499, 1988
3. Savarese JJ: Reply. ANESTHESIOLOGY 70:166-167, 1989

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*In Reply:*—We appreciate the obviously careful reading of our paper by Drs. Brandom and Cook and are grateful to them for drawing our attention to two minor errors.<sup>1</sup> First, in our discussion we stated that Weber *et al.*<sup>2</sup> used a single twitch mode of nerve stimulation and that Choi *et al.*<sup>3</sup> used electromyography to measure neuromuscular response. These authors and their methods were erroneously transposed and, in fact, Weber *et al.* used electromyography and Choi *et al.* used single twitch mode of nerve stimulation. Second, in table 1, the dibucaine number of patient 4 should be 72 and not 84 as printed.

We support the reanalysis which Brandom and Cook have made of their dose-response data. The weakness of the original analysis by Weber *et al.*<sup>2</sup> was that they estimated an ED<sub>95</sub> value by extrapolation from values for ED<sub>25</sub>, ED<sub>50</sub>, and ED<sub>75</sub>. This resulted in an underestimate of the ED<sub>95</sub>. In our study, we derived the ED<sub>95</sub> value from data points covering the entire range of responses from 0% to 100% twitch depression. While it can be argued how best to treat 100% responses, we consider that an accurate determination of ED<sub>95</sub> requires data points both above and below 95% response. The revised estimate for ED<sub>95</sub> obtained by Brandom and Cook, 70  $\mu\text{g} \cdot \text{kg}^{-1}$ , after their reanalysis of the data of Weber *et al.*<sup>2</sup> is similar to the value, 67  $\mu\text{g} \cdot \text{kg}^{-1}$ , which we reported in our paper.<sup>1</sup>

The debate concerning the treatment of data points at the extremes of the dose-response curve is too complex to be covered in this forum. Briefly, we would take the position that extrapolation beyond one's data points is undesirable and that to estimate an ED<sub>95</sub> will inevitably require the inclusion of some points representing 100% twitch depression. If one has data only within the 20-80% range of response, then only the ED<sub>50</sub> should be reported. As we noted in our paper,<sup>1</sup> published estimates of ED<sub>50</sub> are more uniform than are estimates of ED<sub>95</sub>.

We would agree with Drs. Brandom and Cook that the manner by which variations in plasma cholinesterase activity and genotype affect the metabolism of and neuromuscular responses to mivacurium needs to be elucidated. Our data regarding neuromuscular responses in the patients with abnormalities of plasma cholinesterase were purely descriptive and suggested that the pattern of response was inconsistent

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and was not the same as might be seen following succinylcholine administration. For the information of Drs. Brandom and Cook and others who may be interested, the substrate used in our study to estimate plasma cholinesterase activity was acetylthiocholine.

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## Delayed Respiratory Depression Following Alfentanil

*To the Editor:*—We were interested to read the report of delayed respiratory depression following administration of alfentanil.<sup>1</sup> However, in contrast to the authors' statement that this phenomenon had not been reported before, we wish to note that delayed respiratory depression following continuous infusion of alfentanil was first described by

Lamarche *et al.* in 1984<sup>2</sup> and, later that year, two more cases of unexpected respiratory depression were reported after its use.<sup>3</sup>

Delayed respiratory depression has also been described after administration of oxymorphone,<sup>4</sup> and may occur after all opioids. The unstated theme of all these articles is that by whatever route of ad-