

In Reply:—We appreciate the comments of Drs. Shulman and Robelen, and of Dr. Kitagawa, in emphasizing the potential for neurotoxicity of undiluted 10% procaine in spinal anesthesia, consistent with our case report.¹ We also appreciate the correspondents including references to the work of Watkins and colleagues^{2,3} from early publications which have not been included in modern medical indices, as they deserve wider attention than they have received. One of us had earlier pointed out⁴ the relevance of those publications to the question of procaine spinal neurotoxicity, and so did not comment further on them in our case report except to refer to the earlier comment. We note that these references, as well as many other early publications reporting neurotoxicity after procaine spinal anesthesia, were included in the review of Schildt,⁵ which we also referenced in the case report, and which has also been undeservedly neglected.

Both letters pose the question of why 10% procaine was chosen as the spinal anesthetic in our case report. We cannot answer this because we did not provide the spinal anesthetic, but were consulted after the unfortunate development of the patient's cauda equina syndrome.

Drs. Shulman and Robelen correctly note two anesthesia textbooks which do recommend that procaine not be injected at concentrations higher than 5%. At 10 and 21 yr past their publication dates, it is a matter of semantics whether they would be considered recent texts. We respectfully disagree with the statement of Drs. Shulman and Robelen that "there is no evidence at present that it [5% spinal procaine] is neurotoxic." The animal study of MacDonald and Watkins cited by Dr. Kitagawa (his reference 3) and Drs. Shulman and Robelen (their reference 7) found that 10% spinal procaine was neurotoxic in

33% of 33 animals tested, but also found that 5% procaine was neurotoxic in 10% of 20 animals tested.³ This is a higher incidence of spinal neurotoxicity than we are aware of in any animal study testing roughly equipotent single injections of other local anesthetics, although given the limitations in the older report, there is simply not enough data at the present time to compare precisely the potential for neurotoxicity of procaine and lidocaine. Our point is that just because procaine is less likely to cause the syndrome of transient neurologic symptoms, it ought not to be considered an innocuous, risk-free alternative to lidocaine.

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References

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4. Johnson ME: Neurotoxicity of spinal procaine—a caution. *Reg Anesth Pain Med* 2001; 26:288
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When the Model Does Not Fit the Data, the Model Is Wrong

To the Editor:—Pühringer *et al.*¹ provide convincing evidence that sugammadex speeds the reversal of rocuronium and that the benefit increases with dose. Four figures display time to 90% train-of-four recovery as a function of sugammadex dose; in addition to raw data, each figure displays a curve based on fitting an exponential model to the data. Unfortunately, these curves provide misleading information about the dose-effect relationship. In that increasing the sugammadex dose should decrease (or not change) recovery time, the exponential model has the correct form (monotonic nonincreasing) but the wrong shape (as evidenced by its failure to match the data at low doses).*

The authors' intent in fitting this curve is to allow claims independent of the data. For example, based on their figure 1, one might claim that "following a dose of 2 mg/kg, time to 90% train-of-four is expected to be 30 min." Yet, this claim is not supported by the data. Similarly, any claim about the expected response at doses not studied cannot be inferred from the curve drawn by the investigators.

The process of fitting the exponential curve is based on the authors' belief that they have a "model" for the relationship between dose and effect. Pharmacokinetic models are typically based on physiologic principles. For example, after bolus intravenous administration of a

drug, samples drawn after the initial recirculatory phase typically show a monotonic decline that can be described by the sum of 1-3 exponentials; this model depends on the "reasonable" assumptions that clearance is constant and is proportional to plasma concentration. In contrast, there is no *a priori* reason for the authors to assume that their dose-response relationship is described by an exponential equation.

The purpose of this communication is not to berate the authors. In Supplemental Materials (which few readers will examine), they acknowledge that "another nonlinear model [might] have better fitted the . . . results." Instead, it is to remind future investigators (and reviewers and readers) of a maxim taught by our mentor, Lewis B. Sheiner, M.D. (1940-2004): "If the model does not fit the data, the model is wrong."

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Reference

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* The technical problem here is that the response to 2 mg/kg overlaps with the placebo response and doses of 8-16 mg yield near-maximal responses that vary little. Their exponential model cannot accommodate both of these conditions, thereby failing to fit the data at placebo (fig. 3) or 2 mg/kg (figs. 1, 2, and 4).