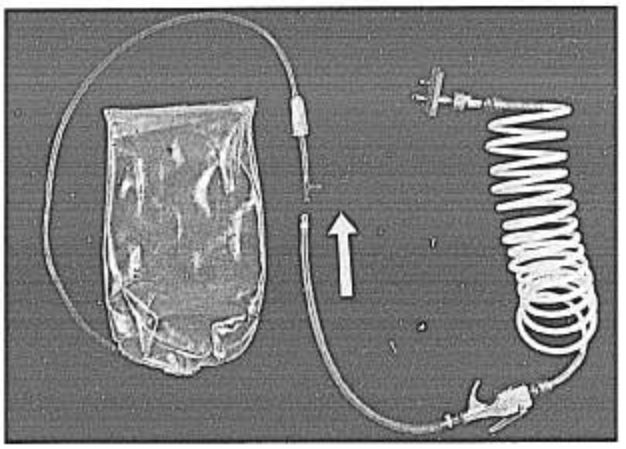

FIG. 1. The high pressure uterine dispacer. The arrow indicates attachment of the jet ventilator to the inflatable bag.

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Calculating the Potency of Mivacurium

To the Editor:—I am confused by some of the results reported by Savarese *et al.*[1] in their recent paper on the pharmacology of mivacurium. Specifically, using the data supplied in table 1, I cannot reproduce the ED_{95} value of 0.081 mg/kg that they calculate. If one performs a log dose-probit transformation and linear regression analysis on only the first four groups (0.03–0.10 mg/kg), the resulting ED_{50} and ED_{95} values are 0.052 and 0.10 mg/kg, respectively (table 1). In fact, this estimate of potency is substantiated by the group of patients receiving 0.10 mg/kg that showed 95.7% twitch depression. If the ED_{95} was, in reality, 0.081 mg/kg, then a dose of 0.10 mg/kg should produce greater than 99% twitch depression; this was not the case.

The authors do not actually state in their paper which groups were employed in calculating the ED_{50} and ED_{95} values. However, since 100% twitch suppression cannot be plotted on a log-probit graph, it appears that only the first four groups (n = 36) could have been used. It would be helpful if the authors could explain in greater detail how they estimated drug potency.

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TABLE 1. Log-probit Transformation of Data from Table 1 of Savarese *et al.*[1]

Dose (mg/kg)	% Effect	Log-dose	Probit
0.03	9.4	−1.5228	−1.3106
0.05	43.7	−1.3010	−0.1637
0.07	75.3	−1.1549	0.6280
0.10	95.7	−1.0000	1.6955

Equation for the dose-response relationship as determined by linear regression (least squares) analysis of the above log-probit data: $y = 5.8598x + 7.513$, $r = 0.998$.

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In Reply:—We appreciate the comments offered by Dr. Kopman. His letter reflects the need for a solution to a debatable question: How does one handle 100% or 0% twitch inhibition during construction of a dose-response curve for a neuromuscular blocking drug?

In our publication on mivacurium,[1] we estimated potency of mivacurium during nitrous oxide-narcotic-barbiturate anesthesia using single-twitch stimulation of the ulnar nerve to evoke thumb adduction at 0.15 Hz. This stimulus parameter was used so that the characteristics of mivacurium block might be easily compared with past literature on other relaxants. The methodology is fairly extensively presented and debated in Donlon *et al.*[2] where both single-bolus and cumulative dose-response curves for pancuronium were constructed.

Although we *calculated* an ED_{95} of 0.081 mg/kg in our paper, when we administered 0.10 mg/kg to nine consecutive patients, we *observed*

only 95.7% twitch depression. However, seven of the nine receiving 0.1 mg/kg achieved 100% twitch inhibition. When we gave 0.15 mg/kg consecutively to nine additional patients, we observed 100% block in everyone. Our philosophy is that, when constructing dose-response curves, data should be included for all subjects in all dosage groups from the lowest exhibiting any measurable block to the first dose where all individuals show 100% block. Doses higher than this are not included. Thus, all individuals at the above included dosage levels who show 100 or 0% block contribute to the curve. In constructing our curve using the log-probit transformation, we arbitrarily assign a value of eight probits to 100% block and two probits to 0% block. We feel it is important to include all these individuals in constructing the curve, because this gives a better estimate of the true population mean at any ED in the curve, especially at the upper end. For clinical purposes, ED_{95} and higher EDs are pertinent because they define doses required for tracheal intubation. If 0 and 100% responders are not included in dosage *groups* where less than 100% block is noted, then the *slope* of the curve is made shallower, thus overestimating higher EDs such as the ED_{95}. An underestimate in this part of the curve would constitute a clinically relevant inaccuracy, since many patients would react strenuously to attempted intubation under these circumstances!

Our data generally show ED95s that are slightly higher than other studies done in similar fashion. For example, the ED_{95} values for mivacurium in studies done in Pittsburgh, San Francisco, and Iowa City[3-5] were 0.070, 0.067, and 0.075 mg/kg, respectively. These slight differences may very well be due to subtle differences in technique, such as fixation of the arm and hand, positioning of transducer, etc.

It is also worth pointing out here that the use of *median* doses as another indication of population sensitivity to relaxants should be considered. The median will skew the data toward a value that appears frequently. For example, the median response for mivacurium at 0.1 mg/kg is 100% block (since seven of nine subjects reached this level), and the ED_{95} derived from the median responses at all doses is 0.08 mg/kg.

We offer this commentary as a more detailed explanation of our method and philosophy of handling the data. We feel that other methods of handling the data, such as linear regression and logit transformation, also provide useful estimates. We do feel, however, that further debate over the issue of inclusion or exclusion of 0 and 100% responses would be particularly useful. Standardization of the methodology would be particularly important.

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Midazolam in a Malignant Hyperthermia-susceptible Patient

To the Editor:—Malignant hyperthermia (MH) is a serious and potentially fatal disorder characterized by acidosis, rigidity, and hyperthermia. Succinylcholine and the halogenated inhaled anesthestics trigger MH,[1] while the benzodiazepines, such as diazepam, do not.[1,2] Midazolam, another benzodiazepine, has been used in 3 MH-susceptible patients without problem.[3] Each of these patients however, was given dantrolene (2.5 mg/kg) prior to the administration of midazolam. A midazolam-induced hyperthermic crisis may have been prevented by the dantrolene pretreatment.[4]

Midazolam was used safely in an MH-susceptible patient at this institution, without dantrolene pretreatment. The patient had previously suffered a hyperthermic crisis during general anesthesia for a kidney transplant, characterized by hyperthermia, hypercarbia, and cardiac arrest. He was successfully treated with dantrolene and survived without sequelae. He was subsequently admitted for core decompression of the right hip, and was given spinal anesthesia with 13 mg tetracaine in 1.3 ml 10% dextrose, with 0.1 ml epinephrine. No known triggering agents were used. A total of 4 mg midazolam was given for intraoperative sedation with good result. His vital signs remained stable both intraoperatively and postoperatively, and he was discharged 48 h after the operation in satisfactory condition.

As a benzodiazepine, midazolam would not be expected to trigger MH. *In vitro* studies of midazolam in biopsied muscle preparations corroborate this hypothesis.[5] In the absence of dantrolene pretreatment, it is reasonable to assume that midazolam was used safely and did not trigger an MH crisis. Further reports, however, will be necessary to firmly establish that midazolam is not a triggering agent of MH.

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