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Questions Regarding a Time-dependent Increase in Sensitivity to *d*-Tubocurarine during Enflurane Anesthesia

To the Editor: —Stanski *et al.*[1] conclude that the sensitivity to *d*-tubocurarine (*d*Tc) increases during the course of enflurane anesthesia. I cannot accept this conclusion without requesting additional analysis of their data.

Their conclusion pivots on the assumption that steady state plasma concentrations of *d*Tc were achieved to the same extent in the halothane group (4 patients) and the enflurane group (5 patients). Did the authors analyze their steady state dTc concentrations in the same manner as their linear analysis of their paralysis data shown in their figure 2? What were the results? Why does their two-compartment mammillary model, which they use to describe and analyze their pharmacokinetic data in their table 1 and figure 1, overestimate the *d*Tc concentrations between 50 and 160 min, and underestimate the concentrations thereafter? Is this a random error or an inherent bias of their model?

These questions become more relevant as we examine several dose response curves for these same drug combinations published previously by investigators from the same institution. The figure presented here (fig. 1) shows the data from three clinical studies of the maximum per cent twitch depression resulting from bolus doses of pancuronium or *d*Tc during halothane or enflurane anesthesia. The doses of pancuronium are multiplied by 10 to facilitate display on the same coordinates.

Curves B and C show the reduced doses of pancuronium required to produce similar degrees of paralysis during enflurane,[2] as compared to halo-

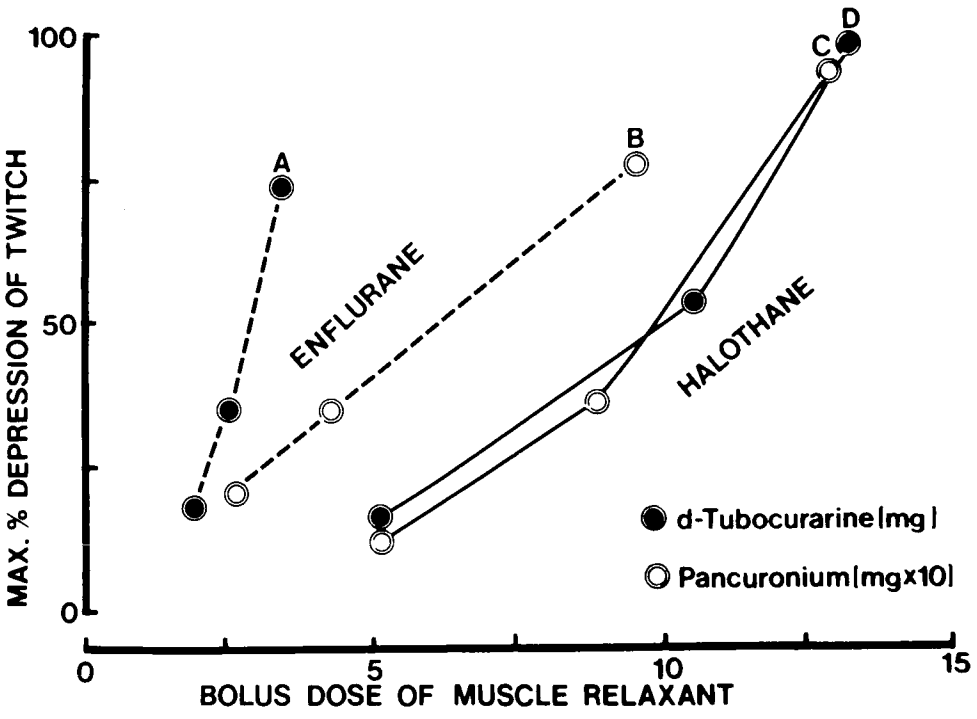

FIG. 1. The mean values of the maximum percent depression of twitch response following bolus doses of either *d*-tubocurarine (closed circles ●) or pancuronium (open circles ○) during either enflurane (broken lines – – –) or halothane (solid lines ——) anesthesia as described in previous studies.[2–4]

thane[3] anesthesia. Note the similar slopes of the dose response curves. Similarly, curves A and D show the reduced doses of *d*Tc required during enflurane[2] as compared to halothane[4] anesthesia. However, the slopes of these curves are remarkably different, with the slope of enflurane (A) much steeper than the slope for halothane (D).

Stanski also notes the nonparallelism of these dose response curves and suggests that this new time-dependent sensitivity effect explains the previous experimental findings. The problem with this explanation is that it is also possible that the nonparallelism observed in the previous studies might explain their time-dependent sensitivity.

Thus, I am left with three questions, the first being most important. Were steady state concentrations of *d*Tc actually achieved? If not, are we observing the pharmacokinetic effects of different approximations to the steady state in the two groups? Or, are we observing the effects of similar increases in *d*Tc concentrations with different pharmacodynamics of *d*Tc during enflurane anesthesia? Neither of these explanations necessitate any speculation about a time-dependent increase in sensitivity.

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In reply: —To be certain that steady state *d*-tubocurarine (*d*Tc) plasma concentrations were present in our study, an analysis similar to that performed on the steady state paralysis data was undertaken, but not reported in the original publication. Linear regression of time *vs.* the *d*Tc plasma concentrations after achieving steady state was performed, and the 95 per cent confidence band of the slope of the regression

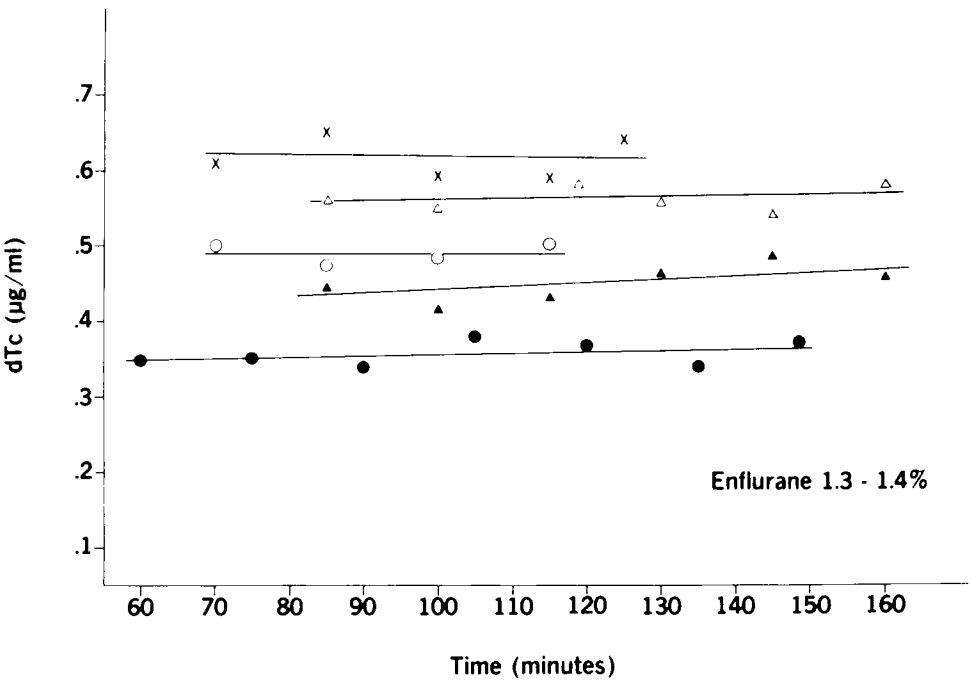

FIG. 1. The steady state *d*Tc plasma concentrations achieved is plotted against the time from the beginning of the first rapid infusion which was followed by a slower maintenance infusion. The solid line represents the linear regression line for the individual patients in the enflurane group.