that could be used as a test dose, regardless of what local anesthetic drug was chosen or whether the regional block was being used for a surgical, obstetrical, diagnostic, or therapeutic procedure. Such a single-dose ampule would hold 2 or perhaps 3 ml of solution containing: 1) 0.015 mg epinephrine to provide evidence of an intravascular injection; 2) 50 mg lidocaine which rapidly results in spinal block of short duration; and 3) 5.0 per cent to 7.5 per cent glucose as a vehicle to provide a specific gravity greater than cerebrospinal fluid, to eliminate the question as to whether the injected solution is iso-, hypo-, or hyperbaric. Although a 1-ml test dose might be more desirable, any loss of it prior to or during injection might result in equivocal results.

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Relaxant Resistance in Disuse Atrophy: Pharmacokinetics *vs.* Pharmacodynamics

To the Editor:—With his recent article,[1] Dr. Gronert has stimulated our interest in muscle relaxant pharmacokinetics and dynamics in altered pathophysiologic states. In a canine model, he has observed an apparent resistance to pancuronium in immobilized, as opposed to active, extremities of the same animal. He concludes that there must be a pharmacodynamic reason for this difference in sensitivity. However, there is an alternative explanation for his results.

After bolus intravenous injection, the plasma concentration of a muscle relaxant will reach a peak immediately, and subsequently decline in a bi-exponential or tri-exponential fashion. However, the effect from that dose requires several minutes to reach a maximum, as we all know from clinical observation. Similarly, the decline in effect lags behind the decline in plasma concentration, and for moderate doses of relaxants, probably includes a component of redistribution as well as elimination of the drug.

Sheiner *et al.*[2] have described a kinetic model for this disequilibrium between plasma concentration and effect after a bolus dose. A rate constant, termed k_{eo}, can be calculated to quantify the time dependent lag between drug concentration in plasma and the site of action. Agents which affect muscle blood flow, such as halothane, have been shown to alter the $t_{1/2}$ k_{eo} for muscle relaxants.[3] If the equilibration time between plasma and the site of action is prolonged, as occurs with halothane, not only will the time to peak effect after a moderate bolus dose be longer, but the fractional effect remaining at a given time interval after the peak will be greater. Conversely, under conditions where muscle blood flow is increased, the peak effect may occur sooner and dissipate faster. It is evident that if one wishes to give repeated small doses of muscle relaxants and measure cumulative effect, the timing of both dosing and effect quantitation relative to this time lag will critically affect the apparent sensitivity to the drug. Sheiner *et al.*[2] demonstrate this relationship very clearly in a series of computer-simulated plasma concentration-response curves (fig. 7 of the article),[2] where a change in $t_{1/2}$ k_{eo}, the equilibration half-time, produces a parallel-shifted curve,

mimicking a pharmacodynamic change in drug sensitivity.

Could this equilibration delay explain Gronert's data? Is perfusion of the neuromuscular junction different in immobilized, atrophied muscle than in normal muscle? The author suggests that muscle blood flow was unchanged by immobilization, but bases that conclusion on earlier work under different anesthetic conditions. Rather than debate this issue from available data, further investigation would seem warranted. The cumulative dose-response technique used by Gronert is not optimal for this sort of study. In fact, when 0.1 mg/kg pancuronium is administered over 90 minutes, the cumulative dose is probably no longer the accurate approximation of a single dose that Donlon *et al.*[4] described when examining the cumulative dose response technique over a 15 minute interval. An infusion of drug to steady state, perhaps accelerated by a loading dose, would be a more satisfactory method of estimating neuromuscular junction sensitivity. At steady state, temporal dysequilibrium between plasma concentration and effect is no longer an issue, since both are constant. A difference in response between two hind limbs of the same animal would then represent a real difference in receptor number or sensitivity—a pharmacodynamic difference.

The clinical reports cited by the author,[5,6] involving patients with upper motor neuron lesions, are suggestive of altered pharmacodynamics. These patients may well have increased receptor number or sensitivity, as manifested by their hyperkalemic response to succinylcholine. The issue of muscle relaxant resistance deserves further investigation, under steady state conditions, in human subjects.

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In reply:—Dr. Holley states that changes in the rate constant for equilibration (k_{eo}) can produce a shift in the dose-response curve and misleadingly suggest relaxant resistance due to pharmacodynamic factors (drug concentration *vs.* biologic effect) rather than pharmacokinetic factors (drug concentration *vs.* time). He refers the reader to figure 7 from the Sheiner *et al.* study[1] which states that k_{eo} equals the ratio of blood flow to tissue partition coefficient, if drug effect is not rate-limited by either diffusion from the blood or a delay after receptor combination.

From the cited figure 7, assuming a constant partition coefficient, blood flow would have to decrease about 50 per cent to account for the relaxant resistance noted in disuse atrophy of the canine gastrocnemius[2] (background anesthetic pentobarbital nitrous oxide). Prior data indicate that blood flow to the canine gastrocnemius is unchanged by total paralysis with gallamine in normal[3,4] and denervated muscle,[4] although the trend is to decrease (background anesthetic halothane). Also, disuse atrophy tends to increase muscle blood flow in this same preparation[5] (background anesthetic halothane; no data regarding nondepolarizing relaxants). As Holley suggests, conditions in these studies are different enough that the data cannot be used to directly answer his criticism. He is of course correct that a study during steady state drug levels should settle the issue in both canine disuse atrophy and humans with relaxant resistance.

One should remember that resistance to nondepolarizing relaxants is estimated by the response of receptor sites activated by nerve terminals. A pharmacokinetic explanation would suggest decreased perfusion or increased tissue partition coefficient in my dog model because the responses of the normal muscle and the contralateral atrophied muscle were measured simultaneously in the intact dog.[2] Immobilization disuse atrophy results in enlargement of the muscle end-plate area and a modest increase in muscle membrane sensitivity to acetylcholine.[6] Thus, the more numerous receptor sites would bind more molecules of relaxant, necessitating a greater total