swelling, one would expect increased serum potassium when 1.5% glycine was given, as the low osmolality of this fluid promotes diffusion of water into the cells.

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References


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In Reply—Hahn highlights an interesting point in regard to hyperkalemia following infusion of isosmotic glycine solution. His study showed that infusion of 1.0 L of isosmotic glycine solution to healthy volunteers induced hyperkalemia, and infusion of 1.0 L of isosmotic mannitol solution induced no change in serum potassium concentration with hyponatremia.1 The latter result corresponds with our result.2 With regard to glycine infusion, he hypothesized that hyperkalemia is related to how much nonelectrolyte solution is transported into the cells. However, if his hypothesis is correct, one would expect that the increase in serum potassium following infusion of hyperosmotic glycine is much more than that of isosmotic glycine. Yet his data showed the same changes in serum potassium caused by hyperosmotic glycine infusion as by isosmotic glycine infusion.3 These results may be due to the differences of renal potassium excretion during his studies. Further studies should be performed to clarify the precise mechanism of serum potassium changes during infusion of several isosmotic nonelectrolyte solutions. We appreciate Hahn’s interesting suggestion.

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Potency Versus Onset of Neuromuscular Blocking Agents

To the Editor:—In the search for the ideal neuromuscular relaxant with rapid onset and short duration of action, the molecular design of such agents through elucidation of the kinetic mechanisms of receptor binding are being pursued and are of great importance. The recent article by Min et al.1 has offered an elegant approach

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to this problem. While recognizing the merits of this important perhaps even landmark contribution, I feel the necessity to make the following comments:

Technical Details: 1) The glass barrel capillary electrodes were filled with various concentrations of the relaxants used, which did not reflect equipotent doses/concentrations; thus the time constants for association and dissociation, as obtained, may be distorted (e.g., relatively much less of gallamine (22.5 mm) than vecuronium (1.6 mm) was delivered during the same time of isotonophoretic diffusion). 2) In figure 3, the dose ratio versus concentration (μ) is shown, but gallamine is not included in the figure. 3) In figures 4–7, the legends state, “Vertical bars indicate the standard deviations for dose ratios,” yet vertical bars cannot be found in any of these figures.

Discussion: The authors state, “In other words, potent drugs have a slow onset and slow onset of action….” Although the data presented in the article seem to support such a hypothesis, one has to consider the following: The idea of applying the dissociation-speed potency concept (described originally for the aspect of duration of action), and thereby to explain speed of onset versus potency correlations, has originated from the animal study of Bowman et al. and an extension of their observations to only three chemically different neuromuscular blocking agents. While these two articles and the present isotonophoretic study seem to support the low potency-fast onset of action hypothesis, generalizations still should be carefully avoided.

To be more specific, in an ongoing study with a large number of trophynl ester-type neuromuscular blocking drugs, we did not observe the proposed low potency-fast onset of action relationship. On the other hand, what we have observed often was a possible correlation between cardiac vagal blocking potency and onset of action. Yet, we would hesitate to make a prediction whereby a new, rapid onset agent would be, a priori, a cardiac vagal blocker. We thus would not propose that one should search for such agents exclusively among cardiac vagal receptor (M₃ muscarinic receptor) blocking drugs.

Furthermore, the proposition that the long awaited rapidly acting nondepolarizing muscle relaxant ought to be of low potency also seems to contradict the conventional approach of new drug design aiming at highly potent and also selective agents. Compounds of low potency often lack specificity and thereby are liable to produce side effects, particularly on chronic administration.

In my opinion, the low potency-rapid onset of action concept may not be applicable as a working hypothesis for the design of new, improved neuromuscular blocking agents.

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In Reply—The concentration of relaxant in the glass electrode is unimportant. For each experiment, several pulses of differing voltages were applied to the electrode until approximately 50% depression was observed. This indicated that the amount of drug released by the electrode was sufficient to produce concentrations at the neuromuscular function that were compatible with neuromuscular blockade. Thus, the concentration of relaxant in the source (the electrode) has no more importance in the concentration in the syringe, when the drug is given to a patient. In the in vitro experiments, the onset and offset times for gallamine were so short that the effect was 100% of steady state when the first acetylcholine pulse was applied. Thus, time constants could not be measured accurately and gallamine is absent from figures 3, 6, 7, and 8. Vertical bars in figures 4 to 7 were deleted for the sake of clarity. The appropriate deletion was not made from the legends. We apologize for this omission.

Potency should be regarded as only one of several factors which may affect onset time in the anesthetized human. We studied the problem in vitro because we wanted to eliminate other confounding factors, such as distribution, elimination, protein binding, cardiac output, and muscle blood flow. We conclude that onset time is directly related to potency, all other factors being equal. However, as potency decreases, the law of diminishing returns applies. Bowman et al.'s data and theoretical considerations suggest that little, if any, decrease in onset time is associated by increasing ED₅₀ beyond 0.1–0.2 mg/kg. This probably explains why Gyermek found no change in onset time among the compounds he tested: the most potent had an ED₅₀ greater than 0.1 mg/kg. Although the likelihood of side