Cumulative Characteristics of Atracurium and Vecuronium: A Simultaneous Clinical and Pharmacokinetic Study

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IN 1979, Steven Weinberg and Abdus Salam were awarded the Nobel Prize for developing the “electroweak” theory of particle physics, the theory that unites quantum electrodynamics with the weak nuclear force. The electroweak theory postulated the existence of W⁺, W⁻, and Z⁰ particles. Identified from theory, the particles finally were observed 5 yr later by experimental physicists at CERN near Geneva.

In this issue of Anesthesiology, we can see, on a smaller stage, the same subtle interplay between theory and experiment. In their model of vecuronium pharmacokinetics, Wright et al. (page 59) saw that vecuronium appeared to become more potent with larger doses. The change wasn’t much: a 250% increase in dose produced a mere 20% decrease in the effect site concentration associated with 75% recovery (e.g., 25% neuromuscular blockade). This small change in potency violated the pharmacodynamic principle of stationarity and prompted an investigation into the mechanism. An unexpected “particle” proved to be the culprit: 3-desacetylvecuronium, an active metabolite of vecuronium. We see the workings of science in the identification of 3-desacetylvecuronium: an unexpected blip in the data, curiosity to pursue an incongruous result, prepared minds open to alternative explanations, and a scientific milieu containing, among other things, individuals knowledgeable about vecuronium metabolites.

Although 3-desacetylvecuronium may not be one of the fundamental building blocks of the universe, (wouldn’t that surprise the physicists!), it is still of importance to the practicing anesthesiologist. Vecuronium use in the intensive care unit has been associated with prolonged neuromuscular blockade,¹ profound myopathy,² and high plasma concentrations of 3-desacetylvecuronium.³ Clearly, 3-desacetylvecuronium is an important molecule about which we know very little and whose clinical effects we need to understand if we intend to administer vecuronium in settings where 3-desacetylvecuronium may accumulate.

Lastly, recognizing that half-lives are difficult to interpret clinically for drugs described by polyexponential pharmacokinetics, Wright et al. have introduced a new term, the “recovery phase half-life.” This half-life is analogous to the “context-sensitive half-time” proposed by Hughes et al.⁴ in that it provides information about the expected time course of drug effect during a clinically relevant portion of recovery. In this case, the recovery phase half-life is the slope of the effect site concentration versus time curve over the period from 25% recovery to 75% recovery. Examining the influence of dose on the recovery phase half-time provides a measure of “cumulation.”

Thus, Wright et al. offer us both theoretical insights and experimental validations to advance our understanding of muscle relaxants. The results are elegant.

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References

HIGHLIGHTS

Jaw Relaxation after a Halothane–Succinylcholine Sequence in Children

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The significance of incomplete jaw relaxation in children given succinylcholine has troubled anesthesiologists for more than a generation. Despite the reported association between isolated masseter muscle rigidity (MMR, variously referred to as “masseter muscle spasm” or “trismus”) and malignant hyperthermia (MH), there is no general consensus as to how a clinician should proceed when faced with the child in whom jaw tightness is perceived after the administration of succinylcholine. This confusion has many causes. Interpretation of jaw relaxation is highly subjective, and terminology has never been standardized. In addition, several widely cited studies present data that appear at variance with common clinical experience. At least two reports suggest that the incidence of MMR in children receiving succinylcholine approximates 1%. Other studies report a 50% association between MMR and vulnerability to malignant hyperthermia. If this is so, then the prevalence of overt MH susceptibility must approach 0.5%. However, large numbers of children (>40,000) have been anesthetized in other series without a single reported case of overt MH. What is the clinician to believe?

In this issue of Anesthesiology, Hannallah and Kaplan (page 99) present a report on the use of succinylcholine in 500 children that puts the above issues into a credible perspective. The paper represents an important contribution to the anesthesia literature on several counts. First, the authors standardize terminology with a simple four-point scoring system: (1) complete jaw relaxation, defined by a mouth that opens fully with simple head extension or pushing on the chin; (2) incomplete jaw relaxation, the mouth opens fully, but firm manual pressure on the teeth is necessary to separate them; (3) masseter muscle rigidity, the mouth cannot be fully opened, but intubation is possible; and (4) trismus, the mouth cannot be opened, the teeth are clamped shut. Second, the study is believable. By these criteria, incomplete jaw relaxation is not an uncommon event. Almost 5% of the children received a score of 2. The authors, however, report only one case of MMR (0.2%) and no episodes of trismus. Hence, modest increases in masseter tone should not be viewed with concern, but MMR or trismus (as defined above) must be treated as possible harbingers of malignant hyperthermia (until proven otherwise).

It should be emphasized that the authors employed a rigid induction sequence. The results reported are unlikely to be reproduced by others who fail to “read the fine print.” Hannallah and Kaplan employed an intubating dose of 2.0 mg/kg succinylcholine, and laryngoscopy was begun 45–60 s later. Intubation time was determined by the clock, not by any temporal relationship to facial fasciculations. It is probable that the high incidence of MMR reported by some investigators was the result of inadequate doses of succinylcholine in the pediatric population.

This study comes at a propitious time in view of recent Food and Drug Administration-mandated changes in the succinylcholine package insert. It represents not only the first prospective investigation (using a standardized scale) of the relationship between succinylcholine and masseter muscle tone but, in all likelihood, the last as well.

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