Rapid Onset/Offset of Rapacuronium Bromide Explained?

To the Editor—The recent article by Wright et al.1 provided interesting and important information on the pharmacodynamics of rapacuronium at the laryngeal adductors and the adductor pollicis. However, we have a number of comments and concerns.

In the Discussion section, the authors mention the observed inverse correlation between the potency (ED50) of nondepolarizing muscle relaxants and their speed of onset, and present their explanation, referencing Hull.2 We would like to call the readers' attention to other work in the field, in particular that of Donati and Meistelman,3 who explained these observations on the basis of “buffering” and presented a plausible pharmacokinetic/pharmacodynamic model quantifying the influence of the acetylcholine receptor concentration and affinity on the time course of action.

The aforementioned explanation is based on the buffering phenomenon by the acetylcholine receptors in the neuromuscular junction (page 20 of Wright et al.'s article). Although there is evidence for the buffering effect in iontophoretic studies in vitro, there is no convincing evidence that buffering plays a role under clinically relevant conditions; therefore, the explanation is still a hypothesis. In addition, the authors do not give an explanation for the rapid offset of rapacuronium.

In the Discussion section, the authors state, “Despite the lack of comparative data, Schiere et al. concluded that Org 9488 is more potent than Org 9487 (rapacuronium),” suggesting there was no solid base for this statement. At that time, however, Schiere et al. already had the data from a similar study on rapacuronium4 and therefore could make this statement on a sound scientific base. In addition, Wright et al. disputed the study design used by Schiere et al., in which the same patients did not receive both rapacuronium and Org 9488 on separate occasions. It should be clear that such a crossover design cannot be performed in a study in surgical patients. The cited study of Caldwell et al.5 was conducted in volunteers. Of course, if the main goal of a study is the assessment of the relative potency of two compounds, a crossover design is preferable. However, if the primary aim of the study is to delineate the pharmacokinetics and clarify the pharmacokinetic/pharmacodynamic relationships in surgical patients, the study design of Schiere et al. might be preferable.

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In Reply.—Proost et al. have several concerns regarding our study. First, they mention other work in the field. We might add the work of Stanski et al.,2 who proposed that "k,, [the rate constant for equilibration between plasma and the effect site] will be directly proportional to perfusion of the neuromuscular junction and inversely proportional to the blood-muscle drug partition coefficient." Proost et al.'s notion of buffering equates to that for partitioning, i.e., a larger tissue/plasma partition coefficient equates to a larger buffering. We assume that within a given series of muscle relaxants, the same magnitude of relaxation results from the action of a specific number of relaxant molecules at the effect site. A drug that has a small muscle/plasma partition coefficient (i.e., is poorly "buffered") requires a large plasma concentration (necessitating a large dose) to yield a sufficient number of (unbuffered) molecules at the neuromuscular junction. Such a drug would have a fast onset, equivalent to the rapid equilibration observed with a poorly soluble inhaled drug such as nitrous oxide. Studies by Bowman et al.,3 Donati and Meistelman,4 Kopman,5 and from our group6 support this relationship between k,,, onset, and potency.

Second, Proost et al. question whether a large k,,, also explains rapacuronium's rapid offset of neuromuscular effect. A large k,,, permits a rapid plasma-effect site equilibration during both onset and offset. Thus, as soon as effect-site concentration peaks, the large k,,, permits effect-site concentration to track the rapidly decreasing plasma concentration. As previously explained, k,,, also affects potency, i.e., the smaller the value for k,,, the larger the dose required to achieve the same peak effect-site concentration. Thus, a smaller k,,, requires administration of a larger dose to achieve the same peak effect. In turn, the larger dose produces a slower recovery. These phenomenon are illustrated in figure 1. An additional factor contributing to rapacuronium's rapid recovery profile is its large plasma clearance. However, differences between drugs in their plasma clearances is not sufficient to explain differences in recovery profile: mivacurium's clearance far exceeds that of rapacuronium. In addition, rocuronium's recovery profile is similar to that of vecuronium despite its smaller clearance.

Proost et al. note our statement that "despite [their] lack of comparative data, Schiere et al. concluded. . ." When our manuscript was published in January 1999, the only public information regarding the study by Schiere et al. was an abstract that included no data regarding the potency of rapacuronium. Although we were aware of Schiere et al.'s results from unpublished sources, it would have been inappropriate for us to "scoop" them regarding their study that was published 2 months later.


Fig. 1. Time course of effect at the adductor pollicis is shown for the same individual displayed in figure 5 in the study by Wright et al.1 The solid line displays the time course after a bolus rapacuronium dose of 1.5 mg/kg. The dotted line displays the time course predicted for the same bolus dose, assuming that k,,, is 2.4 times smaller, i.e., a value similar to that for vecuronium; note that peak effect is less and recovery longer than with the larger k,,,.


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the pharmacokinetics/pharmacodynamics of a compound, then studies need to be performed in patients undergoing those specific procedures; in turn, Schiere et al. should report what types of procedures their patients underwent.

Kopman disputes our claim that time to 25% twitch recovery after rapacuronium is "only slightly longer than after succinylcholine." As Kopman notes, data supporting our statement are provided in the Schildie paper. Rather than debate nuances of language, we note that the onset of rapacuronium is faster than that of presently available nondepolarizing muscle relaxants, and its recovery profile is matched only by mivacurium.

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"Label" Versus "Labeling" of a Drug: There is a Significant Difference

To the Editor—The Special Article by Landow et al.1 is informative. Unfortunately, it correctly intermingles the terms label and labeling. In part, it states: (1) "...the label (package insert)..."; (2) "...using a drug for an indication..."; (3) "...the safely of the drug was precipitated by the discovery that thalidomide, when administered during pregnancy, had caused phocomelia (fetal limb abnormalities) in several thousand infants,"2 and (4) "Table 6. Contents of an Approved Drug Label." In these statements, as well as others in the article, labeling—not label—is the correct term.

Pharmacologically, label and labeling are significantly different terms. The label is the information found on a vial or ampule of a drug as well as on its container.1 It states only the contents of the container (e.g., milligrams per milliliter of the drug, its solvents, etc.), not how to use them safely. The labeling is the package insert.2-4 It and the Physicians' Desk Reference usually contain identical information obtained from clinical information conducted by the sponsor; and (4) "Table 6. Contents of an Approved Drug Label." In these statements, as well as others in the article, labeling—not label—is the correct term!

It was approved for clinical administration.2,4 The amendment to verify the safety of the drug was precipitated by the discovery that thalidomide, when administered during pregnancy, had caused phocomelia (fetal limb abnormalities) in several thousand infants.2

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