CORRESPONDENCE

Anesthesiology
1999; 91:1554

The Onset/Offset Profiles of Rapacuronium and Succinylcholine Are Not Identical

To the Editor:—In their article on the pharmacodynamics of rapacuronium, Wright *et al.*[1] stated that after a 1.5-mg/kg dose, the drug's time course of action (at the adductor pollicis) is similar to what they observed in a previous study after 1.0 mg/kg of succinylcholine.[2] I think this statement is somewhat misleading. Although the onset profiles of both drugs do indeed seem equivalent, the same is not true of offset.

In their study, they reported a bolus to 25% recovery interval of 13.4 ± 3.2 min after rapacuronium. This is not clinically comparable to their data for succinylcholine (8.0 ± 2 min). Certainly, the recovery index noted for rapacuronium (8.8 ± 1.6 min) is far longer than the value usually cited for succinylcholine, which is at most 2–3 min. It should also be noted that 1.5 mg/kg rapacuronium represents not more than 2 times the ED_{95}, whereas 1.0 mg/kg succinylcholine represents 3–4 times the ED_{95}.

Based on currently available information, rapacuronium should be viewed as a rapid-onset blocking agent of short rather than ultrashort duration.

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(Accepted for publication June 23, 1999.)

Anesthesiology
1999; 91:1554–5

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 pharmacokinetic/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 (ED_{95}) 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 that there was no solid base for this statement. At that time, however, Schiere *et al.* already had the data from a similar study on rapacuronium[4] 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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(Accepted for publication June 23, 1999.)

Anesthesiology
1999; 91:1555-6

In Reply:—Proost *et al.* have several concerns regarding our study.[1] First, they mention other work in the field. We might add the work of Stanski *et al.*,[2] who proposed that "k_{eo} [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 group[6] support this relationship between k_{eo}, onset, and potency.

Second, Proost *et al.* question whether a large k_{eo} also explains rapacuronium's rapid offset of neuromuscular effect. A large k_{eo} permits a rapid plasma-effect site equilibration during both onset and offset. Thus, as soon as effect-site concentration peaks, the large k_{eo} permits effect-site concentration to track the rapidly decreasing plasma concentration. As previously explained, k_{eo} also affects potency, *i.e.*, the smaller the value for k_{eo}, the larger the dose required to achieve the same peak effect-site concentration. Thus, a smaller k_{eo} 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[7] 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![8]

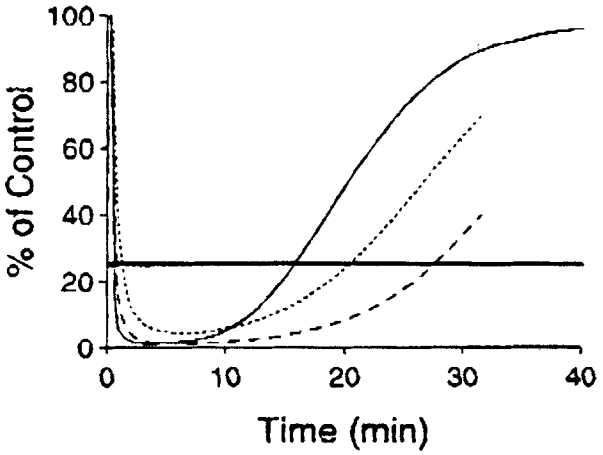

Fig. 1. Time course of effect at the adductor pollicis is shown for the same individual displayed in figure 3 in the study by Wright *et al.*[1] The solid line displays the time course after a bolus rapacuronium dose of 1.5 mg/kg. The dotted line displays the time course predicted for the same bolus dose, assuming that k_{eo} is 2.4 times smaller, *i.e.*, a value similar to that for rocuronium[1]; note that peak effect is less and recovery longer than with the larger k_{eo}. The dashed line displays the predicted time course for a bolus dose (2.3 mg/kg) that yields that same peak effect-site concentration as the solid line, assuming the smaller k_{eo}; note that recovery is yet longer. Therefore, a larger k_{eo} (more rapid equilibration between plasma and effect site) speeds both onset and recovery.

Finally, Proost *et al.* challenge our recommendations to study volunteers using a crossover design to determine the relative potency of rapacuronium and its metabolite. One assumption in analyzing data from an unpaired study is that groups differ only in a single factor, in this case, the drug under investigation. Unless subjects are carefully matched, this assumption may be flawed. One means to assure that subjects in different groups are comparable is to study each individual on more than one occasion, *i.e.*, a crossover design. Proost *et al.* are concerned that studies in volunteers undergoing anesthesia might not apply to patients undergoing anesthesia and surgery. We contend that anesthetized volunteers differ minimally from healthy patients undergoing minimally invasive surgery. If different surgical procedures affect

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 same sentence. 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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(Accepted for publication June 23, 1999.)

Anesthesiology
1999; 91:1556

"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 incorrectly intermingles the terms *label* and *labeling*. In part, it states: (1) ". . .the label (package insert). . ."; (2) ". . .using a drug for an indication. . .a route of administration or a dose not described in the label is considered unapproved or 'off label' use"; (3) "The drug label serves two important functions: it present the indications for which a drug is approved and it summarizes safety and efficacy 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!

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.[2,3] 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.[2,3] It and the *Physicians' Desk Reference* usually contain identical information. Before the passage of the Harris-Kefauver Drug Amendments of 1962, the Pure Food and Drug Act of 1902 required only a label.[2] After passage of the Harris-Kefauver Amendment (1962), labeling (description of the drug, indications and usage, contraindications, warnings, adverse reactions, and so forth), *i.e.*, the safety of the drug, was required before it was approved for clinical administration.[2,3] 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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(Accepted for publication June 22, 1999.)