Volume 62, No. 4
April 1985

THE JOURNAL OF Anesthesiology
THE AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC.

EDITORIAL VIEWS

Anesthesiology
62:381–382, 1985

The Priming Principle

VECURONIUM AND ATRACURIUM are two relatively new nondepolarizing neuromuscular blocking drugs that have durations of action one-third to one-half that of all other currently available nondepolarizing neuromuscular blockers (*e.g.*, pancuronium and *d*-tubocurarine). Although these two new neuromuscular blockers have many desirable characteristics, such as little or no cardiovascular effects and lack of dependence on the kidney for elimination, they have the distinct disadvantage of having a relatively slow onset time (time from administration to peak effect). Doses of atracurium and vecuronium that depress twitch tension less than 100% of control have onset times ranging from 4 to 8 min.[1] Because larger doses depress twitch tension 100%, onset times appear to be shorter. Despite claims that onset times can be less than 2 min, most studies indicate that endotracheal intubation cannot be accomplished in less than 2 min following the administration of large doses of vecuronium (*e.g.*, 0.1 mg/kg) or atracurium (*e.g.*, 0.5 mg/kg).

Furthermore, clinicians should view those studies evaluating intubating conditions with various neuromuscular blocking drugs with caution. Clinically, those factors that contribute to adequate intubating conditions are notoriously difficult to precisely define. For example, with deep anesthesia, intubating conditions are often excellent without a neuromuscular blocking drug. Thus, in the presence of general anesthesia, the contribution of the neuromuscular blocking drug to the overall intubating conditions is difficult to ascertain.

Despite the many problems in judging studies of intubating conditions, the value of vecuronium and atracurium would be enhanced considerably if they had a shorter onset time, especially for those situations in which a rapid sequence of inducing anesthesia and intubating the trachea is necessary (*e.g.*, a patient who has eaten recently). The "priming principle," proposed by Schwartz *et al.*[2] and Mehta *et al.*,[3] appears to accomplish this need. The priming principle basically refers to the administration of a small (usually and hopefully subparalyzing) dose of a nondepolarizing neuromuscular blocking drug several minutes before the intubating dose is given. The hypothesis is that this approach will markedly shorten the onset time of nondepolarizing neuromuscular blocking drugs.

With each neuromuscular blocking drug, three questions need to be answered. First, what is the ideal "priming" dose? Schwartz *et al.*[2] studied two doses of vecuronium (0.015 mg/kg and 0.02 mg/kg) and found no difference in the time required for adequate intubating conditions. However, they defined an adequate intubating condition as a decrease in twitch tension to 15–25% of control. Yet, three of eight patients who received the 0.015 mg/kg dose and two of 12 patients who received the 0.02 mg/kg dose had only good intubating conditions (*i.e.*, diaphragmatic movement was still present). Perhaps waiting until twitch tension had completely disappeared would have created uniform excellent intubating conditions. The onset time tended to be shorter with the larger 0.02 mg/kg priming dose (84 ± 5 s) than the smaller 0.015 mg/kg priming dose (125 ± 18 s), although this apparent difference was not statistically significant. Would a larger priming dose be more effective? If so, would undesirable signs of weakness result? Conversely, would a smaller dose be equally effective?

Secondly, is the time interval between the priming dose and the intubating dose important? Schwartz *et al.*[2] studied only a 6-min time interval based on the documented observation that the time from administration of vecuronium to its peak effect frequently is in the 6-

Accepted for publication November 6, 1984.

min range. Mehta *et al.*[3] arbitrarily decided to study a 3-min time interval. Clearly, a shorter time interval would be helpful, especially in the urgent clinical situation. Obviously, the precise time interval requires further definition.

Lastly, what is the appropriate intubating dose of vecuronium or atracurium? Schwartz *et al.*[2] used only the 0.05 mg/kg and the 0.06 mg/kg intubating dose of vecuronium. Would a larger dose be associated with a shorter onset time? If so, this certainly may be advantageous, despite a possibly longer duration of action. Mehta *et al.*[3] utilized a 0.4 mg/kg intubating dose of atracurium. Only 13 of 30 patients had excellent intubating conditions, which suggests that perhaps a larger intubating dose would be more advantageous.

Many of the conclusions of both studies were based on data from anesthetized patients. Although Schwartz *et al.*[2] were able to intubate the trachea in 80 s in patients in whom the priming dose was given in the awake state, whether a better priming and intubating dose and time interval between these doses exists remains to be seen. One problem with the Mehta *et al.*[3] study is that there was no control group (patients who receive the intubating dose of neuromuscular blocking drugs without the priming dose). In addition, patients in the Mehta *et al.*[3] study did not receive the same neuromuscular blocking drug for both the priming and intubating doses.

Despite all the questions listed above, the priming principle clearly appears to shorten the onset time that certainly will help offset one of the few disadvantages of vecuronium and atracurium. Schwartz *et al.*[2] and Mehta *et al.*[3] are to be congratulated for their extensive studies, which totaled over 200 patients. However, despite the large number of patients studied, the priming dose, the intubating dose, and the time interval between these two doses need better definition. Although the answered questions associated with the priming principle lend themselves to many limited studies, examining only one aspect of this issue, this Editor hopes that investigators will select a more difficult path of performing large and comprehensive studies from which the clinician can better determine the best way to shorten the onset time of vecuronium and atracurium without adverse effect.

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62:382–384, 1985

Clinical Implications of the Modulated Receptor Hypothesis: Local Anesthetics and the Heart

THE RELATIVE CARDIOTOXICITY of some local anesthetics has been discussed widely at anesthesia meetings and in anesthesia journals in recent years, at first on the basis of case reports[1] and then on results drawn from animal experimentation.[2] Before the question was raised as a clinical problem, however, a possible mechanism for selective toxicity of some agents already had been outlined in the basic physiology literature. According to the modulated receptor hypothesis, local anesthetic conduction block is modulated by the conformational state of the sodium channel. The concept of state-dependent channel block in nerves first was presented in a pair of landmark papers in the *Journal of General Physiology* in 1977[3,4]; a version of the concept applied to cardiac muscle was introduced almost simultaneously.[5] State-dependent channel block, when added to restricted access of some local anesthetics to the receptor in the channel, underlies the phenomenon of frequency-dependent (or use-dependent) local anesthetic conduction block. The paper by Clarkson and Hondeghem in this

Accepted for publication November 29, 1984.
Key words: Anesthetics, local: bupivacaine; lidocaine. Heart: conduction; excitability. Toxicity: local anesthetics.