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No Substitute for the Intravenous Route

PEDIATRIC anesthesia is a world of many challenges, and the difficulty of intravenous access in young patients has triggered many investigations into the feasibility of administering drugs, including neuromuscular blocking agents, *via* the intramuscular route. In this issue, Denman *et al.*[1] describe the findings of a multicenter study about intubating conditions after intramuscular administration of rapacuronium. The results are disappointing: Intubating conditions were poor, onset was slow, and duration of action was prolonged. Then, the question of the proper place of intramuscular neuromuscular blocking drugs arises.

Until the 1990s, succinylcholine was the only drug that had been tested for intramuscular use in infants and children. The proper dose was suggested to be 4 mg/kg in infants[2] and children,[3] based on a twitch depression of more than 90%. Unfortunately, onset time at the adductor pollicis was long (approximately 4 min). The authors conclude that "the onset time . . . may be too long for emergency situations,"[2] and, "In an already asphyxiated child, the 3 or 4 min required for maximum relaxation after 4 mg/kg argues against its use."[3] Duration of action was 15–20 min. In the 1990s, two other considerations led to a reexamination of intramuscular neuromuscular blockers in children. Onset of blockade in centrally located muscles, such as the larynx and the diaphragm, was found to be faster than in the hand, and this indicated that adequate intubating conditions might be present before block at the adductor pollicis reached its maximum value. Secondly, reports of cardiac arrest after administration of succinylcholine in previously undiagnosed muscular dystrophy patients led to a controversial warning on the succinylcholine package insert that suggested to reserve its use in children "to emergency situation or for instances when immediate securing of the airway is necessary."[4] This prompted the study of newer, nondepolarizing drugs administered intramuscularly.

The usefulness of intramuscular mivacurium was considered to be limited because doses as high as 800 μg/kg failed to produce consistent twitch depression, onset time averaged 15 min, and recovery took as long as 1 h.[5] In an attempt to obtain information on respiratory muscles, minute ventilation was measured. As expected, ventilation was depressed before twitch height at the thumb was, but the time course of blockade at the respiratory muscles was still too slow. Rocuronium was the object of a more thorough and focused investigation. First, a dose-ranging study was performed with tracheal intubating conditions as the endpoint. The recommended doses (1 mg/kg in infants and 1.8 mg/kg in children) produced paralysis for 60–120 min.[4] In a follow-up pharmacokinetic study by the same group,[6] peak plasma concentrations of rocuronium were found 13 min after intramuscular injection, which explains the slow onset and the need for large doses. Fortunately, the technique was tested in a large multicenter trial, and, surprisingly, the results somewhat contradict the dose-ranging study. After waiting 3.5 min in infants and as long as 4 min in children, good to excellent intubating conditions were found in only 25% of infants and 35% of children, compared with 85 and 93% after a modest 0.45 mg/kg rocuronium administered intravenously.[7]

With a rapid onset and short duration when administered intravenously, rapacuronium offered enough potential advantages to deserve a similar investigation as an intramuscular drug. The dose for tracheal intubation was 2.8 and 4.8 mg/kg in infants and children, respectively, when intubation was attempted at 3 and 2.5 min, respectively. Onset time at the adductor pollicis was more than 5 min, and duration to 25% recovery was 39 min in infants and 49 min in children.[8] This represented an improvement over rocuronium. Pharmacokinetic analysis also suggested a peak plasma concentration of rapacuronium 5 min after injection, better than the 13 min obtained with rocuronium.[9] The multicenter study reported in this issue was prompted by the promising results of this study. Again, history repeated itself. Good to acceptable intubating conditions were found in only half the patients if laryngoscopy was attempted 3 min or less after intramuscular injection of rapacuronium and only 64–71% if the interval was 4 min.[1] Measured onset times and duration of action at the adductor pollicis were essentially a carbon copy of the pilot study.

It might be interesting to speculate on the reasons why the results of two multicenter trials were different from those of the pilot studies. Differences in response to the drugs between centers cannot be an explanation because onset and recovery were virtually identical in the pilot and multicenter studies. A large variability in the assessment of intubating conditions is unlikely. Careful scrutiny of the design of the pilot study provides a clue. The dose was chosen on the basis of time to depression

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of ventilation, which is not necessarily a good indicator of intubating conditions. When the dose was found, an up-and-down method was used, using tracheal intubating conditions as the endpoint, to determine the interval before laryngoscopy was attempted, in a design analogous to minimum alveolar concentration determination. If conditions were rated as good or excellent, the interval was decreased for the next patient, and increased if they were not. Just as minimum alveolar concentration determination finds the dose at which 50% of patients do not move in response to a skin incision, this design determined the interval required for good to excellent conditions in only 50% of patients, which is more or less what the multicenter studies found.

Two considerations come to mind with respect to the use of intramuscular neuromuscular blocking drugs in pediatric anesthesia. First, the insertion of an intravenous catheter should be planned for every anesthetic, regardless of whether muscle relaxants are administered for, among other reasons, fluid replacement and treatment of bradycardia. Second, intramuscular nondepolarizing agents are an uninteresting proposition. Although intramuscular rapacuronium is superior to either mivacurium or rocuronium administered *via* the same route, its onset is slow (> 4 min), the intubating conditions are inadequate, and clinical duration is too long (30–60 min). If the airway is controlled, intravenous access should be obtained instead of administering intramuscular relaxants. If a difficult airway is anticipated or if the patient has a full stomach, an intravenous catheter should be secured before induction of anesthesia.

If anesthesia is induced *via* face mask without previous intravenous access and laryngospasm occurs, the comment made in 1981 about intramuscular succinylcholine applies to intramuscular rapacuronium: "In an already asphyxiated child, the 3 to 4 min required for maximum relaxation . . . argues against its use."[3] The "cannot insert the intravenous catheter, cannot ventilate" scenario should be dreaded as much as the "cannot intubate, cannot ventilate" situation. Help should be sought to search for intravenous access, and no site, including the femoral route,[10] should be rejected. At the same time, all possible strategies to relieve laryngospasm should be considered, including airway suctioning, repositioning, and rapid positive-pressure breaths with application of positive end-expiratory pressure. If intravenous access is obtained before the airway becomes patent, muscle relaxants are not the only option. Propofol might break laryngospasm and allow spontaneous breathing to resume, thus making rapid awakening of the patient possible.

The poor performance of intramuscular relaxants should be another reason, among many others, to insert an intravenous catheter in all pediatric patients who are administered an anesthetic. With good planning and careful practice, the need for intramuscular neuromuscular relaxants should be a rare occurrence.

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