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Atracurium Infusion in Infants

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Atracurium can be given as a continuous infusion to maintain a constant degree of neuromuscular blockade in adults and children,[1–3] but this use has not been demonstrated in infants. In this study, atracurium was administered to small infants *via* continuous infusion to establish the dose requirements in this patient group, and to determine whether these very young patients are more sensitive to this drug, as has been suggested by some investigators.[4–6]

MATERIALS AND METHODS

The study was approved by the Subcommittee on Human Studies, Committee on Research. Ten infants 2 days to 3 months of age (mean ± SE 28 ± 8 days) requiring neuromuscular relaxation for their surgical procedures were evaluated. Their weight varied between 2.6–4.4 kg (3.8 ± 0.2 kg). None of the infants was premature at birth or was receiving aminoglycoside antibiotics.

Anesthesia was induced by inhalation of N_2O:O_2 and halothane. The inspired halothane concentration was maintained at approximately 1% and adjusted according to the requirement of the patient. The EKG, arterial blood pressure, and pulse oximeter were monitored; the esophageal temperature was 35.5–37° C; and the end-expired CO_2 concentration was maintained between 28–40 mmHg. The ulnar nerve was stimulated at the wrist *via* surface electrodes. The single supramaximal stimuli (duration 0.2 ms) were generated by a Grass® S88 stimulator at a rate of 0.1 Hz. The response of the adductor pollicis muscle was recorded *via* a Grass® force displacement transducer (FT-03).

Following a minimum of 2 min of stable twitch response, 0.4 mg/kg iv of atracurium was administered. When the twitch response had recovered to about 25% of control twitch height, a continuous infusion of atracurium was initiated. The infusion solution was prepared by mixing atracurium 50 mg in 245 ml dextrose 5% and water to yield an atracurium concentration of 200 μg/ml. The solution was administered *via* an IMED infusion pump. The initial infusion rate was set in the range of 8–14 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and then adjusted as necessary to maintain 90–99% muscle twitch suppression for the duration of the surgical procedure. The atracurium infusion was discontinued near the end of the surgical procedure.

The polygraph record of the twitch response for each patient was examined to determine the onset (time from injection of the bolus dose of atracurium to the occurrence of maximum neuromuscular depression), the maximum neuromuscular blockade (percent of control twitch height), and the time of recovery to 5% and 25% control twitch response. Beginning with the initiation of the infusion and every 3 min thereafter, the atracurium infusion rate and twitch suppression (percent of control) were analyzed; these data were then used to calculate the mean infusion rate and neuromuscular blockade for each patient.

RESULTS

The neuromuscular effects of 0.4 mg/kg atracurium during single twitch stimulation of the ulnar nerve in the studied infants are summarized in table 1. This dose caused complete suppression of the twitch response in six of the ten patients; 90–99% twitch suppression was observed in the other four patients. The maximum suppression of the twitch response was achieved in a mean time of 1.8 ± 0.3 min.

The mean (±SE) infusion rate required to maintain 93.2 ± 0.6% depression of the twitch response in the first 90 min of observations was 7.6 ± 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$. In the initial 30 min, when frequent adjustments of infusion rates were needed, the mean infusion rate was 8.8 ± 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ achieving 90.2 ± 1.6% neuromuscular blockade. In the next 60 min, 7.3 ± 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was needed to achieve 93.8 ± 0.4% blockade (fig. 1). A lesser number of patients were observed in the following 90 min of infusion. Initially, there were seven patients, and then three at the end of 180 min. In this latter interval, the mean

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TABLE 1. The Neuromuscular Effect of 0.4 mg/kg Atracurium in the Infants Studied

	Mean ± SE	Range
Maximum twitch suppression (%)	98 ± 1	90–100
Time from atracurium administration to maximum twitch suppression (min)	1.8 ± 0.3	1–3
Time from maximum neuromuscular depression to recovery to 5% of control twitch height (min) n = 9	22.7 ± 3.7	9–42
Recovery from 5–25% of control (min) n = 7	8.1 ± 1	5–12

infusion requirement to maintain 92.5 ± 0.3% depression of the twitch was 7.6 ± 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

Figure 2 depicts the individual atracurium infusion requirements noted in the present study. The two smallest infants in this series showed different types of response; the first was relatively sensitive, requiring only 3.6 ± 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during the 30–90-min infusion period. The second infant required 6.8 ± 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$, a rate near the mean of all infants studied. At the individual level, a marked variation was noted in the infusion requirements of our sample of ten infants.

At the termination of infusion, a mean twitch depression of 94 ± 2% was present. Recovery to 25% of control occurred in 13 ± 2 min. In three subjects, surgery terminated at 25% spontaneous recovery. In these subjects, neuromuscular blockade was satisfactorily antagonized by atropine 0.01 mg/kg and neostigmine 0.03 mg/kg in 2–5 min. In the remainder, the twitch response recovered to 95% in 26 ± 6 min following the termination of infusion. All infants showed complete clinical recovery from neuromuscular blockade as evidenced by ability to lift their legs, open their eyes, and cry upon stimulation.

DISCUSSION

In this study of infants 2–90 days old, onset of maximum twitch suppression occurred in 1.8 ± 0.3 min after the initial 0.4 mg/kg of atracurium. This is a comparable interval to that observed in an earlier trial of older infants 6 weeks to 1 yr old.[7] In the latter study, complete ablation of the train-of-four response was noted in 1.6 ± 0.3 min. Subjects in both studies were anesthetized with halothane and had received the same dose of atracurium. Whereas the present study used single twitch stimuli, the previous study did use train-of-four stimuli. In both studies, each stimulus was delivered every 10 s (0.1 Hz). It has been noted that faster onset times can be obtained by stimulation with the train-of-four method.[3] I conclude, then, that small infants less than 6 weeks of age may possibly, but not necessarily, respond faster to atracurium than do older infants. In the early study, complete suppression of the twitch occurred in all subjects, while, in the present study, only six out of the ten subjects showed complete paralysis, producing a mean twitch suppression of 98 ± 1%.

Using additional primary data, a further comparison can be made of infants *versus* older children when the dosage of atracurium and mode of stimulation are the same.[3] With single twitch stimulation at an initial dose of 0.4 mg/kg atracurium, infants do seem to respond faster. In children in the presence of halothane anesthesia, 99.3 ± 0.3% twitch suppression occurred in 3.7 ± 0.8 min; in the present study of infants, 98 ± 1% suppression occurred in 1.8 ± 0.3 min.

The atracurium infusion requirements observed in the present study of small infants (7.6 ± 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$) are slightly lower, but not significantly different, from those values obtained in children (8.3 ± 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$) in the earlier investigation.[3] The subjects in both studies were anesthetized with the same technique, and the same frequency of stimulation was

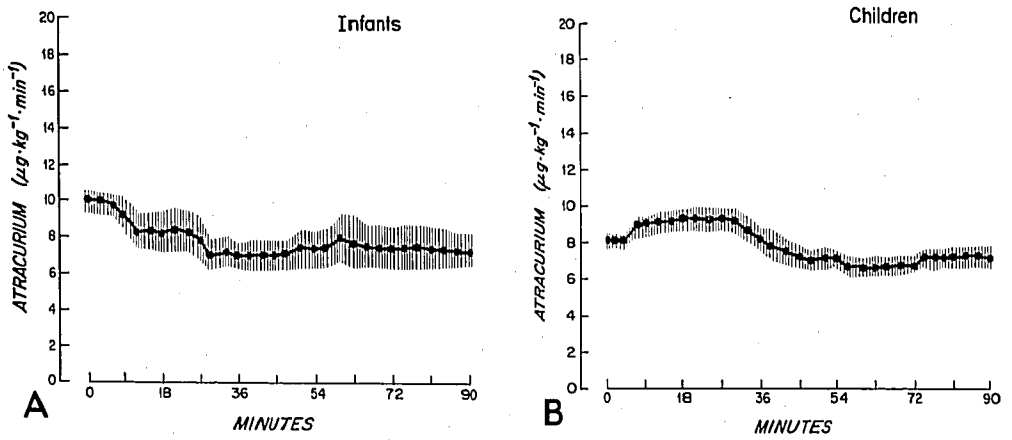

FIG. 1. The mean (±SE) atracurium infusion requirements of infants (*A*), and children (*B*). The data for children are from the study of Goudsouzian *et al.*[3] performed in the same institution with the same technique.

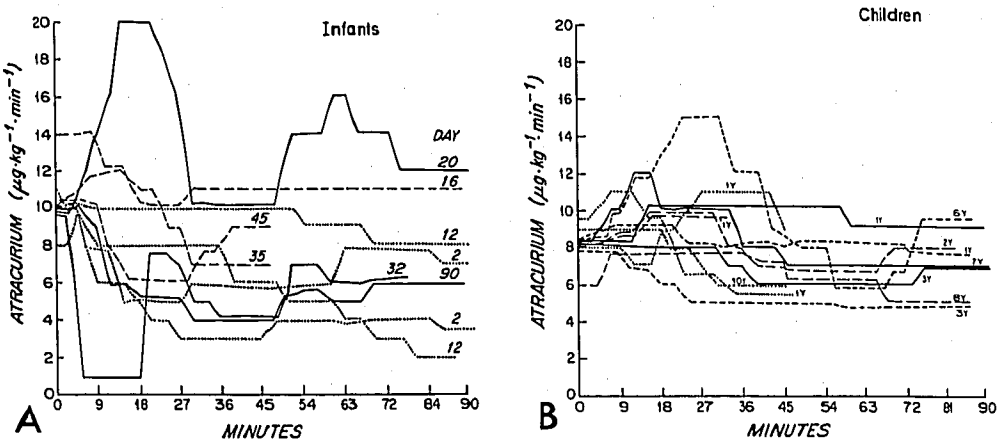

FIG. 2. *A.* The individual atracurium infusion requirements of the infants studied. *B.* Atracurium infusion requirements of children (data derived from Goudsouzian et al.[5]). Note the more marked individual variations in infants.

used. In the present investigation, the duration of infusion lasted more than four times the elimination half-life of atracurium. Consequently, I presumed that an equilibrium is established between the drug concentration in plasma and the tissues, including the site of drug action.[8] Using the steady-state infusion technique, the requirement of the small infants did not markedly differ from children. If such difference does exist, it is a relatively small one and probably clinically insignificant.

Brandom *et al.*[4] have found that the effective dose of atracurium was slightly lower in infants than in children. In a later pharmacokinetic study,[9] they found that the volume of distribution (area) was larger in infants than in children (176 *vs.* 139 $ml \cdot kg^{-1}$), whereas the clearance was faster in infants (9.1 *vs.* 5.1 $ml \cdot kg^{-1} \cdot min^{-1}$). From these observations, we might presume that infants require lower plasma concentrations than do children to achieve the same degree of neuromuscular relaxation and, hence, have lesser infusion requirements. In fact, no such difference was observed when a continuous infusion was used to administer the drug. Indeed, if infants require lower plasma concentrations, then the two factors—larger distribution volume and faster clearance—may compensate for each other and, hence, the maintainance requirements would basically remain the same.

In my observations, the need for atracurium did not change once a steady state was established, even after 180 min of infusion. Once the infusion was discontinued, the recovery occurred at a predictable rate and was complete in approximately 30 min. These facts indicate that infants, like children and adults, do not develop tachyphylaxis or bradyphylaxis after lengthy continuous infusion, and that the modes of elimination of atracurium are as effective in infants as in adults.

In conclusion, this study demonstrated that atracurium infusion can be used in infants. We observed that these very young patients require practically the same rates as do children, with large individual variations.

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