

Continuous Infusion of Atracurium in Children

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Atracurium infusion requirements were determined in 28 children anesthetized with N₂O:O₂ narcotic, N₂O:O₂ halothane (1% inspired), and N₂O:O₂ enflurane (2% inspired). When the patient was recovering from a bolus dose of 0.4 mg/kg atracurium, a continuous infusion of atracurium was started and the rate was adjusted to maintain 90–99% muscle twitch depression. Patients receiving enflurane anesthesia required atracurium at an infusion rate of $4.9 \pm 0.3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ which was a significantly lower rate ($P = 0.0001$) than those anesthetized with halothane ($8.3 \pm 0.4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) or with N₂O:O₂ and narcotic ($9.3 \pm 0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). At the onset of neuromuscular blockade, the twitch response disappeared faster after train-of-four stimulation repeated every 10 s than after single twitch rates of stimulation at 0.1 Hz. In children, during halothane anesthesia after 0.4 mg/kg atracurium, the response of the adductor of the thumb was ablated in 2.0 ± 0.3 min with train-of-four stimulation, and in 3.7 ± 0.4 min with single twitch stimulation. The authors recommend the use of a nerve stimulator during continuous infusion of atracurium because of the marked interpatient differences in infusion-rate requirements. (Key words: Anesthesia: pediatric. Neuromuscular relaxants: atracurium.)

ATRACURIUM, A NONDEPOLARIZING neuromuscular blocking agent with an intermediate duration of action, is degraded mostly by ester hydrolysis in plasma and by Hofmann elimination; thus, it is suitable for administration as a continuous intravenous infusion.^{1,2} In this study, the feasibility of administration and dose requirement was evaluated in children on continuous atracurium infusion during N₂O:O₂:narcotic, N₂O:O₂:halothane, and N₂O:O₂:enflurane anesthesia.

Methods

This study was approved by the Subcommittee on Human Studies, Committee on Research of the Massachusetts General Hospital. Parental written informed consent was obtained for each patient.

Twenty-eight ASA Class I children, age 1 to 10 yr (mean ± SEM, 3.9 ± 0.6 yr), who required neuromuscular relaxation for their surgical procedure were studied. The

children were premedicated with rectal methohexital (20–30 mg/kg). General anesthesia was induced in each patient with N₂O:O₂ administered in conjunction with enflurane, halothane, or intravenous thiopental and morphine.

Children were assigned randomly to one of the three anesthetic groups. Group I (n = 9) received N₂O/O₂ (2:1 ratio), followed by thiopental (2 mg/kg increments) and morphine (mean ± SE, 0.17 ± 0.02 mg/kg). Group II (n = 11) received N₂O/O₂ and halothane (1% inspired concentration). Group III (n = 8) received N₂O/O₂ and enflurane (2% inspired). After the initial stabilization of the patient, the inspired anesthetic concentration was kept constant almost to the end of the surgical procedure.

The ECG, blood pressure, and esophageal temperature were monitored in each patient. The end-expired carbon dioxide concentration was maintained between 36–44 mmHg. The ulnar nerve was stimulated at the wrist *via* surface electrodes. Each single supramaximal stimulus (duration = 0.2 ms) was generated by a Grass S88 Stimulator® at a rate of 0.1 Hz. The response of the adductor pollicis muscle of the thumb was recorded through a Grass FT-03® force-displacement transducer on a Grass Polygraph®.

Following initial stabilization of the vital signs and the twitch height, each patient was given 0.4 mg/kg atracurium as an intravenous bolus injection over less than 15 s. Endotracheal intubation was performed 2 to 3 min following atracurium administration.

The muscle-twitch response to repetitive stimulation was monitored and recorded throughout the surgical procedure. Once the twitch response started to recover following the initial atracurium bolus dose, a continuous infusion of atracurium was initiated. The infusion solution was prepared by admixing atracurium, 50 mg, in 245 ml of dextrose 5% and water to yield an atracurium concentration of 200 μg/ml. The solution was administered *via* an IMED® infusion pump. The initial atracurium infusion rate was set in the range of 6–10 μg · kg⁻¹ · min⁻¹ atracurium. Typically, patients under enflurane anesthesia initially were administered 6–7 μg · kg⁻¹ · min⁻¹ of atracurium; whereas, patients under narcotic or halothane anesthesia were administered 8–10 μg · kg⁻¹ · min⁻¹. In each patient, the rate of the continuous atracurium infusion was adjusted to maintain 90–99% muscle-twitch suppression for the duration of the surgical procedure. Initially, it was discovered that the twitch response would disappear if the patients on enflurane were started at a

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TABLE 1. Depth, Onset, and Recovery from Neuromuscular Blockade Following 0.4 mg/kg Atracurium and Infusion Data

Variable	Anesthesia Type		
	N ₂ O:Morphine (n = 9)	N ₂ O:Halothane (n = 11)	N ₂ O:Enflurane (n = 8)
Maximum twitch suppression (%)	99.2 ± 0.4	99.3 ± 0.3	99.0 ± 0.4
Time to onset of maximum twitch suppression (min)	3.9 ± 0.4	3.7 ± 0.4	3.7 ± 0.8
Time from bolus dose to beginning of recovery (min)	16.2 ± 1.6	19.4 ± 1.6	25.6 ± 4.2
Time from bolus dose to initiation of infusion (min)	18.3 ± 1.7	24.5 ± 1.8	30.7 ± 4.7*
Duration of infusion (min)	101.0 ± 17.1	76.3 ± 9.5	102.6 ± 15.1

Values Presented as mean ± SEM.

* Significant differences from N₂O:morphine group, $P = 0.006$.

higher infusion rate, necessitating discontinuation of infusion until the twitch response was again detectable.

The polygraph record of the twitch response for each patient was examined to determine the onset, depth, and time to recovery from the initial atracurium bolus dose. Beginning with the initiation of the infusion and every 3 min thereafter, the atracurium infusion rate and level of muscle-twitch suppression (neuromuscular blockade) were recorded and subsequently analyzed. Atracurium infusion requirements were estimated by calculating the infusion rates observed at each of the 3-min time points to determine a mean infusion rate for each patient. These average rates were grouped together by anesthesia type. A similar method was used to calculate corresponding average levels of neuromuscular blockade. The infusion rate and the neuromuscular blockade were analyzed by using analysis of variance methodology to make three pairwise comparisons among the types of anesthesia (narcotic *vs.* halothane, narcotic *vs.* enflurane, and halothane *vs.* enflurane).³ Observed differences were considered significant when $P < 0.05$.

Results

Atracurium, 0.4 mg/kg, produced a mean $99.2 \pm 0.5\%$ suppression of the muscle-twitch response within an av-

erage of 3.8 ± 0.9 min. The time interval for the beginning of spontaneous recovery of twitch following the bolus dose did not differ significantly between the three groups (table 1). Infusion of atracurium was initiated approximately 5 min following the beginning of recovery and was continued for at least 45 min in 90% of the patients studied.

Table 2 displays the average atracurium infusion rates and corresponding levels of neuromuscular blockade calculated. Continuous atracurium infusion rates averaging 9.3, 8.3, and $4.9 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ produced the desired level of muscle relaxation (averages of 93–95% depression of twitch) in patients receiving N₂O and morphine, halothane, or enflurane anesthesia, respectively. Infusion rate requirements were diminished significantly in the patients receiving enflurane anesthesia ($P = 0.0001$), when compared with patients receiving narcotic or halothane anesthesia.

Figure 1 displays the average infusion rate data observed at each consecutive 3-min time point during the initial 72 min of atracurium infusion. This cutoff was established because the number of patients per anesthetic group was decreased disproportionately beyond the 72-min point. In all three groups, an initial period of approximately 30 min was required to optimize the atracurium rate for maintenance of neuromuscular blockade in the desired range. During this initial stage, frequent adjustments had to be made to keep neuromuscular depression between 90–99%. Infusion rate requirements became relatively constant following this adjustment period during the more stable period (30–72 min). During the first 72 min of atracurium infusion, 88% of the consecutive 3-min observations of neuromuscular blockade had twitch-depression values between the range of 89 to 100%. When the initial 30-min adjustment period was excluded from the infusion-rate calculations, neuromuscular blockade was within the desired range of 94% at the 3-min observation points. Although infusion-rate requirements became relatively constant for each individual patient, there was considerable variation among patients in absolute requirements. For example, in patients receiving N₂O-morphine anesthesia, the average infusion rate ranged from 5.9 to $10.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (table 2).

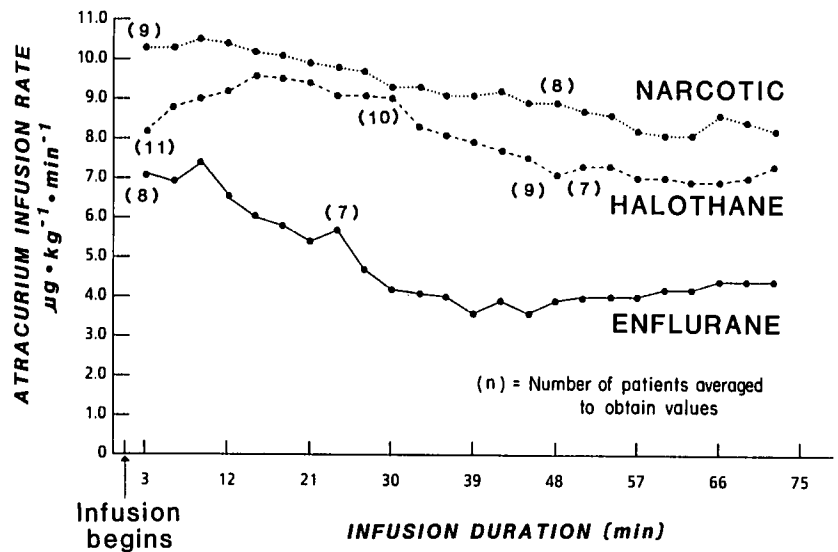
TABLE 2. Summary of Mean Infusion Rate and Muscle Twitch Suppression

Anesthesia Type	N	Mean Infusion Rate ($\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	Mean Twitch Suppression (%)
N ₂ O:morphine Mean ± SE Range	9	9.3 ± 0.5* (5.9–10.2)	95.0 ± 0.5 (92.2–97.8)
N ₂ O:halothane Mean ± SE Range	11	8.3 ± 0.5† (5.7–10.2)	93.2 ± 0.8 (88.2–97.5)
N ₂ O:Enflurane Mean ± SE Range	8	4.9 ± 0.3 (3.7–6.5)	94.1 ± 0.91 (88.8–95.9)

Values Presented as mean ± SEM.

* $P < 0.0001$ between N₂O:halothane and N₂O:enflurane.† $P < 0.0001$ between N₂O:morphine and N₂O:enflurane.

FIG. 1. Average infusion rates at consecutive 3-min intervals in patients receiving N₂O and morphine, halothane, or enflurane anesthesia.



The average level of neuromuscular blockade present at the time of infusion termination ranged from 93 to 95% for the three anesthetic groups. Subsequent onset of neuromuscular recovery occurred in less than 3 min following termination of infusion, and recovery to the 25% recovery level was observed in a mean of 8.2, 7.9, and 8.4 min in patients receiving N₂O and morphine, halothane, or enflurane anesthesia, respectively. Regardless of anesthesia type, recovery of the twitch to more than 90% of the control twitch from 93 to 95% neuromuscular blockade usually was observed within 30 min of the cessation of the infusion in patients allowed to recover spontaneously. In 12 patients, reversal was accelerated by the administration of atropine, 0.01 mg/kg, and neostigmine, 0.03 mg/kg, because of termination of surgery.

No adverse experiences were observed in any of the patients studied.

Discussion

This study demonstrated that the administration of an atracurium bolus dose followed by a continuous atracurium infusion is a practical technique for inducing and maintaining neuromuscular relaxation for pediatric surgical procedures lasting over 1 h. Atracurium infusion rates approximating 9, 8, and 5 µg · kg⁻¹ · min⁻¹ can be used initially for maintenance of neuromuscular blockade in children receiving N₂O and morphine, halothane, or enflurane anesthesia, respectively. There was marked interpatient variation in the absolute atracurium requirements of each patient; therefore, monitoring of neuromuscular transmission with a peripheral nerve stimulator is required in determining the appropriate infusion rate for maintaining neuromuscular blockade within the clinically desired range.

Other studies designed to evaluate atracurium infusion have been reported recently.^{1,2,4} At our institution, Gargarian, *et al.*,¹ using the same methodology employed in this study, found that adults under narcotic (fentanyl) anesthesia required approximately 8.4 µg · kg⁻¹ · min⁻¹ atracurium to maintain 90–99% suppression of the twitch response. This rate is comparable to the average rate of 9.3 µg · kg⁻¹ · min⁻¹ observed in our group of similarly anesthetized children.

Brandom *et al.* have evaluated the continuous infusion technique in children under N₂O-fentanyl and N₂O-halothane anesthesia.⁴ In children under narcotic anesthesia, the group observed a nearly identical atracurium infusion rate (9.3 µg · kg⁻¹ · min⁻¹) to ours. However, in patients during halothane anesthesia, the observed average requirement was 6.8 µg · kg⁻¹ · min⁻¹, or about 80% of our average of 8.3 µg · kg⁻¹ · min⁻¹. In that study, train-of-four rate of stimulation was used and the end-expired halothane concentration was 0.8%.

An important observation of the present study was the marked potentiation of the neuromuscular blocking effects of atracurium by enflurane. In the children studied, the infusion rate required to maintain twitch height suppression in the range of 89 to 99% during N₂O:enflurane anesthesia was 40–50% of that observed in patients receiving N₂O:halothane or N₂O:morphine anesthesia. However, the presence of residual enflurane did not appear to slow the recovery rate from atracurium following infusion termination. In most instances, the enflurane concentration was decreased or was discontinued after the termination of infusion, indicating that this technique does not prolong the atracurium recovery times.

Comparison of the present data concerning onset of neuromuscular blockade with that obtained in a previous study of atracurium revealed a notable difference.⁵ In the

previous study, we used train-of-four stimulation. At that time, onset of maximum neuromuscular blockade was observed in a mean time of 2 ± 0.3 min following a 0.4 mg/kg bolus dose of atracurium in children receiving N_2O -halothane anesthesia. In this study, the corresponding onset time was 3.7 ± 0.4 min with single twitch stimulation. This difference in onset time between the two studies was significant ($P < 0.005$). The inspired halothane concentrations were similar in both studies, and the technique of neuromuscular monitoring was the same, except for the rate of stimulation. A similar observation has been made in adults.⁶ This effect seems to be more important during onset than during recovery. Repeated observations during recovery have shown good marked correlation between train-of-four and single-twitch stimuli,⁶⁻⁹ whereas train-of-four has been demonstrated to be a more sensitive indicator of neuromuscular blockade than the single twitch rate. This probably is due to the faster depletion of acetylcholine reserves during train-of-four stimulation (2 Hz for 2 s repeated every 10 s) than during twitch rates of stimulation at 0.1 Hz.

In conclusion, continuous infusion of atracurium is a satisfactory technique for maintaining constant neuromuscular relaxation in children. Children anesthetized with enflurane require about one-half the infusion rate ($5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) of children anesthetized with halothane ($8 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) or morphine $N_2O:O_2$ ($9 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) anesthesia.

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