INFUSION OF ATRACURIUM IN NEONATES, INFANTS AND CHILDREN

A Study of Dose Requirements

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Atracurium, a non-depolarizing neuromuscular blocking agent with an intermediate duration of action, is decomposed spontaneously by Hofmann elimination and metabolized by non-specific esterases [1]. The main reasons for using atracurium during prolonged operations are: its elimination does not depend on renal or hepatic mechanisms, and there is little, if any, cumulation and only a minor risk of postoperative residual neuromuscular blockade [2, 3]. On account of the short elimination half-life of atracurium [4, 5], it is logical to give the drug by continuous infusion during long surgical procedures.

The aim of this study was to determine the doses of atracurium (given by infusion) required to maintain a steady 90–95% neuromuscular block in neonates, infants and children during balanced anaesthesia.

PATIENTS AND METHODS

Seventy-five patients (aged 9 days to 17 yr) undergoing elective operations were selected for the study and allocated to seven groups according to body weight (table I). The patients did not suffer from any disease, nor were they receiving medication known to influence neuromuscular transmission. The operations on the neonates (n = 7: aged less than 1 month) consisted of four orthopaedic and three urological procedures. The infants (n = 17; aged between 1 and 12 months) underwent two orthopaedic, three abdominal, 11 open heart operations and one closure of patent

SUMMARY

The doses of atracurium (by infusion) required to maintain steady-state (90–95%) neuromuscular block were assessed in 75 children aged 9 days to 17 yr during balanced anaesthesia. Following the intubating dose of atracurium 0.4 mg kg⁻¹ and after the recovery of single twitch to 5–10% of control (monitored by evoked EMG of hypothenar muscle), an infusion of atracurium 0.5 mg kg⁻¹ h⁻¹ was started. In 22 of the patients this initial rate resulted in the desired steady state; 32 patients required one, and 21 required two or more adjustments in rate. The mean single twitch value at steady-state was 6.6±0.3% (SEM), which is equal to 93% neuromuscular block. The infusion requirement to maintain the steady state neuromuscular block in all paediatric patients more than 1 month old was constant (0.53±0.01 mg kg⁻¹ h⁻¹). The infusion requirement of neonates up to 1 month old was 25% less (0.40±0.02 mg kg⁻¹ h⁻¹; P = 0.003). A significant correlation (n = 75, r = 0.76, P < 0.001) was found between the infusion rate (mg m⁻² h⁻¹) and the logarithm of the body surface area.

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<th>Table 1. Patient characteristics (mean ± SEM). BW = body weight range of a patient group; BSA = body surface area [6]</th>
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ductus arteriosus. The operations on the children (n = 51; older than 1 yr) consisted of nine orthopaedic, seven abdominal, 31 open heart and four vascular operations. The detailed information of the seven neonates is shown in table II.

The design of the study was approved by the Ethical Committee of the Children's Hospital, University of Helsinki. Premedication consisted of flunitrazepam 0.1 mg kg\(^{-1}\) by mouth (maximum dose 2.0 mg) for all but those patients who were less than 5 kg in body weight; they received 10 mg kg\(^{-1}\) of methohexitone per rectum. Premedication of the children weighing less than 15 kg was supplemented, when indicated, with the same dose of methohexitone. The induction of anaesthesia was carried out with fentanyl 3 µg kg\(^{-1}\), thiopentone 1-2 mg kg\(^{-1}\) and nitrous oxide in oxygen (2:1).

To monitor the neuromuscular transmission by EMG, the stimulating surface electrodes were placed over the ulnar nerve near the wrist, and the recording electrodes on the hypothenar muscles. Following the induction of anaesthesia, supra-maximal stimuli with trains of four (TOF) impulses at 20-s intervals were given (Relaxograph, Datex Oy, Helsinki, Finland). The evoked compound electromyogram was amplified, integrated and recorded on a thermal printer. After the calibration and baseline recording, atracurium 0.40 mg kg\(^{-1}\) was given and the trachea was intubated when the first twitch (T1) of the train-of-four was less than 10% of the calibration control value.

The infusion of atracurium 20 or 50 mg diluted in 100 ml of cold 5% glucose was commenced at a rate of 0.50 mg kg\(^{-1}\) h\(^{-1}\) (Ivac 700, Ivac Corp., San Diego, California) after the recovery of T1 to 5-10% of control. The infusion was adjusted gradually by increasing or decreasing its rate every 20-30 min to maintain the first twitch height between 5 and 10% of control. If there was a marked increase in the height of the single twitch, small bolus increments of atracurium were given to restore the neuromuscular block to the desired value before the infusion rate was increased. The individual steady-state infusion rate was judged to be that which maintained the neuromuscular block constant at 90-95% for at least 20 min. This final rate was calculated on the basis of both body weight (BW) and body surface area (BSA).

During anaesthesia, the end-tidal carbon dioxide concentration was maintained at 5.0-5.5% (Normocap, Datex Oy, Finland), and the core temperature at 35.5-37.0 °C. No inhalation anaesthetics were used at any time during the study, but fentanyl was administered in doses of 1-2 µg kg\(^{-1}\) as required. There was no notable blood loss during the recording period. The conditions were the same for the patients undergoing open heart surgery, in whom the study was carried out before the period of cardiopulmonary bypass.

Statistical differences between the groups were assessed using analysis of variance (ANOVA), with the Welch modification in cases of unequal variances [7], and the t test (Bonferroni's correction in comparison between group means after ANOVA). Linear regression analysis was used in appropriate instances. The values are expressed as mean ± SEM. Statistical difference was considered significant at P < 0.05.

**RESULTS**

In 22 patients, the desired steady-state degree of neuromuscular block was achieved with the initial infusion rate. Thirty-two patients required one
and 21 patients two or more adjustments in rate before steady-state neuromuscular block was achieved and maintained. The mean duration of the recordings was 122 ± 13 min, and the mean duration of the steady-state period was 60 ± 5 min. Once constant neuromuscular block was reached, the mean T1 level was 6.6 ± 0.3 %, which was equal to 93 % neuromuscular block.

The requirements at steady state in the seven patient groups are presented in table III. The infusion rate based on body weight was lower in patients weighing less than 5 kg than in heavier patients (0.44 mg kg⁻¹ h⁻¹ vs. 0.53 mg kg⁻¹ h⁻¹) (P < 0.01). The infusion rate in patients heavier than 5 kg was constant when calculated on the basis of body weight (table III).

The infusion rates in neonates, infants and children are shown in table IV. The table shows that the infusion rate in neonates (0.40 mg kg⁻¹ h⁻¹) was 25 % lower than the infusion rate in older patients (P = 0.004).

The requirements of atracurium by infusion in neonates has not been studied previously. We found that the neonates required a mean infusion rate of 0.40 mg kg⁻¹ h⁻¹, which was 25 % less than that recorded by Brandom and colleagues [8] and Goudsouzian and co-workers [9], who studied the infusion requirements of children between 2 and 10 years of age and between 1 and 10 years of age, respectively. The requirement was the same in adult surgical patients [10, 11]. The greater interindividual variation of the infusion requirements (range 0.30–0.88 mg kg⁻¹ h⁻¹ in our study) is a typical finding. Thus a neuromuscular monitoring device should be used to ensure success of the infusion technique.

The infusion rate based on body surface area increased in proportion to the growth of the patient (table III). There was a statistically significant correlation (r = 0.76, P < 0.001) between the logarithm of BSA and the infusion rate based on BSA (fig. 1).

DISCUSSION

The results of this study demonstrated that the infusion rate of atracurium needed to maintain a steady 90–95 % neuromuscular block remained constant when calculated on a body weight basis, in paediatric patients with body weights greater than 5 kg.

The mean infusion rate in infants and children (0.53 mg kg⁻¹ h⁻¹) was similar to that recorded by Brandom and colleagues [8] and Goudsouzian and co-workers [9], who studied the infusion requirements of children between 2 and 10 years of age and between 1 and 10 years of age, respectively. The requirement was the same in adult surgical patients [10, 11]. The greater interindividual variation of the infusion requirements (range 0.30–0.88 mg kg⁻¹ h⁻¹ in our study) is a typical finding. Thus a neuromuscular monitoring device should be used to ensure success of the infusion technique.

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<table>
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<tr>
<th>n</th>
<th>Age (yr)</th>
<th>mg kg⁻¹ h⁻¹</th>
<th>mg m⁻² h⁻¹</th>
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<tr>
<td>Neonates</td>
<td>7</td>
<td>0.05 ± 0.01</td>
<td>0.40 ± 0.02†</td>
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<tr>
<td>Infants</td>
<td>17</td>
<td>0.61 ± 0.06</td>
<td>0.52 ± 0.03</td>
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<tr>
<td>Children</td>
<td>51</td>
<td>6.61 ± 0.64</td>
<td>0.53 ± 0.01</td>
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<td>P (ANOVA)</td>
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**Significant difference between all three groups after ANOVA and the comparison between group means (Bonferroni's correction is used in both): P < 0.017

FIG. 1. Atracurium infusion requirement based on body surface area increases in proportion to growth. A statistically significant correlation between the infusion rate (mg m⁻² h⁻¹) and the logarithm of body surface area (BSA) is shown.
the infusion requirements of older infants and children.

The lower infusion requirement can be explained by the immaturity of the neuromuscular junction and muscle contraction, which is known to exist for 2–3 months postnatally [12, 13]. The influence of the distribution volume of atracurium at different ages, and the possibility of delayed elimination in neonates is only speculative, and has still to be tested in pharmacokinetic studies in the newborn. The results of the present study are in agreement with our previous study, which showed that the recovery index (time elapsed between the single twitch recovery 25% and 75%) during spontaneous recovery after a bolus dose of atracurium was significantly longer in patients younger than 3 months than in older infants and children [14]. Possibly atracurium, like tubocurarine [15], is effective at a lower plasma concentration in neonates than in older pediatric patients.

When the infusion requirement was calculated on the basis of body surface area, a logarithmic correlation was found between the BSA of the patient and the infusion rate (mg m⁻² h⁻¹). The infusion requirements found by Brandom and colleagues [8] for the group of children between 2 and 10 years of age and by d’Hollander and associates [10] in adults, fit well the regression obtained in the present study. However, the calculation of the infusion rate needed by an individual patient is, for practical reasons, more complex if calculated on the basis of BSA instead of body weight.

In conclusion, the present clinical study demonstrates that the requirements of atracurium (by infusion) in paediatric patients older than 1 month is constant when calculated on a body weight basis (mg kg⁻¹ h⁻¹). The infusion requirement of neonates was found to be 25% lower.

ACKNOWLEDGEMENT

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REFERENCES