USE OF ATRACURIUM IN NEONATAL ANAESTHESIA

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Following the modification of Ayre's T-piece by Jackson Rees (1950), the Liverpool technique of paediatric anaesthesia became established some 35 years ago. In 1950, the technique was based upon routine tracheal intubation and manual ventilation with nitrous oxide and oxygen, supplemented by a low concentration of diethyl ether. Thiopentone i.v. soon became the induction agent of choice and the volatile adjuvant was replaced by a neuromuscular blocking drug, which was given in a large dose that caused clinically complete blockade of voluntary muscle. Virtually the same method of anaesthesia is still in use today in the Liverpool Children's Hospitals, having been administered to over 300,000 children in the intervening period.

TUBOCURARINE, SUXAMETHONIUM AND PANCURONIUM

In the beginning, tubocurarine was the neuromuscular blocking drug of choice in older children, but the early, and very limited, experience with this drug in the newborn infant led to some problems with the re-establishment of adequate spontaneous ventilation at the end of the surgical procedure. This apparent adverse response of the neonate to tubocurarine prompted the study by Stead (1955) in which he showed that the muscles of ventilation were indeed more sensitive to the action of this drug in the neonatal period. A dose of only 80 \( \mu g \) \( kg^{-1} \), about one-tenth of that used in older children at the time, caused a marked diminution of the amplitude of the ventilatory excursions of two neonates.

In the same study Stead also showed that the muscles of ventilation of the neonate were more resistant to the action of suxamethonium, an observation borne out in clinical practice, and this drug was preferred in neonatal anaesthesia during the 1950s. Technical difficulties with the administration of suxamethonium and concern about the uncertainty of onset of a prolonged phase II block led to a reappraisal of tubocurarine (Bush and Stead, 1962). This investigation used a simple clinical approach in that tubocurarine was given in divided doses until the infant's muscles were under sufficient blockade to allow both easy control of ventilation and good surgical access. The results demonstrated a "clinical sensitivity" of the neonate to tubocurarine—most marked in the first few days of life.

SUMMARY

Atracurium was administered to neonatal patients on 270 occasions without any difficulties being encountered. More detailed observations in 60 patients showed that, in 16 neonates 3 days of age and older, with a core temperature greater than 36 °C, the standard dose of atracurium 500 \( \mu g \) \( kg^{-1} \) had a mean duration of clinical effect of 23.1 ± 3.4 min—the shortest in any group of children so far studied in Liverpool. In only three of the 16 was antagonism of residual neuromuscular blockade considered to be necessary. In 34 infants, anaesthetised within 48 h of birth, we identified distinct subgroups. In 12, comparable except for age to the patients described above, 500 ± 50 \( \mu g \) \( kg^{-1} \) lasted a mean time of 32.4 ± 8.6 min, nearly 50% longer and with more than twice the standard deviation. In eight infants in whom the central body temperature decreased to less than 36 °C, the standard dose of atracurium lasted a mean time of 47.5 ± 11.8 min. These results suggest that it might be advantageous to reduce the initial dose of atracurium in the smaller newborn infants, particularly if their body temperature is less than normal. To date, a reduced dose of 300 ± 30 \( \mu g \) \( kg^{-1} \) has been given to 10 patients and in this small group the mean duration of clinical effect was 24.5 ± 10.1 min.
During the past 25 years, tubocurarine has been used on approximately 5000 occasions in neonates in the Liverpool Children's Hospitals and this considerable experience leaves us in no doubt that, clinically, the newborn infant is in general substantially more sensitive, often by a factor of 2 or 3, to the action of tubocurarine than is the older child. There is also a marked variation in dose requirements between individual infants, and this variability is the reason for our long-standing recommendation that the dose of a competitive neuromuscular blocking drug should be titrated for each neonate. This is in marked contrast to our approach in older children, to whom these drugs are given on a simple dose-for-weight basis.

Using a comparable method of clinical assessment Bennett and others (1975) have obtained similar results with both tubocurarine and pancuronium in the U.S.A. In contrast, Goudsouzian and his colleagues in Boston, in sophisticated studies based on the mechanical twitch response of the short adductor muscle of the thumb to electrical stimulation—with a background of halothane anaesthesia—were not able to demonstrate any difference in the dose–response curves of this muscle to tubocurarine in the different age groups (Goudsouzian et al., 1975). This work was foreshadowed by a limited study by Churchill-Davidson and Wise in 1964, in which they were unable to show any increased sensitivity of the hypothenar muscles of three neonates to tubocurarine using the EMG response. However, they also noted that in these infants the muscles of ventilation were affected by the same doses as were those of the little finger—quite unlike the response of adults.

ATRACURIUM

Clinical sensitivity to alcuronium and pancuronium in the neonate has been demonstrated both in Liverpool and elsewhere, so the use of atracurium was approached with caution when permission to study this drug in the newborn infant was granted in May 1982. Almost from the start of the investigation, however, it became apparent that, clinically, atracurium might be different from all the other competitive neuromuscular blocking drugs studied previously in the Liverpool Children's Hospitals.

The first newborn infant to be given atracurium in the present study (a female 24 h old weighing 2.44 kg and suffering from intestinal obstruction) required five doses of 100 μg kg⁻¹ over a period of 10 min to produce adequate clinical neuromuscular blockade. She then needed no further atracurium for 78 min. Two additional incremental doses of 100 μg kg⁻¹ gave clinical blockade lasting 25 min and 21 min, respectively. This compares with a mean duration of effect of about 15 min in older children. Thus it seemed that, whereas there might be no marked increase in initial sensitivity, there was the possibility of a more prolonged duration of clinical action in the newborn. Experience with different initial doses in the next five patients led to the adoption as standard of the same dose as is used in older children, namely 500 μg kg⁻¹.

The duration of effect of atracurium 500 μg kg⁻¹ in the first 24 neonates studied, when they were grouped together, appeared to be similar to that in the other study groups. However, if these patients were divided by age into two subgroups, the newborn aged < 48 h and the rest aged 3–28 days, then there did seem to be a significant difference in duration of effect (0.02 > P > 0.01).

CLINICAL STUDY

To date (October 1985) some 270 neonatal patients have been given atracurium in Alder Hey Children's Hospital, but because this is purely a clinical study observations are confined to the patients anaesthetized by either G. H. Bush or the author, in order to reduce the inevitable variations that occur between individual anaesthetists even in the application of an apparently identical technique. There has been one change during the course of this continuing study, and that is that the ability to monitor, and therefore control, end-tidal carbon dioxide concentrations only became available to us about 18 months ago. Thus there is the possibility that some of the patients in the early part of the study may have had carbon dioxide concentrations less than 3.5 kPa, rather than the desired value of approximately 4.5 kPa. Although this would have been unlikely to affect the rate of degradation of atracurium, it might have influenced the apparent duration of action by delaying the onset of spontaneous ventilation.

The first group to be considered consisted of 16 patients aged between 3 and 28 days in whom the central body temperature remained greater than 36 °C (table I). There were 14 boys and two girls in this group and they weighed between 1.64 and 4.54 kg. All were given an initial dose of atracurium 500 ± 5 μg kg⁻¹ and the mean duration
Table I. Patient data

<table>
<thead>
<tr>
<th>Group</th>
<th>M</th>
<th>F</th>
<th>Total</th>
<th>Age (h)</th>
<th>Core temp. (°C)</th>
<th>Weight (kg)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>14</td>
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<td>&gt;48</td>
<td>&gt;36</td>
<td>3.2</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>6</td>
<td>12</td>
<td>&lt;48</td>
<td>&lt;36</td>
<td>3.1</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>5</td>
<td>8</td>
<td>&lt;48</td>
<td>&lt;36</td>
<td>2.3</td>
</tr>
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</table>

Table II. Duration of effects

<table>
<thead>
<tr>
<th>Group</th>
<th>Initial dose (μg kg⁻¹)</th>
<th>Duration of effect (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Range</td>
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<tr>
<td>1</td>
<td>500 ± 25</td>
<td>23.1 ± 3.4</td>
</tr>
<tr>
<td>2</td>
<td>500 ± 50</td>
<td>32.4 ± 8.6</td>
</tr>
<tr>
<td>3</td>
<td>500 ± 50</td>
<td>47.5 ± 11.8</td>
</tr>
</tbody>
</table>

Table III. Overall dose to spontaneous ventilation or antagonism

<table>
<thead>
<tr>
<th>Group</th>
<th>Overall dose (μg kg⁻¹ min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD Range</td>
</tr>
<tr>
<td>1</td>
<td>13.6 ± 1.9 10.1-16.3</td>
</tr>
<tr>
<td>2</td>
<td>12.1 ± 3.2 6.2-19.2</td>
</tr>
<tr>
<td>3</td>
<td>7.4 ± 1.3 5.8-9.4</td>
</tr>
</tbody>
</table>

of clinical effect (i.e. the time to movement or the need for an incremental dose) was 23.1 ± 3.4 min with a range of 17-29 min. This is the shortest duration of effect to be seen in any of the groups of children studied in Alder Hey Children’s Hospital to date. The overall dose rate of atracurium, that is from induction to the onset of spontaneous movement at the end of anaesthesia or to the pharmacological antagonism of the neuromuscular blockade was 13.6 ± 1.9 μg kg⁻¹ min⁻¹ (range 10.1-16.3 μg kg⁻¹ min⁻¹). This is similar to the mean overall dose rate of 12.3 μg kg⁻¹ min⁻¹ found in a group of 175 children of all ages (13 days to 16 yr), given atracurium by infusion. It is of interest to note that of this group of 16 infants, pharmacological antagonism of residual neuromuscular blockade was considered to be necessary in only three patients (< 20%) and this represents a remarkable—some might say astonishing—departure from normal practice in Liverpool.

Within the group of 34 newborn infants, that is patients anaesthetized within the first 48 h of life, it is possible to identify some distinct subgroups. In the first of these there were 12 patients in whom central body temperature remained > 36 °C and to whom atracurium 500 ± 50 μg kg⁻¹ was given. In this subgroup the mean duration of clinical effect was 24.5 min ± 10.1 min and the range 13-43 min. The overall dose of atracurium was 12.1 ± 3.2 μg kg⁻¹ min⁻¹, but the range of doses was large—from 6.2 to 19.2 μg kg⁻¹ min⁻¹—emphasizing the point already made about variability in the response of the newborn to neuromuscular blocking drugs.

The second subgroup contained eight smaller neonates, mean birth weight 2.32 kg, in whom the central body temperature decreased to less than 36 °C. In these patients the mean duration of clinical effect of the same dose of atracurium (500 μg kg⁻¹) was 47.5 min ± 11.8 min with a range of 32-70 min (table II). The mean overall dose rate was substantially lower at 7.4 ± 1.3 μg kg⁻¹ min⁻¹ and the range of doses was 5.8-9.4 μg kg⁻¹ min⁻¹ (table III).

If these results are compared graphically, then there does seem to be a real difference between the three groups of patients despite the small numbers in each group, and in fact the differences between the means are significant at the 0.01 level using a two-tailed t test (fig. 1). Because of these results a smaller dose of 300 μg kg⁻¹ is now used routinely in infants who need surgery within the first 48 h of life. So far this subgroup contains 10 patients with a mean weight of 2.93 kg, in four of whom central body temperature decreased to less than 36 °C. The mean duration of clinical effect was 24.5 min ± 10.1 min and the range 13-44 min. Overall dose rate was 7.3 ± 2.3 μg kg⁻¹ min⁻¹ with a range of 5.01-11.9 μg kg⁻¹ min⁻¹.

Discussion

In the past there has been disagreement between many investigators as to whether or not the neonate is sensitive to the action of the competitive neuromuscular blocking drugs. In Liverpool it has long been maintained that the neonate is clinically more sensitive to their action, whereas as already mentioned, the elegant work by Goudsouzian and his colleagues has demonstrated that, under halothane anaesthesia, the adductor muscle of the thumb exhibits a similar dose–response to tubocurarine in children of all ages. However, an explanation of these conflicting views can now be offered.
The most important paper to date on the pharmacokinetics and dynamics of tubocurarine in neonates, infants, children and adults was published in 1982 by Fisher and his colleagues, who gave tubocurarine by infusion until 70–90% depression of EMG twitch height of the adductor pollicis was achieved, against a background of equal anaesthetic depths of nitrous oxide and halothane (0.58 MAC) in all age groups. In this paper Fisher and his colleagues showed that the distribution half-life of tubocurarine was not statistically significantly different in any of the four groups, although it did appear to be shorter in the neonates. The elimination half-life was approximately twice as long in the neonates as in the children and adults because, although the clearance was similar in all groups, the steady-state volume of distribution was significantly greater in the neonates.

The same authors were also able to demonstrate that the steady-state plasma concentration for 50% depression of neuromuscular function in the neonate was only one-third that in the adult, thus establishing beyond reasonable doubt that, under the conditions of this study, the adductor pollicis muscle of the neonate was substantially more sensitive to the action of tubocurarine. They also determined \( D_{50} \), the total drug present at steady-state, at 50% blockade; this value, the product of the steady-state plasma concentration and the steady-state volume of distribution, was not significantly different in any of the age groups. However, the actual values of \( D_{50} \) in the neonatal group varied from 50 to 350 \( \mu \text{g kg}^{-1} \) —a ratio of 7:1 in a population of only five patients. As a consequence of this variability, Fisher and colleagues recommend that, in neonates, tubocurarine should be given in small doses until the desired effect is achieved. Furthermore, because of the longer elimination half-life, and therefore the slower rate of recovery, second and subsequent doses of tubocurarine should be given only when indicated by recovery of neuromuscular function.

Where does atracurium stand at present among the competitive neuromuscular blocking drugs? It does seem that the newborn infant may show increased sensitivity to this drug, as it almost certainly does to all the other non-depolarizing drugs, including vecuronium, and there is no doubt that in the first 48 h of life there is greater variability in the response to atracurium than is shown by older infants. However, the advantage that atracurium possesses over all its competitors is a non-enzymatic process of degradation with an elimination half-life of about 20 min under normal physiological conditions. Thus the chances of an
unexpectedly prolonged duration of action are very small. Moreover, it is relatively easy to manage the conduct of the anaesthetic so that pharmacological antagonism of residual neuromuscular blockade is not required, and this is a major advantage in a sick neonate who has just suffered a bowel resection.

What are the disadvantages of atracurium in the neonate? So far no real problems have been encountered and the drug is now used for approximately 70% of all neonatal surgery in Alder Hey Children's Hospital. However, total experience amounts to only 270 patients in less than 3½ years, and this must be regarded as limited experience when side-effects are considered. It is to be hoped that serious side-effects will not threaten the position of this drug, for atracurium may well represent an important advance in neonatal anaesthesia.

In conclusion, atracurium is probably the neuromuscular blocking drug of choice for procedures lasting more than 30 min in the neonate. In infants of 3 days and older there would seem to be no reason for using other than a standard dose of 500 µg kg⁻¹. In the newborn of <48 h of age, particularly if the central body temperature is less than 36 °C, it may be prudent to use a reduced initial dose of approximately 300 µg kg⁻¹.

ACKNOWLEDGEMENT

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REFERENCES


