USE OF ATRACURIUM DURING MAJOR ABDOMINAL SURGERY IN INFANTS WITH HEPATIC DYSFUNCTION FROM BILIARY ATRESIA

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Infants with hepatic dysfunction caused by biliary atresia presenting for the operation of hepaticoportoenterotomy (Kasai operation) pose problems for the anaesthetist which make the selection of an appropriate neuromuscular blocking drug worthy of consideration. The patients are very young (< 2–3 months), as correction before the development of irreversible liver damage improves the prognosis (McClement, Howard and Mowat, 1985). The effects of an immature neuromuscular system (Brandom and Cook, 1985) are worsened by the decrease in respiratory reserve caused by a large abdominal incision, hepatomegaly, ascites and, when required, the transfusion of substantial quantities of blood. Consequently, residual neuromuscular blockade would be most undesirable in the postoperative period. In addition, since the surgical correction involves the anastomosis of a loop of small bowel on to the porta hepatis, it would seem preferable to avoid the potentially harmful effects on the anastomosis associated with the administration of neostigmine (Wilkins et al., 1970).

The unique property possessed by atracurium, of spontaneous degradation at body pH (Hofmann elimination), removes the influence of changes in hepatic metabolism on the antagonism of blockade induced by this drug, and its intermediate duration of action may make it possible to omit the use of antagonist agents altogether.

The aim of this study was to assess the use of atracurium for major abdominal surgery in a group of infants with hepatic dysfunction.

SUMMARY

The use of atracurium during major abdominal surgery was assessed in 20 infants with hepatic dysfunction caused by biliary atresia. An initial dose of 0.6 mg kg⁻¹ provided excellent intubating conditions in all patients. Subsequent neuromuscular blockade was monitored with a peripheral nerve stimulator and incremental doses of atracurium were given on reappearance of a single twitch. Neuromuscular conduction was allowed to return at the end of surgery and by careful timing of increments it was necessary to antagonize the neuromuscular blockade in only two patients.

PATIENTS AND METHODS

Twenty consecutive patients (11 male) who were about to undergo hepaticoportoenterotomy entered the study. All had been extensively evaluated in the preoperative period. Premedication consisted of atropine 0.1 mg i.m. given 30–60 min before surgery.

On arrival in the operating theatre, the patient was placed on a warming blanket on the operating table and connected to an electrocardiograph. Anaesthesia was induced by the inhalation of 2–3% halothane and nitrous oxide in 30% oxygen via a Jackson–Rees modification of Ayre’s T-piece. Once the patient was asleep, an arterial pressure cuff was placed on the right arm and two small self adhesive ECG electrodes were fixed over the median nerve at the elbow. These allowed for subsequent monitoring of neuromuscular blockade via a portable peripheral nerve stimulator (Ministim R) using “train-of-four” stimuli with a frequency of 2 Hz; the resultant twitches were assessed visually.
An i.v. infusion was commenced and after the position of the stimulating electrodes had been verified, atracurium 0.6 mg kg\(^{-1}\) was administered. The trachea was intubated when no twitches were visible, and the lungs ventilated with humidified nitrous oxide and 0.5–1\% halothane in oxygen using a Vickers "Neovent" ventilator. Blood loss was measured by the weighing of swabs, and was replaced accordingly. Rectal temperature was monitored throughout the operation.

Incremental doses of atracurium were given as soon as the first twitch reappeared, and the times of administration noted. No further increments were given after the closure of the peritoneum. Immediately before extubation, the train-of-four was assessed and, unless the fourth twitch was significantly less than the first on visual scoring, the residual neuromuscular blockade was not antagonized. The trachea was extubated once the patient was awake. If there was any doubt as to the adequacy of neuromuscular function (either clinically or by train-of-four ratio), atropine 0.03 mg kg\(^{-1}\) and neostigmine 0.06 mg kg\(^{-1}\) were given i.v. A recording of the integrated electromyographic response to peripheral nerve stimulation was obtained in two patients (Datex Relaxograph) to provide a more accurate monitor of neuromuscular blockade and support the method of visual scoring. The increments for these patients were still given according to the previous criteria.

### RESULTS

The characteristics of the 20 patients studied are shown in table I.

Preoperative liver function tests were all indicative of hepatic dysfunction, with marked increases in the serum bilirubin concentration, and in the concentrations of the liver enzymes (table II).

Following the initial dose of atracurium of 0.6 mg kg\(^{-1}\), intubation of the trachea was possible within 3 min, by which time no twitch was visible on train-of-four stimulation. The conditions for intubation were considered to be excellent in all patients. The first incremental dose was required by all patients and was given on average (\(\pm\) SD) at 43 \pm 10 min (range 30–65 min). The dose administered was usually 1 mg (0.5 or 0.75 mg for the smaller infants). Eighteen patients required a second, and 12 patients a third increment, and the interval between these doses was consistent at 31 \pm 5 and 32 \pm 8 min, respectively. Four patients, in whom surgery was prolonged, required more than three increments; subsequent doses were given at similar intervals.

The total dose of atracurium used was 5.1 \pm 1.4 mg (range 2.75–8 mg) with a duration of surgery (from time of first dose of atracurium to extubation) of 133 \pm 48 min. The dose of atracurium was also calculated in mg kg\(^{-1}\) h\(^{-1}\) and this value was remarkably consistent at 0.45 \pm 0.1 mg (range 0.33–0.68 mg) (table III).

The interval between the last dose of atracurium and the end of the operation was 44 \pm 10 min (range 25–60 min), and only two patients required formal antagonism of neuromuscular blockade with atropine and neostigmine—although relaxation was considered adequate by the surgeon. Evidence that reversal had occurred spontaneously was obtained using the nerve stimulator (as...
FIG. 1. Individual tracing of neuromuscular blockade.

<table>
<thead>
<tr>
<th>Mark</th>
<th>Time</th>
<th>T1%</th>
<th>T1/ T4%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Initial atracurium 2.5 mg</td>
<td>10.49</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>1st increment atracurium 1.0 mg</td>
<td>11.25</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>2nd increment atracurium 1.0 mg</td>
<td>11.57</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>Start peritoneum</td>
<td>12.36</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>Skin closure</td>
<td>12.45</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Extubation</td>
<td>12.50</td>
<td>70</td>
</tr>
</tbody>
</table>

Loss of twitch height during procedure is probably caused by worsening electrode contact.

In biliary atresia, there is progressive inflammation of the biliary tract, possibly a type of sclerosing cholangitis, which usually starts extrahepatically and then spreads to involve all of the bile duct system (Howard, 1983). The aetiology of extrahepatic biliary atresia remains obscure and the majority of untreated patients die from cirrhotic liver failure before 2 years of age. Surgical treatment at King’s College Hospital follows the approach first described by Kasai and Suzuki (1959). The obliterated extrahepatic ducts are excised at the level of the porta hepatitis which leaves bile to drain from minute residual channels. A Roux-en-Y loop of jejunum is then anastomosed to the cut surface. Frequently, it is necessary to resect a portion of liver to allow suitable access.

The hepatic dysfunction seen in these patients is mainly of the cholestatic type as reflected by the marked increases in the concentrations of alkaline phosphatase and gamma GT (table II). As the untreated infants age, progressive hepatocellular damage ensues as indicated by the increased transaminase (AST) concentrations. However, this could not have been severe in the patients studied since the albumin concentration was still normal.

Many commonly used non-depolarizing neuromuscular blocking agents are partly metabolized in the liver and thus one would expect their duration of action to be prolonged in patients with hepatic dysfunction. There may also be apparent resistance to these drugs, requiring a larger initial dose in these subjects. This has been observed for tubocurarine (Dundee and Gray, 1953) and pancuronium (Ward, Adu-Gyamfi and Strunin, 1975). The latter effect is probably caused by a large volume of distribution, as has been shown for pancuronium by Westra and colleagues (1981). This larger volume of distribution will also increase the elimination half-life of the drug, even if the plasma clearance proceeds at the same rate.

In contrast, Ward and Neill (1983) have shown that the pharmacokinetics of atracurium were unaffected by hepatic failure and this has been confirmed in children (Cook et al., 1984). In addition, Brandom and coworkers (1984) noted that the recovery of neuromuscular function following atracurium was quicker in infants (2–6 months of age) than in adult patients. Thus atracurium would seem to be the ideal non-depolarizing neuromuscular blocker for procedures on infants with hepatic dysfunction who require profound neuromuscular blockade.

Selection of a relatively large initial dose of atracurium (0.6 mg kg\(^{-1}\) or four times the ED\(_{50}\)) was determined by the following factors:

1. Duration of surgery: since most Kasai operations exceed 120 min, a large initial dose would seem appropriate.
2. Lack of agreement on the ability of
0.3 mg kg\(^{-1}\) (Brandom et al., 1984) or 0.4 mg kg\(^{-1}\) (Goudsouzian et al., 1985) to produce excellent intubating conditions in patients of similar age.

(3) The apparent lack of histamine release or cardiovascular effects of atracurium in infants, even at four times the ED\(_{95}\) (Brandom and Cook, 1985).

In this study, intubating conditions were excellent in all patients and there was no clinical evidence of histamine release or cardiovascular dysfunction.

After the intubating dose, there was some variation between patients in the time until the return of the first twitch and, thus, between the subsequent incremental doses (table III). The mean intervals between these were 43 ± 10 min, 31 ± 5 min and 32 ± 8 min, respectively. We consider this represents good clinical predictability for this class of drug. The total requirements of atracurium also showed consistency at 0.45 ± 0.1 mg kg\(^{-1}\) h\(^{-1}\). Using the nerve stimulator in the way described, reliable information was obtained easily as to the degree of paralysis in each patient, and allowed the appropriate administration of incremental doses.

It proved necessary to antagonize neuromuscular blockade in two patients using the T4:T1 ratio obtained from the visual score. Previous studies in adults (Ali, Utting and Gray, 1971a, b; Ali et al., 1975) have shown electromyographically and mechanically that the T4:T1 ratio is an accurate measurement of recovery from neuromuscular blockade and that it correlated well with the depression of respiratory function caused by residual paralysis. A ratio of 0.5 - 0.7, together with clinical evidence of return to "normal" neuromuscular function would seem adequate to allow extubation of the trachea without formal antagonism with neostigmine (Brandom and Cook, 1985).

In summary, it has been shown that atracurium is a suitable non-depolarizing neuromuscular blocking drug for major abdominal surgery in infants with hepatic dysfunction caused by biliary atresia. Its clinical effect was predictable and, with the aid of a nerve stimulator, it was possible to titrate dose to effect and avoid unnecessary antagonism with neostigmine.

ACKNOWLEDGEMENTS

We thank Mr E. R. Howard for kindly allowing us to use his patients in this study and Dr S. Ward for reviewing the manuscript.

REFERENCES


