USE OF ATRACURIUM IN CARDIAC SURGERY INVOLVING CARDIOPULMONARY BYPASS WITH INDUCED HYPOTHERMIA

P. J. FLYNN, R. HUGHES AND B. WALTON

SUMMARY

Atracurium was administered by infusion to 12 anaesthetized patients undergoing cardiac surgery with cardiopulmonary bypass and induced hypothermia. Following an initial bolus dose of 0.6 mg kg$^{-1}$, an infusion of atracurium was continued at an average rate of $0.0066 \pm 0.0003$ mg kg$^{-1}$ min$^{-1}$ (0.4 mg kg$^{-1}$ h$^{-1}$) which was sufficient to maintain 90-95% block of the single twitch or train-of-four responses before bypass. Adequate surgical relaxation was provided with approximately half the rate of infusion of $0.0034 \pm 0.0003$ mg kg$^{-1}$ min$^{-1}$ (0.2 mg kg$^{-1}$ h$^{-1}$) during cardiopulmonary bypass with induced hypothermia (25-26°C) for 70-166 min. This rate of infusion during hypothermia was significantly slower ($P<0.001$) than that during normothermia. Thus, atracurium appeared to be suitable for use by continuous infusion in cardiac surgery and the temperature-dependent inactivation of atracurium was used to advantage because less drug was required during induced hypothermia.

The rapid rate of recovery which is characteristic of atracurium may lead to undesirable fluctuations in the degree of neuromuscular blockade unless increments are given promptly at regular intervals, and the patient is monitored carefully. The use of an infusion should overcome this difficulty and the lack of cumulative effects suggest that atracurium may be a suitable neuromuscular blocker for administration in this manner (Payne and Hughes, 1981). Such a study has already been undertaken in patients undergoing general surgery (Eagar, Flynn and Hughes, 1984). Furthermore, the temperature-dependent inactivation of atracurium (Merrett, Thompson and Webb, 1983) may be used to advantage during induced hypothermia.

The purpose of this study was twofold: to assess the use of atracurium administered by infusion to patients undergoing cardiac surgery, and to study the effect of induced hypothermia on the rate of infusion required to maintain surgical relaxation. A preliminary account of this work has been reported previously (Flynn et al., 1983).

PATIENTS AND METHODS

Studies were carried out on 12 patients aged 29-72 yr (average 60 yr) undergoing open heart surgery for mitral or aortic valve replacement, or both, and who had given their informed consent. The trial was conducted with the authority of a clinical trial certificate issued with the approval of the Committee on Safety of Medicines and the study was approved by the Ethics Committee of the London Hospital.

The patients were premedicated with papaveretum 15-20 mg and hyoscine 0.3-0.4 mg i.m. 1 h before surgery. Following arrival in theatre, a force transducer was strapped in the patient’s left hand and attached to the thumb; an i.v. and an i.a. cannula were inserted under local anaesthesia to a peripheral vein and a femoral artery, respectively. Following pre-oxygenation, anaesthesia was induced with phenoperidine 1-2 mg and thiopentone 200-400 mg i.v. When the patient lost consciousness, needle electrodes were inserted adjacent to the ulnar nerve and a control recording of the responses of the adductor pollicis muscle to train-of-four or single twitch stimulation every 10 s was obtained. Endotracheal intubation was accomplished following the administration of a bolus dose of atracurium 0.6 mg kg$^{-1}$ i.v. Before bypass, anaesthesia was maintained with 66% nitrous oxide in oxygen with increments of phenoperidine 1-2 mg, as required. Ventilation was adjusted to maintain normocarbia and any acid-base deficit of greater than $-5$ mmol litre$^{-1}$ was corrected with appropriate amounts of 8.4% sodium bicarbonate. During bypass, perfusion pressure was maintained between 50 and 100 mm Hg using 1-mg increments of phenylephrine or metaraminol i.v., as required. Arterial pressure, central venous pressure, heart rate, the...
electrocardiogram and peripheral and core temperatures were recorded.

When the initial twitch response had returned to between 5 and 10% of the control height an infusion of atracurium was begun. The concentration of the solution used for infusion was made up according to the patient's weight (i.e. kg × 10⁻² mg ml⁻¹) diluted in normal saline (Eagar, Flynn and Hughes, 1984). Studies have shown that, at concentrations of 0.6–0.9 mg ml⁻¹, this solution remains stable at ambient temperature for at least 4 h. The infusion was administered from a 50-ml syringe driven by a Vickers Treonic 3 Digital Syringe pump at rates which ranged from 10 to 60 ml h⁻¹. The infusion was discontinued just before the completion of surgery. All patients were transferred to the intensive care unit and maintained on IPPV for at least 12 h. Results are presented as mean values (± SEM) and statistical analyses were carried out using Student's t tests.

RESULTS

The initial bolus dose of atracurium 0.6 mg kg⁻¹ i.v. provided satisfactory conditions for endotracheal intubation within 60–300 s (mean 130 ± 19.5 s) after its administration. The maximum change in mean arterial pressure was ±10 mm Hg and in heart rate was ±10 beat min⁻¹ except in one patient in whom the heart rate increased by 27 beat min⁻¹ on intubation. Analysis of the results for the patient group did not show any changes of statistical significance.

In six patients, after the initial bolus dose of atracurium 0.6 mg kg⁻¹, a mean time of 33 ± 3.9 min was required for 5–10% recovery of the first train-of-four response when the infusion was begun. Before bypass at a core temperature of 36—37°C the individual infusion rates required to maintain 90–95% block of the first train-of-four response were varied between 0.0050 and 0.0100 mg kg⁻¹ min⁻¹ according to the desired degree of peripheral neuromuscular blockade, and in response to the demands of surgery. The mean infusion rates ranged from 0.0050 to 0.0086 mg kg⁻¹ min⁻¹ (average 0.0068 ± 0.0006 mg kg⁻¹ min⁻¹) in the six patients studied (table I).

The commencement of cardiopulmonary bypass had no effect on the degree of neuromuscular blockade, but the train-of-four response disappeared abruptly during cooling to a core temperature of 25–26°C. In the first two patients, the infusion of atracurium was discontinued and about 30 min later, despite no response to train-of-four stimulation or to an applied tetanus (50 Hz for 5 s), the patients began to breathe spontaneously and the infusion was recommenced, but at a lower rate. In the remaining four patients in the group, as soon as hypothermia was established, the mean infusion rates were reduced by 34–51% and surgical relaxation was assessed clinically and judged to be adequate. During bypass, the individual infusion rates varied from 0.0017 to 0.0067 mg kg⁻¹ min⁻¹ and mean infusion rates from 0.0036 to 0.0045 mg kg⁻¹ min⁻¹ (average 0.0039 ± 0.0002 mg kg⁻¹ min⁻¹) in the six patients studied (table I). Following cardiopulmonary bypass the individual infusion rates ranged from 0.0025 to

Table 1. Mean infusion rates of atracurium administered to six patients undergoing cardiopulmonary bypass with induced hypothermia monitored with train-of-four responses of the adductor pollicis muscle

<table>
<thead>
<tr>
<th>Before bypass</th>
<th>During bypass</th>
<th>After bypass</th>
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<tbody>
<tr>
<td>Mean infusion rate (mg kg⁻¹ min⁻¹)</td>
<td>Mean infusion rate (mg kg⁻¹ min⁻¹)</td>
<td>Mean infusion rate (mg kg⁻¹ min⁻¹)</td>
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<tr>
<td>Duration (min)</td>
<td>Duration (min)</td>
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<tr>
<td>0.0067</td>
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<td>0.0067</td>
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<tr>
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<tr>
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<td>0.0042</td>
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</tr>
<tr>
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<td>0.0035</td>
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</tr>
<tr>
<td>Average</td>
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<td>0.0041</td>
</tr>
<tr>
<td>SEM</td>
<td>±0.0006</td>
<td>±0.0002</td>
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P < 0.001

n.s.
ATRACURIUM IN CARDIOPULMONARY BYPASS

0.0050 mg kg\(^{-1}\) min\(^{-1}\). Mean infusion rates of \(0.0030\) and \(0.0050\) mg kg\(^{-1}\) min\(^{-1}\) were used (average \(0.0041 ± 0.0004\) mg kg\(^{-1}\) min\(^{-1}\)) and recovery began \(25.7 ± 2.0\) min following termination of the infusion. A typical tracing is shown in figure 1.

In the other group of six patients, following the initial bolus dose of atracurium, the time taken for 5–10% recovery of the control single twitch response was \(37 ± 2.7\) min; the infusion was then commenced. Before bypass the infusion rates required to maintain 90–95% twitch depression varied from 0.0067 to 0.0100 mg kg\(^{-1}\) min\(^{-1}\) and the mean infusion rate from 0.0050 to 0.0078 mg kg\(^{-1}\) min\(^{-1}\) (average 0.0065 ± 0.0004 mg kg\(^{-1}\) min\(^{-1}\)) as shown in table II. During cardiopulmonary bypass with induced hypothermia the individual rates of infusion ranged from 0.0017 to 0.0067 mg kg\(^{-1}\) min\(^{-1}\) and the mean infusion rates were 0.0019 to 0.0050 mg kg\(^{-1}\) min\(^{-1}\) (average 0.0029 ± 0.0005 mg

FIG. 1. Responses of the adductor pollicis muscle to train-of-four stimulation (2 Hz) during infusion of atracurium to a patient undergoing cardiopulmonary bypass with induced hypothermia.

| Table II. Mean infusion rates of atracurium administered to six patients undergoing cardiopulmonary bypass with induced hypothermia monitored with single twitch responses of the adductor pollicis muscle |
|---|---|---|---|
| Before bypass | During bypass | After bypass |
| Mean infusion rate (mg kg\(^{-1}\) min\(^{-1}\)) | Duration (min) | Mean infusion rate (mg kg\(^{-1}\) min\(^{-1}\)) | Duration (min) | Mean infusion rate (mg kg\(^{-1}\) min\(^{-1}\)) | Duration (min) |
| 0.0067 | 21 | 0.0019 | 87 | 0.0040 | 38 |
| 0.0060 | 26 | 0.0026 | 75 | 0.0050 | 28 |
| 0.0050 | 30 | 0.0025 | 78 | 0.0045 | 46 |
| 0.0078 | 32 | 0.0050 | 102 | 0.0067 | 67 |
| 0.0069 | 7 | 0.0023 | 110 | 0.0046 | 76 |
| 0.0066 | 50 | 0.0031 | 77 | 0.0061 | 41 |
| Average | 0.0065 | 0.0029 | 0.0052 |
| SEM | ±0.0004 | ±0.0005 | ±0.0004 |

\(P<0.001\)
Atracurium infusion 0.0067 mg kg\(^{-1}\) min\(^{-1}\) for 58 min
0.0033 mg kg\(^{-1}\) min\(^{-1}\) for 44 min
0.0017 mg kg\(^{-1}\) min\(^{-1}\) for 44 min
Total dose 0.66 mg kg\(^{-1}\) in 154 min

FIG. 2. Responses of the adductor pollicis muscle to single twitch stimulation (0.1 Hz) during infusion of atracurium to a patient undergoing cardiopulmonary bypass with induced hypothermia.

DISCUSSION

A bolus dose of atracurium 0.6 mg kg\(^{-1}\) provided satisfactory surgical relaxation without affecting cardiovascular stability in 12 patients undergoing open-heart surgery. Since each patient was being treated for heart failure, a low cardiac output and slow circulation could account for the longer time taken to accomplish intubation in some of the patients compared with that reported in previous studies (Payne and Hughes, 1981; Scott and Goat, 1982).

Monitoring of neuromuscular blockade during hypothermia is complicated by the fact that cooling affects nervous conduction, neuromuscular transmission and muscular activity (Hodgkin and Katz, 1949; Hill, 1951; Katz and Miledi, 1965; Harris and Leach, 1968; Hubbard, Jones and Landau, 1971). Furthermore, the evoked response obtained in a peripheral muscle during cardiopulmonary bypass may be influenced by peripheral and core temperature gradients and alterations in skeletal muscle blood flow (Gazzaniga et al., 1972).

In this study, the train-of-four response disappeared when hypothermia was rapidly induced to a core temperature of 26°C. Although it has been reported that twitch height is reduced during cooling (Feldman, 1973), the single twitch response was less affected by hypothermia and allowed a finer adjustment of the rates of infusion. These rates tended to be lower during bypass and higher following bypass than those obtained when train-of-four stimulation was used, although the differences be-
between these rates were not significant (tables I and II). It is likely that the train-of-four response was more affected by low temperature than the single twitch because synaptic activity is greater during train-of-four than single twitch stimulation and acetylcholine release may be depressed by hypothermia (Feldman, 1979). Furthermore, the difference observed between the single twitch and train-of-four responses suggests that hypothermia had a more pronounced effect at the neuromuscular junction relative to its effect on nervous conduction and muscle contraction.

The average infusion rate required to maintain surgical relaxation before bypass was similar to that used in patients undergoing prolonged general surgery (Eagar, Flynn and Hughes, 1984), but during cardiopulmonary bypass with induced hypothermia a significant reduction of 45–55% ($P < 0.001$) in the average infusion rates was obtained (tables I and II). Previous studies have shown that the action of competitive neuromuscular blocking agents is prolonged during hypothermia and cardiopulmonary bypass (Park and Macnamara, 1979). This effect has been attributed to a decrease in renal and hepatic clearance (Ham et al., 1978; Shanks and Walker, 1982). However, the effect of hypothermia should be easier to assess with atracurium since its inactivation is mainly dependent on renal and hepatic clearance (Ham et al., 1978; Hodgerick, L. L. (1978). Pharmacokinetics and pharmacodynamics of d-tubocurarine during hypothermia in the cat. Anesthesiology, 49, 324.


REFERENCES


UTILISATION DE L’ATRACURIUM EN CHIRURGIE CARDIAQUE AVEC CIRCULATION EXTRACORPORELLE ET HYPOTHERMIE PROVOQUEE

RESUME

De l’atracurium a ete administre en perfusion a 12 patients anesthesies subissant des actes de chirurgie cardiaque avec CEC et hypothermie provoquee. Apres une injection rapide initiale de 0,6 mg kg⁻¹, une perfusion d’atracurium etait instituee au debit
moyen de 0,0066 ± 0,0003 mg kg⁻¹ min⁻¹ (0,4 mg kg⁻¹ h⁻¹), suffisante pour maintenir un bloc de 90–95% du twitch isolé ou en train de quatre avant la CEC. Pendant la CEC avec hypothermie provoquée (25–26 °C), un relâchement musculaire compatible avec la chirurgie était obtenu avec un débit de perfusion diminué à peu près de moitié (0,0024 ± 0,003 mg kg⁻¹ min⁻¹ soit 0,2 mg kg⁻¹ h⁻¹) et ce pendant 70–166 min. Ce débit de perfusion en hypothermie était significativement inférieur (P<0,001) à celui en normothermie. Ainsi, l’atracurium apparaît comme un agent utilisable en perfusion continue pour la chirurgie cardiaque et l’inactivation température-dépendante de l’atracurium a été exploitée pour utiliser moins de produit au cours de l’hypothermie provoquée.

**ZUSAMMENFASSUNG**

Zwölf narkotisierten Patienten, die herzchirurgisch mit kardiopulmonalem Bypass und induzierter Hypothermie operiert wurden, wurde Atracurium über Infusion verabreicht. Nach einem initialen Bolus von 0,6 mg kg⁻¹ wurde eine Atracurium-infusion mit einer mittleren Geschwindigkeit von 0,0066 ± 0,0003 mg kg⁻¹ min⁻¹ (0,4 mg kg⁻¹ h⁻¹) verabreicht, die ausreichte, um vor dem Bypass Einzelreize oder Train-of-four-Reaktionen um 90–95% zu blockieren. Während kardiopulmonalem Bypass mit induzierter Hypothermie (25–26 °C) konnte mit annähernd halber Infusionsgeschwindigkeit (0,0034 ± 0,0003 mg kg⁻¹ min⁻¹ oder 0,2 mg kg⁻¹ h⁻¹) über 70 bis 166 Minuten adäquate chirurgische Relaxation erzielt werden. Die Infusionsgeschwindigkeit während Hypothermie war signifikant langsamer (P<0,001) als während Normothermie. Atracurium schien geeignet für kontinuierliche Infusion während Herzoperationen, und die temperaturabhängige Inaktivierung von Atracurium erwies sich als vorteilhaft, da während Hypothermie mit geringeren Dosen ausgekommen werden konnte.

**EL USO ATRACURIO EN CIRUJIA CARDIACA CON PUENTE CARDIO-PULMONAR E HIPOTERMIA INDUCIDA**

Se administró atracurio por infusión a 12 pacientes anestesiados sometidos a cirugía cardíaca con puente cardio-pulmonar e hipotermia inducida. Después de una dosis inicial de bolo de 0,6 mg kg⁻¹, se prosiguió con una infusión de atracurio a un ritmo promedio de 0,0066 ± 0,0003 mg kg⁻¹ min⁻¹ (0,4 mg kg⁻¹ h⁻¹) que fue suficiente como para mantener un bloqueo del 90–95% de la contracción única o de las respuestas al tren de cuatro antes del puente. Se proveyó una relajación quirúrgica adecuada con la mitad aproximadamente del ritmo de infusión de 0,0034 ± 0,0003 mg kg⁻¹ min⁻¹ (0,2 mg kg⁻¹ h⁻¹) durante el puente cardio-pulmonar con hipotermia inducida (25–26 °C) por 70 a 166 min. Este ritmo de infusión durante la hipotermia fue mucho más lento (P<0,001) que el usado durante la normotermia. Entonces, el atracurio parece adecuarse al uso mediante infusión continua en cirugía cardíaca y se usó la inactivación del atracurio a raíz de la temperatura con el mayor provecho porque se necesitó menos droga durante la hipotermia inducida.