Comparison of the pharmacodynamics and pharmacokinetics of an infusion of cis-atracurium (51W89) or atracurium in critically ill patients undergoing mechanical ventilation in an intensive therapy unit

A. H. BOYD, N. B. EASTWOOD, C. J. R. PARKER AND J. M. HUNTER

Summary

We have studied 12 critically ill, sedated patients who required a neuromuscular blocking drug to assist mechanical ventilation in an intensive care unit. Patients were randomized to receive an infusion of cis-atracurium 0.18 mg kg\(^{-1}\) h\(^{-1}\) (group 1, \(n = 6\)) or atracurium 0.6 mg kg\(^{-1}\) h\(^{-1}\) (group 2, \(n = 6\)) preceded, if necessary, by a bolus dose of 2 \(\times\) ED\(_{95}\) of the same drug (cis-atracurium 0.1 mg kg\(^{-1}\) or atracurium 0.5 mg kg\(^{-1}\)). Neuromuscular block was monitored using an accelerograph and the infusion rate adjusted regularly so that it was possible to detect the first response to train-of-four (TOF) stimulation of the ulnar nerve at the wrist. Blood samples were obtained for estimation of plasma cis-atracurium and laudanosine concentrations (group 1) or the three groups of atracurium isomers and laudanosine (group 2). There was no apparent haemodynamic or allergic response to either drug. The mean infusion time in group 1 was 37.6 h and in group 2, 27.5 h. On termination of the infusion, the time for the TOF ratio to reach 0.7 was similar in the two groups (group 1 = 60 min; group 2 = 62 min). The mean infusion rate of cis-atracurium was 0.19 mg kg\(^{-1}\) h\(^{-1}\) and of atracurium 0.47 mg kg\(^{-1}\) h\(^{-1}\) (expressed as mg of bis-cation): cis-atracurium was 2.5 times more potent than atracurium. Using the NONMEM program, a single compartment pharmacokinetic model was fitted to the plasma concentrations of cis-atracurium and the cis-cis, cis-trans and trans-trans isomers of atracurium. The mean population pharmacokinetic values for cis-atracurium were: volume of distribution \((V) = 21900\) (SEM 416) ml; clearance \((Cl) = 549\) (79) ml min\(^{-1}\); half-life \((T\_1\) \(_2\)) = 27.6 (3.6) min; and for the three groups of atracurium isomers were: cis-cis, \(V = 15100\) (720) ml, \(Cl = 449\) (42) ml min\(^{-1}\), \(T\_1 = 23.4\) (1.2) min; cis-trans, \(V = 18000\) (667) ml, \(Cl = 1070\) (43) ml min\(^{-1}\), \(T\_1 = 11.7\) (0.1); trans-trans, \(V = 13100\) (1280) ml, \(Cl = 1560\) (55) ml min\(^{-1}\), \(T\_1 = 5.8\) (0.4) min. Plasma laudanosine concentrations were lower in the cis-atracurium (peak value 1.3 \(\mu\)g ml\(^{-1}\)) than in the atracurium (maximum 4.4 \(\mu\)g ml\(^{-1}\)) group. (Br. J. Anaesth. 1996; 76: 382–388)

Key words


In the management of critically ill patients requiring mechanical ventilation in an intensive care unit, it may occasionally be necessary to administer a neuromuscular blocking drug together with sedative and analgesic agents. Indications for the use of neuromuscular blocking agents in such circumstances include: poor lung compliance, as in patients with adult respiratory distress syndrome; inability to synchronize the patient’s own respiratory pattern with intermittent positive pressure ventilation (IPPV); raised intracranial pressure; status epilepticus; and to facilitate radiological imaging or inter-hospital patient transfer [1].

Atracurium, given by constant infusion, has proved useful in the management of the critically ill. It breaks down spontaneously in plasma (Hofmann elimination) and undergoes ester hydrolysis [2]. Thus its clearance is partially independent of renal and hepatic function, making it suitable for use in patients with multiple organ failure (MOF) [3]. Laudanosine, a metabolite of Hofmann degradation, is excreted partly by the kidney [4] and also by the liver [5]. Electroencephalographic changes in cats have been reported at plasma concentrations of > 4.4 \(\mu\)g ml\(^{-1}\) and convulsions in rats and dogs at a concentration of 17 \(\mu\)g ml\(^{-1}\) [6–8]. In pharmacokinetic studies of critically ill patients receiving atracurium by constant infusion without neuromuscular monitoring, plasma concentrations of laudanosine of up to 5 \(\mu\)g ml\(^{-1}\) have been detected [9, 10]. Although this concentration is higher than after a single bolus dose of atracurium 0.5–0.6 mg kg\(^{-1}\), when plasma laudanosine concentrations peak at approximately 0.2–0.3 \(\mu\)g ml\(^{-1}\) [11, 12] there is as yet no evidence to suggest that laudanosine concentrations reported in patients with MOF are epileptogenic.

Atracurium is a mixture of 10 geometric isomers.
The physical characteristics, medical history and diagnosis of each patient were recorded (table 1), and also all medications administered in the 12-h period before and during administration of the neuromuscular blocking agent (table 2). A physical examination was performed and baseline recordings of vital signs such as arterial pressure, heart rate and temperature. Blood samples were obtained for estimation of haemoglobin, MCV, platelet count, white cell count, and serum concentrations of sodium, potassium, bicarbonate, creatinine, total bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin and glucose. Illness severity scores (Apache II) [17] were recorded for the 24-h period immediately after commencement of the study. Urine was analysed for protein and blood.

Neuromuscular monitoring was quantified using an accelerograph (TOF-Guard, Biometer, Denmark). The skin over the ulnar nerve at the wrist was cleansed and gently abraded. Paediatric electrocardiographic electrodes were then applied to allow stimulation of the ulnar nerve at the wrist, using the train-of-four (TOF) twitch technique. The transducer was attached to the thumb to measure acceleration in response to contraction of the adductor pollicis muscle. The accelerograph records the ratio (T4 : T1), expressed as a percentage. Baseline measurements were determined before administration of the neuromuscular blocking agent.

Depending on the clinical situation, a bolus of the neuromuscular blocking agent followed by a constant infusion of the same drug was commenced or, if the patient had already received such a drug, the infusion was started without a bolus dose.

Those patients receiving cis-atacurium (group 1) were given a bolus dose of $2 \times ED_{95}$ (0.1 mg kg$^{-1}$), over 5–10 s, followed immediately by an initial infusion of 0.18 mg kg$^{-1}$ h$^{-1}$; alternatively, a constant infusion was started at the same rate. Patients receiving atracurium (group 2) were given a bolus of $2 \times ED_{95}$ (0.5 mg kg$^{-1}$) or an initial infusion of 0.6 mg kg$^{-1}$ h$^{-1}$, or both. The infusion of cis-atacurium or atracurium was subsequently adjusted to maintain the TOF count at 1 response only (T1). As few adjustments as possible to the infusion rates were made, and any changes were small. A record of the TOF count was noted whenever the infusion rate was changed, and at least once every 8 h if no alteration in the infusion rate had occurred during that period. The TOF count was also documented just before discontinuing the infusion and every 5 min thereafter until the TOF ratio was $> 0.7$.

A blood sample (5 ml) was obtained from each patient before administration of the drug. Further samples were obtained 15 min and 1 h after the initial bolus dose of either cis-atacurium or atracurium, or after commencement of the infusion (if a bolus dose had not been given). Blood samples were then obtained 15 min and 1 h after any alteration in the infusion rate and approximately every 8 h, if there had been no alteration in the infusion rate. Samples were also collected immediately before termination of the drug, at 2, 5, 10 and 20 min after

The study was approved by the Hospital Ethics Committee. A clinical trial exemption certificate for the use of cis-atacurium was issued by the Committee on Safety of Medicines. Informed consent was obtained from the next of kin of all patients. Twelve patients, aged $> 18$ yr, were investigated consecutively, after a predetermined randomized sequence; six were allocated to receive cis-atacurium (group 1) and six to receive atracurium (group 2). Patients were considered suitable for entry into this study only when their medical management required the use of a neuromuscular blocking agent. Exclusion criteria included: pregnancy; known sensitivity to atracurium; personal or family history of malignant hyperthermia; clinically significant neuromuscular disease; major thermal injury; recent administration of a neuromuscular blocking agent for more than 24 h in the presence of renal failure; failure to demonstrate partial recovery of the train-of-four count after a previously administered neuromuscular blocking agent; prior administration of atracurium of more than 3 mg kg$^{-1}$ within the previous 8 h; or administration of an atracurium infusion within the previous 4 days.

All patients admitted to the intensive therapy unit (ITU) were treated as indicated clinically, with sedative and analgesic agents given in accordance with the sedation policy of the ITU. If the patient had already received a neuromuscular blocking agent and did not have any of the exclusion criteria listed above, evidence of recovery from neuromuscular block was sought, using an accelerograph, before inclusion in the study. Thus a previously administered neuromuscular blocking agent might have been detectable in the plasma on entry into the study.

### Patients and methods

The study was therefore designed to compare cis-atacurium with atracurium, given by constant infusion, in critically ill patients requiring neuromuscular block to facilitate mechanical ventilation. The aim was to assess dose requirements and any possible side effects of cis-atacurium. Plasma concentrations of cis-atacurium and the three groups of isomers of atracurium were measured and an attempt was made to compare the pharmacokinetics of cis-atacurium with the individual isomer groups of atracurium. The plasma laudanosine concentrations produced by the two drugs were also compared.

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<table>
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<th>Patient No.</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Sex (M/F)</th>
<th>Apache II score</th>
<th>Diagnosis</th>
<th>Sedation and analgesia</th>
<th>Outcome</th>
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<tr>
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<td>1</td>
<td>71</td>
<td>65</td>
<td>F</td>
<td>9</td>
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<td>P, M</td>
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<td></td>
<td>2</td>
<td>38</td>
<td>50</td>
<td>F</td>
<td>22</td>
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<td>P, A</td>
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<td>25</td>
<td>75</td>
<td>M</td>
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<td></td>
<td>4</td>
<td>69</td>
<td>75</td>
<td>M</td>
<td>10</td>
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<td></td>
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<tr>
<td></td>
<td>6</td>
<td>22</td>
<td>80</td>
<td>M</td>
<td>19</td>
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<td>Group 2: atracurium</td>
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<td></td>
<td>8</td>
<td>50</td>
<td>80</td>
<td>F</td>
<td>3</td>
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<td>74</td>
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<td>13</td>
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<td>M</td>
<td>17</td>
<td>Renal artery stenosis, renal failure ▼</td>
<td>P, M</td>
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</table>

Each blood sample was placed immediately into a lithium heparin tube containing 0.02 ml of sulphuric acid 1.5 mol litre⁻¹ and centrifuged. The plasma (2 ml) was decanted and acidified with 8 ml of sulphuric acid 15 mmol litre⁻¹. The acidified plasma was kept on ice and deep frozen within 30 min for subsequent analysis by solid phase extraction and high pressure liquid chromatography (HPLC) with fluorescence detection. The assay was validated using quality control samples derived from pooled human plasma. The lower limit of quantification (LOQ) was 10 ng ml⁻¹ for all analytes. In group 1, the upper LOQ for cis-atracurium was 2140 ng ml⁻¹ and for laudanosine 1410 ng ml⁻¹. In group 2 the upper LOQ values for cis-cis, cis-trans and trans-trans isomers of atracurium were 2800, 1580 and 250 ng ml⁻¹; the upper LOQ for laudanosine was 2000 ng ml⁻¹. The coefficient of variation for all analytes was <11.3%, except for the trans-trans atracurium isomers, which was 20.8%.

The non-linear mixed effects model program (NONMEM) [18] was used to fit a one-compartment model to the plasma concentrations of cis-atracurium from patients in group 1, and to the plasma concentration profiles of each of the atracurium isomer groups in those patients who received atracurium (group 2). The program fits a model to the data for all individuals collectively; rather than attempting to identify the pharmacokinetic variables of each individual separately, a population mean is determined. In principle, the inter-individual random variability in pharmacokinetic variables is also determined, but these results are not presented in view of the small sample size.

The models were described in terms of compartment volume and clearance. Elimination half-life was determined in additional NONMEM runs with the model described in terms of V and T1/2. Attempts to fit a two-compartment model were unsatisfactory, presumably as a consequence of the sparsity of data points in the periods just after starting and finishing the infusion. In one patient who received atracurium (patient No. 7), the final three plasma concentrations were obtained soon after extensive debridement of soft tissue under general anaesthesia and within a few hours of death. Their inclusion in the data set used to fit the model was associated with large residual errors and difficulty in obtaining convergence of the routine to minimize the objective function. They were therefore omitted from the data set used to fit the model.

**Results**

The physical characteristics and diagnoses of the patients are shown in table 1. Patient No. 6 had received atracurium 135 mg and vecuronium 74 mg in the 24 h before admission into the study: he had
surgery for orthopaedic procedures and had also been transferred to another hospital for intracranial surgery during that time. Patient No. 9 had received vecuronium 10 mg, 2.5 h previously. Urea and electrolyte concentrations and liver function tests in each patient on entering the study are shown in table 2.

Medication administered to each patient concurrent with the infusion of neuromuscular blocking drug is given in table 3. All patients completed the study except for patient No. 7 who died while an infusion of atracurium was in progress. Brain stem death, after a severe head injury, was diagnosed in patient No. 6, 19.5 h after discontinuation of the infusion.

Of the six patients who received cis-atracurium, five were given an initial bolus dose together with an infusion. Patient No. 6, who had received atracurium and vecuronium before inclusion in the study, still had evidence of residual neuromuscular block when entered into the study (TOF count = 1). He received no initial bolus dose. The mean infusion rate for each patient, number of changes of the infusion rate, duration of each infusion and total dose given are shown in table 4. The TOF count on discontinuing the infusion and the time for the TOF ratio to reach greater than 0.7 are also given. The mean infusion rate for patients given cis-atracurium was 0.19 (range 0.16–0.21) mg kg\(^{-1}\) h\(^{-1}\) and the mean time for the TOF ratio to reach 0.7 was 60 (20–85) min.

Five patients were given a bolus of atracurium followed immediately by an infusion. Atracurium was initiated by infusion to patient No. 9, who had previously been given vecuronium, but she required an additional bolus 15 min later. The mean infusion rate for atracurium in group 2 was 0.47 (range 0.3–0.74) mg kg\(^{-1}\) h\(^{-1}\). The mean duration of infusion for the atracurium group was shorter than that for the cis-atracurium group (27.53 vs 37.62 h).

In patient No. 10 it was not possible to measure the time to a TOF ratio >0.7 because of a fault with the accelerograph. The mean time to achieve a TOF ratio greater than 0.7 was 62 (41–82) min in the four other patients.

Analysis of the two batches of cis-atracurium used in the study showed one batch to contain 105.8 % of the stated amount (5 mg ml\(^{-1}\)) and the other to contain 110.1 %. Analysis of the atracurium used in the study indicated that it contained 109.2 % of the stated amount (10 mg ml\(^{-1}\)) and the following isomer composition: cis-cis 58.7 %, cis-trans 35.9 %, trans-trans 5.4 %. Pharmacokinetic variables, derived using the NONMEM program for cis-atracurium and each of the three groups of isomers of atracurium, are given in table 5.

The plasma concentrations of laudanosine in each of the patients during the infusion are shown in figure 1, and after discontinuing the infusion in figure 2.

As patient No. 7 died while still receiving an infusion of atracurium, there are only 11 plots in figure 2. Peak laudanosine concentrations obtained and values for area under curve of laudanosine against time are given in table 6. The peak plasma laudanosine concentration in patients given cis-
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atracurium was 1.3 \( \mu \text{g ml}^{-1} \), whereas in patients who received atracurium it was 4.4 \( \mu \text{g ml}^{-1} \).

No haemodynamic disturbances or allergic reactions were associated with either the bolus dose or infusion of both neuromuscular blocking agents.

Discussion

In this study, the mean infusion rates of \textit{cis}-atracurium and atracurium required for six critically ill patients were 0.19 and 0.47 \( \text{mg kg}^{-1} \text{ h}^{-1} \), respectively. The mean infusion rate of \textit{cis}-atracurium was comparable with that reported by Stone, Pollard and Harper (0.17 \( \text{mg kg}^{-1} \text{ h}^{-1} \)) in 12 intensive care patients [19]. The atracurium infusion rates were also similar to those reported in other studies in the critically ill [10, 20]. In this study, \textit{cis}-atracurium was therefore approximately 2.5 times more potent than atracurium (with the dose of both drugs expressed as milligrams of the bis-cation). The dose of atracurium in the commercial preparation is expressed as milligrams of the salt: for our patients,
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this is equivalent in clinical use to atracurium 0.63 mg kg\(^{-1}\) h\(^{-1}\).

An infusion of cis-atracurium provided adequate neuromuscular block in our patients. As with previous clinical studies of this new drug [15], no obvious adverse cardiovascular or allergic effects were noted. None was noted in the atracurium group. Allergic responses to drugs are, in fact, uncommon in critically ill patients [21]. On discontinuing the infusion, the mean time for the TOF ratio to recover to greater than 0.7 was very similar after cis-atracurium or atracurium (60 vs 62 min).

The TOF count on stopping the infusion, measured using the accelerograph, varied between 0 and 4 in patients given cis-atracurium, but was 0 in all patients given atracurium. However, we noted that it was possible, on occasion, to see the first response to the TOF without it being detected by the accelerograph. We do not therefore believe that there were significant differences in the degree of neuromuscular block on discontinuing the infusion between the patients studied; the accelerograph is not always accurate for use in this group of patients. It was chosen because it is compact, easy to use and does not require immobilization of the patient’s arm for long periods of time. The time to achieve a TOF ratio > 0.7 of 60 min after either drug compares very favourably with vecuronium, after which the time to achieve a similar degree of recovery may taken more than 35 h in patients with MOF [22]. It is interesting to note that in the vecuronium study, the possibility of metronidazole inhibiting metabolism of the drug was raised [22]. Five of the patients in this study were receiving metronidazole (table 3), but there was no evidence of such an effect. It would seem that rapid recovery can be achieved after cis-atracurium has been given for many hours to critically ill patients, in the same way as has been reported after the use of atracurium [3, 20].

There was no evidence for the development of tolerance to the action of each of the neuromuscular agents in the two groups. In the cis-atracurium group, only patient No. 1 required a slightly greater infusion rate at the end of the study than at the beginning. In the atracurium group, a similar pattern was found: only patient No. 7 had increased requirements at the end of the infusion period. Although the maximum duration of infusion was only 47.6 h in group 1 and 34.2 h in group 2, Stone, Pollard and Harper also found no evidence for increasing requirements of cis-atracurium with time, even after infusions of up to 135 h duration. Evidence for the development of tolerance to neuromuscular blocking agents in the critically ill is mainly anecdotal [9] although it has been demonstrated in paediatric practice and in anaesthetized dogs [23, 24].

In the pharmacokinetic analysis of plasma concentrations of cis-atracurium (group 1) and the three groups of atracurium isomers (group 2), it was only possible to fit a one-compartment pharmacokinetic model to the data because of the relative sparsity of data points for individual patients at the times when the infusion was changed. Clearance of cis-atracurium was found to be 549 ml min\(^{-1}\), with an elimination half-life of 28 min. These values were similar to those found in a study of healthy patients and patients with chronic renal failure given a bolus dose of cis-atracurium 0.1 mg kg\(^{-1}\) [25]. It was reassuring to find that the clearance of cis-atracurium...
was unchanged, and possibly increased, in these six critically ill patients. Once again there is evidence of spontaneous atracurium (or its isomer) breakdown irrespective of the residing body compartment [10,12].

It is interesting to compare the pharmacokinetics of cis-atracurium with those of the three cis-cis isomers of atracurium (group 2), where clearance was 449 ml min\(^{-1}\) and \(T_{\text{1/2}}\) 23 min. These differences probably reflect the presence of the two cis-cis isomers in atracurium. There were other differences in the derived pharmacokinetic variables for the three groups of atracurium isomers. Clearance of the cis-trans isomer was approximately twice that of the cis-cis isomer, and that of the trans-trans group over three times that of the cis-cis isomer. The values for clearance and elimination half-life of the cis-cis and cis-trans isomers in this study were comparable with those of Tsui, Graham and Torda in a study of eight ASA I and II patients who were given a single bolus dose of atracurium 0.3 or 0.5 mg kg\(^{-1}\) [26]. These workers did not determine the kinetics of the very short-acting trans-trans isomer. Our study is the first to examine the pharmacokinetics of the three groups of isomers of atracurium in the critically ill patient.

Plasma laudanosine concentrations were smaller after cis-atracurium than after atracurium. The highest measured plasma concentration of laudanosine in group 1 was 1.3 μg ml\(^{-1}\), and in group 2 4.44 μg ml\(^{-1}\). Laudanosine concentrations after atracurium were comparable with those reported previously in the critically ill [9,10]. No attempt was made to fit a pharmacokinetic model to the plasma laudanosine concentrations for several reasons. After administration of cis-atracurium or atracurium, laudanosine is produced continually as a metabolite at various sites. Thus the total dose of laudanosine given is unknown and the time course of laudanosine production cannot be determined. The AUC was calculated, however, to give an indication of the overall formation of laudanosine; it tended to be less in the group who received cis-atracurium than atracurium.

Acknowledgement

We thank the Wellcome Foundation plc for providing a grant towards this study and the cis-atracurium and atracurium.

References