CLINICAL EXPERIENCE AND PLASMA LAUDANOSINE CONCENTRATIONS DURING THE INFUSION OF ATRACURIUM IN THE INTENSIVE THERAPY UNIT

P. M. YATE, P. J. FLYNN, R. W. ARNOLD, B. C. WEATHERLY, R. J. SIMMONDS AND T. DOPSON

The use of neuromuscular blockade in the intensive therapy unit (ITU) is controversial: many clinicians are concerned about the risk of awareness when the patient is paralysed, and of accidental disconnection from the ventilator (Willatts, 1985). However, there is evidence which suggests that neuromuscular blockade may be beneficial in the management of certain conditions, notably adult and neonatal respiratory distress syndrome (Pollitzer et al., 1981; Greenough et al., 1984), tetanus (Edmondson and Flowers, 1979) and head injury (McDowall, 1983). Surveys of intensive therapy units suggest that the use of neuromuscular blocking agents is widespread (Miller-Jones and Williams, 1980; Merriman, 1981). However, there are very few data on the appropriateness of the individual agents in the ITU, and choices have been based largely on experience gained in the operating theatre.

The requirements for the ideal drug would include good cardiovascular stability, lack of histamine release, no cumulation, and a means of elimination which is independent of hepatic and renal function. It is important that the neuromuscular blockade can be antagonized easily and rapidly when required, to permit assessment of the patient and for weaning from mechanical ventilation—even in the presence of multiple organ failure. In addition, the drug should be suitable for administration by infusion, a technique that offers the advantage of convenience and avoids the need for i.v. bolus doses which may be associated with serious cardiovascular- and histamine-related effects (Scott et al., 1985). Atracurium, a relatively new competitive neuromuscular blocking agent of intermediate duration, would appear to have many of these features. It has been used successfully by infusion for prolonged surgery (Eagar, Flynn and Hughes, 1984; Gargarian et al., 1984). Thus it would seem appropriate to extend investigation of this agent into the ITU. There are already several case reports of the use of atracurium in the ITU (Hutchinson and Pinnock, 1984; Powles and Ganata, 1985; Thomas and Windsor, 1985); in addition, there are reports of infusions of up to 22 days' duration (Wadon, Dorga and Anand, 1986). However, the unique metabolism of atracurium has given rise to new anxieties: in particular, concern has been expressed regarding possible seizure activity caused by laudanosine, a product of both the Hofmann degradation and ester hydrolysis of atracurium (Hennis et al., 1984).

The aim of this investigation was twofold; first

SUMMARY
Twenty patients in the intensive care unit received an infusion of atracurium to permit mechanical ventilation. The duration of infusion ranged from 38 to 219 h and the average rate of infusion during the study was 0.76 mg kg⁻¹ h⁻¹. In 14 patients an increase in atracurium requirement occurred within the first 72 h of the infusion. Recovery from neuromuscular blockade after a prolonged infusion was sufficiently rapid to avoid pharmacologically induced reversal. In six patients maximum plasma concentrations of laudanosine were 1.9–5 µg ml⁻¹, and there was no evidence of cerebral excitation.
a dose-finding study and, second, to make serial measurements of plasma laudanosine concentrations during the infusion of atracurium in the ITU.

PATIENTS AND METHODS

Twenty patients admitted to our ITU who required the administration of neuromuscular blocking agents (to facilitate satisfactory intermittent positive pressure ventilation (IPPV)) were entered to the trial. Ethical committee approval and informed consent from the patients’ next-of-kin were obtained.

An infusion of undiluted atracurium solution 10 mg ml⁻¹ was delivered from a 50-ml syringe driven by a Tronic IP3 Syringe Pump (Vickers). The infusion was commenced at a rate of 0.4 mg kg⁻¹ h⁻¹ and then adjusted by the clinical staff of the ITU to provide good conditions for IPPV. All patients received regular doses of midazolam 2.5 mg i.v. supplemented in some cases by phenoperidine 1–2 mg to provide sedation and analgesia. At regular intervals, neuromuscular transmission was allowed to recover spontaneously to permit neurological assessment. No attempt was made to achieve any fixed degree of neuromuscular blockade, although some moni-

<table>
<thead>
<tr>
<th>Initials</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Duration of infusion (min)</th>
<th>Dose (mg kg⁻¹)</th>
<th>Mean infusion rate (mg kg⁻¹ h⁻¹)</th>
<th>Max. infusion rate (mg kg⁻¹ h⁻¹)</th>
<th>Diagnosis on admission</th>
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<tr>
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<td>68</td>
<td>F</td>
<td>50</td>
<td>124</td>
<td>103</td>
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<td>162</td>
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<td>147</td>
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<td>0.83</td>
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<td>80</td>
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<td>0.62</td>
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<tr>
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<td>69</td>
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</tr>
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<td>112</td>
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<td>1.0</td>
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<tr>
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<td>M</td>
<td>70</td>
<td>40</td>
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<td>0.61</td>
<td>0.71</td>
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<tr>
<td>B.C.†</td>
<td>58</td>
<td>M</td>
<td>70</td>
<td>113</td>
<td>83</td>
<td>0.73</td>
<td>0.87</td>
<td>Faecal peritonitis, Respiratory failure*</td>
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LAUDANOSINE CONCENTRATIONS IN PATIENTS

Monitoring was performed by assessment of the response of the muscles of the hand to train-of-four stimulation of the ulnar nerve, either by visual inspection or by recording the evoked electromyogram (Datex Relaxograph).

Blood samples were taken in six patients before the commencement of the infusion, and during the infusion, for estimation of plasma laudanosine and atracurium concentrations. Immediately after collection the samples were centrifuged in a high speed centrifuge, 0.2 ml of the plasma was mixed with 0.8 ml of sulphuric acid 0.015 mol litre⁻¹ and frozen. Samples were later analysed by high pressure liquid chromatography (Simmonds, 1985).

Statistical tests were used where appropriate as specified in the text and results are expressed as mean values ± SEM with ranges.

RESULTS

Twenty patients (mean age 41 ± 4.5 yr and mean weight 66 ± 2.5 kg) requiring prolonged artificial ventilation were studied. Patient characteristics, together with doses of atracurium, infusion rates, duration of infusion and diagnoses are given in table I. Eight patients were in renal failure and were undergoing haemodialysis.

The average infusion rate throughout the study was 0.76 ± 0.05 mg kg⁻¹ h⁻¹ (range 0.45–1.22). The mean infusion rate over the first 12 h was 0.48 ± 0.03 mg kg⁻¹ h⁻¹. In most patients an increase in atracurium requirement occurred within the first 72 h of infusion as indicated in figure 1 (mean rate at 72 h 0.76 ± 0.06 mg kg⁻¹ h⁻¹).

Statistical analysis (one-way analysis of variance) showed this increase to be significant (P < 0.01). This feature is also illustrated in figure 2, which shows segments of the recording of the evoked electromyogram from patient G. S. It can be seen that the degree of neuromuscular blockade achieved did not markedly change over the 38 h of infusion, despite the large increase in the rate of infusion. In addition, this stable level of blockade was associated with an increase in the plasma atracurium concentration from 1.5 µg ml⁻¹ at 70 min to 5.3 µg ml⁻¹ at 38 h.

Another feature illustrated in figure 2 is the modest degree of neuromuscular blockade required to facilitate mechanical ventilation—a finding common to all the 20 patients studied. Despite wide changes in temperature (from 35 to 39 °C) and blood pH (from 7.2 to 7.5) during the infusions of atracurium, there was no significant correlation between changes in these variables and the increase in the infusion rate.

Details of recovery were not available for all the patients for a variety of reasons, including change to another neuromuscular blocking drug, satisfactory IPPV without neuromuscular blockade, and death. In eight patients the mean time from the end of the infusion to satisfactory spontaneous ventilation was 75 min (range 30–120 min) after infusions of a mean duration of 111 h. The decision to discontinue IPPV was not solely based on recovery from neuromuscular blockade, but was also determined by recovery from the sedative and analgesic agents used. In no patient was antagonism of neuromuscular blockade considered necessary.

The plasma concentrations of laudanosine in the six patients studied are shown in figure 3. The maximum laudanosine concentrations in each patient ranged from 1.9 to 5.1 µg ml⁻¹ and there was an indication of a plateau after 2–3 days of infusion. The highest laudanosine concentration was found in patient R. S. who, at the time, had no biochemical evidence of serious hepatic or renal failure. The two patients with the highest concentrations (R. S. and B. C.) were weaned successfully from cardiovascular support. The decrease in concentration in patient V. B. was the result of a temporary cessation of the infusion.

FIG. 1. Mean infusion rates ± SEM of atracurium required after various periods of infusion.
Two patients died while the atracurium infusion was in progress, and another seven patients died between 3 h and 18 days after the infusion was stopped. In no case was the clinical course surprising, and no death was attributed to the atracurium. In one patient, infusion of atracurium was discontinued prematurely when the patient developed a generalized erythematous rash; histological diagnosis subsequently identified the cause as infection. No other side effects were observed which were considered to be related to the atracurium, and the clinical impression was favorable.

There was no evidence of seizure activity in any patient, and it is unlikely that this would have been concealed by the neuromuscular blockade in view...
of the modest degree of blockade achieved. In two patients, electroencephalograms performed at days 5 and 6 of the infusions showed no evidence of cerebral excitation.

DISCUSSION

The average infusion rate (0.76 mg kg$^{-1}$ h$^{-1}$) required to maintain relaxation in patients under sedation in the intensive care unit was substantially higher than that of 0.4 mg kg$^{-1}$ h$^{-1}$ used previously during a balanced anaesthetic technique for prolonged surgery (Eagar, Flynn and Hughes, 1984), but similar to that reported in a study of atracurium infusions in patients in renal failure on an ITU (Griffiths, Hunter and Jones, 1986). Although there was a tendency for the temperature and blood pH to increase in some patients during the infusion of atracurium, there was no correlation between the increase in infusion rate over the first 72 h of infusion and the changes in these variables. It seems unlikely, therefore, that it could be attributed to a more rapid breakdown of atracurium by "Hofmann elimination", a process which is dependent on temperature and pH. In addition, it is unlikely to be the result of the declining effect of recent anaesthesia, as none of these patients had received an anaesthetic for 2 days before the commencement of the infusion, and some not for more than 1 week. A possible explanation for this phenomenon is the development of resistance to atracurium, since a similar effect has been observed in cats after prolonged paralysis with tubocurarine (Matteo and Diaz, 1984), and in man with pancuronium (Callanan, 1985). The reason for this apparent decrease in sensitivity is uncertain, but it has long been known that denervation of skeletal muscle leads to supersensitivity to acetylcholine (Axelsson and Thesleff, 1959). In particular, Berg and Hall (1975) demonstrated increased extrajunctional acetylcholine sensitivity after the chronic administration of tubocurarine. Other possible reasons have been reviewed by Gronert (1986) and include: altered pharmacokinetics as a result of altered metabolism, distribution or excretion—this is not supported by the plasma atracurium concentrations in patient G. S., disuse atrophy (Gronert, 1981); drug interaction—as is in the nature of intensive care, many of these patients were receiving multiple drug therapy and the possibility of drug interaction cannot be discounted.

Of the currently available competitive neuromuscular blocking drugs, atracurium has the shortest elimination half-life and is, probably, the only agent the half-life of which is unaffected by hepatic or renal failure (Ward and Neill, 1983). It has been shown to be the least cumulative of the currently available drugs (Ali et al., 1983). In addition, atracurium has been demonstrated to have minimal cardiovascular effects (Hilgenberg, Stolting and Harris, 1983), although it has been shown to provoke the release of small but significant amounts of histamine (Basta et al., 1983). Whether the theoretical pharmacokinetic advantages of atracurium over other competitive blockers can be demonstrated to have clinical advantages in the ITU is yet to be seen. Vecuronium has a very similar clinical profile but, as yet, there has been little experience of the drug in the ITU. Powles and Ganata (1985) reported a patient with tetanus who was treated initially with an atracurium infusion, but developed numerous episodes of bradycardia which resolved on changing to vecuronium. However, clinical experience gained during the present study showed no evidence of cardiovascular instability associated with atracurium.

Recently, the issue of the potential toxicity of the metabolites of this drug has been raised. This is especially important in the ITU where large doses of atracurium may be administered in the course of several days. One metabolite in particular, laudanosine, has caused concern. This compound has a substantially longer half-life (197 min (Ward et al., 1985)) than atracurium and could be expected to accumulate in an ITU setting. Laudanosine, a product also of morphine metabolism, has long been known to cause convulsions in high doses (Mercier and Mercier, 1955). A recent study (Chapple, Miller and Wheatley, 1985) identified the threshold for convulsions in dogs as 17 mg ml$^{-1}$. This plasma concentration may be significantly higher in man in view of the far lower cerebrospinal fluid: plasma ratios in man of 0-14% (Fahey et al., 1983) compared with those in the dog of 40-60% (Hennis et al., 1984). In our study we found a maximum plasma laudanosine concentration of 5.1 mg ml$^{-1}$. Although a small group of patients with a wide variety of pathology were studied, the plasma concentrations of laudanosine should give a reliable indication of the maximum concentration likely to be achieved. In fact, the plasma laudanosine concentrations in this study were in accordance with previous pharma-
cokinetic predictions for steady-state values (Ward et al., 1985). Thus it seems unlikely that concentrations of laudanosine great enough to provoke seizures will be reached. Of more importance is whether these concentrations could provoke more subtle changes which could be harmful to the critically ill patients. At clinical concentrations of atracurium a 30% increase in the minimum alveolar concentration of halothane was found in rabbits (Shi et al., 1985). Furthermore, electroencephalographic changes were found in cats at concentrations of laudanosine greater than 4.4 μg ml⁻¹ (Ingram et al., 1985). However, in studies with atracurium in dogs (Lanier, Milde and Mitchenfelder, 1985) and cats (Litwak et al., 1985), no effects could be detected on intracranial pressure, cerebral blood flow or cerebral metabolic rate for oxygen.

In conclusion, data were collected from 20 patients receiving an infusion of atracurium for a prolonged period in the ITU. There was an impression of increasing drug requirement with time. The clinical impression gained was favorable. Maximum plasma laudanosine concentrations (measured in six patients) gave a range of 1.9–5.1 μg ml⁻¹, substantially below concentrations required to cause seizures in dogs. Further information is required on the effects of these concentrations in man and any concern raised by these figures should be balanced against the extensive clinical experience with this drug.

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REFERENCES


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