PRODUCTION OF LAUDANOSINE FOLLOWING INFUSION OF ATRACURIUM IN MAN AND ITS EFFECTS ON AWAKENING

G. H. BEEMER, A. R. BJORKSTEN, P. J. DAWSON AND D. P. CRANKSHAW

The continuous infusion of a neuromuscular blocking drug provides a flexible method for maintaining adequate muscle relaxation during surgery, and is particularly suited to atracurium. Its short elimination half-life (20 min) and limited volume of distribution allow a stable infusion rate to be attained within the first 30 min after the start of infusion while ensuring prompt spontaneous recovery when the infusion is discontinued [1,2]. However, there is concern on the possible accumulation of laudanosine, a major metabolite of atracurium, because of its significantly longer elimination half-life (220 min) [1,3].

Laudanosine has been shown to induce epileptiform activity in plasma concentrations of 5 μg ml⁻¹ (healthy rabbits [4]) and 17 μg ml⁻¹ (healthy dogs [5]), but concentrations up to 100 μg ml⁻¹ do not induce epileptiform activity in cats [6]. This large interspecies variation makes it impossible to make extrapolation to man. However, following a study in rabbits in which laudanosine 0.5-0.9 μg ml⁻¹ produced a 30% increase in the MAC for halothane, Shi and colleagues concluded that “if these data apply to humans, the incidence of awareness in lightly anaesthetized patients may be increased during the administration of atracurium” [7].

The aims of this study were to determine the plasma concentrations of laudanosine resulting from infusion of maximal clinical doses of atracurium during anaesthesia in man and to determine if central nervous system (CNS) stimulation can be detected under these conditions.

SUMMARY

Twenty patients were given maximal doses of atracurium or vecuronium by infusion during surgery. Anaesthesia was maintained with an infusion of thiopentone, nitrous oxide and fentanyl. In patients administered atracurium, the plasma laudanosine concentration at cessation of surgery was 0.34 (SD 0.22) μg ml⁻¹; there was little tendency to cumulate during operation. A 20% higher arterial concentration of thiopentone was found at awakening in patients given atracurium, suggesting CNS stimulation by laudanosine, although the effect is too modest to be of clinical significance.

PATIENTS AND METHODS

We studied 20 adult patients undergoing major orthopaedic or vascular surgery. The patients gave informed consent and the study was approved by the Board of Medical Research of The Royal Melbourne Hospital. The patients had no clinical or biochemical evidence of hepatic, renal or neurological disease. A standard anaesthetic technique was used. Each patient was premedicated 1 h before surgery with temazepam 5–10 mg by mouth. Anaesthesia was induced with thiopentone 3–5 mg kg⁻¹ and fentanyl 1–3 μg kg⁻¹ and maintained with a continuous infusion of thiopentone and 70% nitrous oxide in oxygen. Incremental doses of fentanyl, to a maximum dose of 0.5 μg kg⁻¹ h⁻¹, were administered as necessary by the responsible anaesthetist, but none was
administered in the 30 min before the end of surgery. The infusion was designed to maintain a constant arterial plasma concentration of thiopentone 10 µg ml⁻¹ with a variable rate infusion profile based on the concept of Plasma Drug Efflux [8].

The 20 patients were allocated to pairs according to the neuromuscular blocking drug used. The patients were matched according to sex, age and expected duration of the surgical procedure, with the initial patient of each pair allocated randomly to receive either atracurium or vecuronium. Muscle paralysis was monitored following stimulation of the ulnar nerve at the wrist via cutaneous electrodes with a peripheral nerve stimulator (Bard Biomedical Peripheral Nerve Stimulator model 750 digital, Billerica, Ma, U.S.A.) with manual evaluation of the response of adductor pollicis. An initial bolus dose of either atracurium 0.5 mg kg⁻¹ or vecuronium 0.1 mg kg⁻¹ was administered to facilitate tracheal intubation, and intense muscle paralysis was maintained with a variable rate infusion adjusted to maintain a post-tetanic count of 1–3 (the number of responses to 1 Hz stimulation 3 s after a 50-Hz tetanus for 5 s) [9].

Controlled ventilation was adjusted to maintain normal blood-gas tensions and acid-base status. Nasopharyngeal temperature was maintained greater than 35 °C.

The infusion of neuromuscular blocking drug was stopped 10–15 min before the anticipated cessation of surgery. The residual neuromuscular block was antagonized with neostigmine 0.035 mg kg⁻¹ and atropine 0.015 mg kg⁻¹ when there were two or more responses to train-of-four (TOF) stimulation. On completion of surgery and when there was no fade to TOF stimulation, the thiopentone infusion was stopped and the patient's lungs ventilated with 100% oxygen. Each patient was asked by name at 30-s intervals to open the eyes. A response was taken as positive when the patient opened the eyes 2 mm or more. The trachea was then extubated and the patient transferred to the recovery room.

Arterial blood samples were taken for drug analysis from a radial artery cannula at cessation of the thiopentone infusion, when the patient opened eyes to command, and in the recovery room. The samples were immediately acidified to prevent continued breakdown of atracurium to laudanosine, centrifuged and the plasma frozen for later analysis. In five patients who received atracurium, arterial blood samples were taken every 30 min during the procedure to determine the intraoperative time course of plasma laudanosine concentration.

The total plasma concentrations of thiopentone and of laudanosine were measured by high pressure liquid chromatography. A reverse-phase system was used for thiopentone, with a 10-µm octadecylsilane column and mobile phase of 52% methanol, 43.5% water and 4.5% isopropanol at pH 3.5 [8]. This assay was sensitive to a thiopentone concentration of 20 ng ml⁻¹ with a co-efficient of variation of 1% at 12 µg ml⁻¹. A 5-µm silica column was used for laudanosine, with a mobile phase of 50% acetonitrile in sulphuric acid 0.0001 mol litre⁻¹, with the assay sensitive to a laudanosine concentration of 20 ng ml⁻¹ and a co-efficient of variation of 2.8% at 5 µg ml⁻¹.

All patients were interviewed after operation. They were asked specifically for the last thing remembered before going to sleep, the first thing remembered on awakening and recall of anything during the procedure, including dreams.

The results are presented as mean values (SD). Comparison between means was performed using Student's t test for unpaired samples. Linear regression and correlation were calculated by the least square method, and assessed by analysis of variance. A probability level of P < 0.05 was considered significant.

RESULTS

The groups administered atracurium or vecuronium were similar with regard to patient parameters, anaesthetic drug dose, and arterial thiopentone concentrations at cessation of the infusion (t test, ns) (table I). The mean dose of vecuronium was 0.17 (0.02) mg kg⁻¹ h⁻¹ and atracurium 0.70 (0.04) mg kg⁻¹ h⁻¹.

<table>
<thead>
<tr>
<th>Patient details and anaesthetic drug doses (mean (SD))</th>
<th>Vecuronium group</th>
<th>Atracurium group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>64 (16)</td>
<td>62 (18)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65 (12)</td>
<td>69 (8)</td>
</tr>
<tr>
<td>Thiopentone dose (mg kg⁻¹)</td>
<td>17.5 (3.5)</td>
<td>20.1 (4.8)</td>
</tr>
<tr>
<td>Thiopentone concentration end infusion (µg ml⁻¹)</td>
<td>7.23 (2.02)</td>
<td>8.28 (1.70)</td>
</tr>
<tr>
<td>Fentanyl dose (µg kg⁻¹)</td>
<td>3.32 (0.77)</td>
<td>2.78 (1.21)</td>
</tr>
<tr>
<td>Duration of infusion (min)</td>
<td>163 (41)</td>
<td>189 (63)</td>
</tr>
</tbody>
</table>
The arterial plasma concentration of laudanosine during and following infusion of atracurium in five patients is illustrated in figure 1. At cessation of surgery, the arterial plasma concentration of laudanosine was 0.34 (0.22) µg ml⁻¹ (range 0.07–0.81 µg ml⁻¹) in the 10 patients who received atracurium. This concentration was related significantly to the total dose and mean infusion rate of atracurium (fig. 2). Normalization of the dose and infusion rate to the patient’s weight abolished the relationship.

The time from cessation of the thiopentone infusion until patients opened their eyes 2 mm or more on command was similar for patients administered atracurium and vecuronium (9 (7) min v. 10 (7) min, ns). However, patients administered atracurium had a 20% higher mean arterial concentration of thiopentone (6.12 (1.16) µg ml⁻¹ v. 5.12 (1.20) µg ml⁻¹; t test, P < 0.05) at awakening (fig. 3).

Postoperative interviews elicited no evidence of awareness or dreams in any patient. No significant correlation was found between the total dose of thiopentone and the plasma concentration of thiopentone when patients opened eyes on command (vecuronium group r = 0.01, atracurium group r = 0.49; n = 10, ns), or between the arterial plasma concentration of laudanosine and the plasma concentration of thiopentone when patients opened eyes to command (r = −0.53, n = 10, ns).
DISCUSSION

The post-tetanic count allows assessment of profound peripheral muscle paralysis [7]. Such paralysis may be required occasionally during surgery because of the varying sensitivity of different muscle groups to neuromuscular blocking drugs. The diaphragm may not be paralysed at a time of apparent total paralysis of the peripheral muscles [10]. The maintenance of a post-tetanic count of 1–3 during surgery required a mean infusion rate of atracurium 0.7 mg kg\(^{-1}\) h\(^{-1}\) and should represent the maximal clinical infusion rate for atracurium. This infusion rate compares with a previously reported infusion rate of atracurium 0.4 mg kg\(^{-1}\) h\(^{-1}\) to achieve neuromuscular blockade during intra-abdominal surgery [11].

The plasma laudanosine concentrations following infusion of atracurium in this study were highly variable for 105–303 min, but similar to the peak values reported following single bolus doses of atracurium [12]. This is in contrast to prolonged infusions of atracurium in intensive care patients in whom peak concentrations of laudanosine as great as 5.1 μg ml\(^{-1}\) have been reported [13]. The infusion of atracurium during surgery did not appear to result in a tendency for the plasma concentration of laudanosine to increase, in contrast to pharmacokinetic predictions based on single bolus dose data. A steady state plasma concentration of laudanosine 1 μg ml\(^{-1}\) would be expected to be produced by an atracurium infusion of 0.6 mg kg\(^{-1}\) h\(^{-1}\) [1]. The failure of the plasma laudanosine concentration to increase early in the infusion may result from continuing distribution of laudanosine to fat and other tissues, as laudanosine is a highly lipophilic tertiary amine with a large volume of distribution [14].

The higher arterial plasma concentration of thiopentone at awakening in patients who received atracurium suggests that laudanosine, in concentrations that occur in surgical patients, may have a small but detectable CNS stimulatory effect. The intensity of effect corresponds to the 20–30% increase in the MAC of halothane found in rabbits with similar plasma concentrations of laudanosine [7]. Using opening of eyes on command as a criterion, awakening from anaesthesia has previously been found to occur at a relatively constant alveolar concentration for several of the volatile anaesthetic agents [15] and of thiopentone following infusion anaesthesia [16]. Eye opening on command may be considered an all-or-none response and does not require a blind observer for accurate assessment. Pain resulting from the surgery does not appear to be an important stimulus for awakening in the period immediately after operation [15]. Residual effects of nitrous oxide are unlikely to have influenced the observation in this study, as the time from discontinuation to responding was similar in the two groups.

The clinical significance of the stimulatory effect of laudanosine is difficult to determine as it was only modest, such that the mean concentration of thiopentone at awakening of patients who received atracurium was still within 1 SD of that of control patients who received vecuronium. The stimulant effect of laudanosine would be expected to hasten recovery from anaesthesia in patients administered atracurium and to cause these patients to be more alert in the immediate postoperative period. However, in this study there was no difference in the time to recovery from anaesthesia, although this may have been masked by the slightly greater plasma concentration of thiopentone at cessation of surgery in the atracurium group.

Although the vecuronium group received a greater (but not significantly so) mean dose of fentanyl than the atracurium group, the dose regimen of fentanyl was restricted to very small amounts in all patients, to ensure low plasma concentrations in all patients at awakening. Fentanyl has a shallow dose–response curve [17], so small variations in individual doses should not have a significant effect on the thiopentone concentration at which patients awaken.

Acute tolerance to thiopentone was not observed in this study. This is in agreement with a previous infusion study of thiopentone [12] and the consistent EEG changes with three successive short term infusions of thiopentone [18]. Venous sampling following a single dose is the probable reason for the suggestion in previous studies that acute tolerance to thiopentone occurs in man [19]. Because of the longer sleeping time, a larger dose of thiopentone has longer to diffuse into muscle and fat, allowing a higher venous concentration at awakening as the concentration gradient between arterial blood and tissues decreases, with less extraction of thiopentone at awakening than for a smaller dose [20].
The lack of relationship between the arterial concentration of laudanosine and the thiopentone concentration at awakening suggests that there may be a ceiling effect to the stimulatory effects of laudanosine. Shi and colleagues have suggested previously [7] that there may be a ceiling effect to the increase in the MAC of halothane produced by laudanosine in rabbits.

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REFERENCES