CEREBROSPINAL FLUID CONCENTRATIONS OF LAUDANOSINE AFTER ADMINISTRATION OF ATRACURIUM

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SUMMARY

The concentration of laudanosine in cerebrospinal fluid (CSF) was measured in four patients undergoing brain electrode placement after the administration of atracurium. CSF: plasma laudanosine concentration ratios ranged from < 1 to 14%, with a range of CSF laudanosine concentrations of < 2-14 ng ml⁻¹. One patient had no detectable laudanosine in CSF, but sampling in this patient was possible for only 30 min. There was no atracurium detectable in the CSF of any patient. We conclude that laudanosine crosses the blood–brain barrier and further study of its central nervous system effects in man is warranted.

KEY WORDS


Laudanosine, a metabolite of atracurium, can produce central nervous system (CNS) stimulation in animals, ranging from increases in anaesthetic requirement in rabbits [1] to seizure activity in dogs [2]. Measurements of the ability of laudanosine to penetrate the blood–brain barrier in dogs which developed seizures have shown CSF:plasma laudanosine concentration ratios of 40–60% [2]. In order to determine the relevance to humans, we determined the ratios in patients given atracurium.

METHODS AND RESULTS

Four patients gave their informed consent to a procedure approved by the University of California Committee on Human Research. All patients had chronic pain syndromes that had been relieved after placement of deep brain electrodes and an Ommaya reservoir which communicated with the cerebral ventricular system. The patients were to undergo surgical implantation of a stimulator. Premedication consisted of diazepam 10 mg orally and morphine sulphate 10 mg i.m. Anaesthesia was induced with thiopentone 1–2 mg kg⁻¹ and halothane and nitrous oxide in oxygen via a mask. Tracheal intubation was performed without the use of neuromuscular blockers. Ventilation was controlled to maintain arterial carbon dioxide tension between 3.7 and 4.3 kPa and temperature was kept at 35–37.0 °C by surface warming. Anaesthesia was maintained with 0.6% end-tidal halothane and 60% nitrous oxide in oxygen, as measured continuously by mass spectrometry.

Following tracheal intubation, atracurium was administered as an i.v. bolus of 0.5 mg kg⁻¹. Simultaneous blood and CSF samples were obtained before and 15, 30, 45 and 60 min after administration of atracurium. Samples were heparinized immediately, acidified and separated. Plasma and CSF samples were stored at −30 °C until analysis.

Atracurium and laudanosine were assayed as described previously [2]. The results showed that CSF:plasma laudanosine concentration ratios ranged from < 1 to 14%, with a range of CSF laudanosine concentrations of < 2-14 ng ml⁻¹ (table I). In patients Nos 1 and 3, sampling of blood and CSF could...
not be completed because of short operative times. In patient No. 1, no CSF laudanosine could be measured. No CSF samples contained atracurium.

**COMMENT**

This study confirms that laudanosine can penetrate the blood–brain barrier in man after i.v. administration of atracurium. It is not complete penetrance (CSF:plasma ratios of 14% or less), but it is greater than that observed with more water-soluble drugs. For example, Shapiro, Young and Mehta [3] measured CSF:plasma concentration ratios of methotrexate not exceeding 0.06% after a 50-mg i.v. bolus. The greater penetrance of laudanosine is probably a result of its greater lipid solubility.

The results of our study agree with those of Harris and his colleagues [4] who measured CSF laudanosine concentrations in children aged 7 months to 15 yr receiving atracurium for revision of ventricular–peritoneal shunt. At 15, 30 and 60 min after atracurium 0.5 mg kg\(^{-1}\) i.v., they found CSF laudanosine concentrations (SD) of 2.7 (6.5), 5.0 (8.2) and 5.0 (11.2) ng ml\(^{-1}\), respectively. In our study, the corresponding laudanosine concentrations (SD) were 5 (1), 6 (2) and 12 (2) ng ml\(^{-1}\). Harris and colleagues could not accurately determine CSF:plasma laudanosine ratios because of errors in processing the blood samples for analysis of laudanosine. Thus laudanosine shows a similar degree of blood–brain barrier penetration in adults and children.

It is possible that the laudanosine found in the CNS may have originated from breakdown of atracurium in CSF. Matteo and colleagues [5] were able to detect tubocurarine in lumbar CSF after i.v. administration, but the patients had altered CNS physiology. In our study and that of Harris and colleagues [4], no atracurium could be detected in CSF samples. Other studies have shown no penetrance into the CNS of vecuronium and pancuronium [6]. It would appear unlikely, therefore, that atracurium penetrates the CNS and contributes to the presence of laudanosine.

Our results suggest that laudanosine has less ability to penetrate the blood–brain barrier of man compared with dogs [2]. This difference may be a result of the large dose of laudanosine (1.0 mg kg\(^{-1}\)) given to these animals. It would appear unlikely that the laudanosine produced from routine operative use of atracurium results in a sufficiently high concentration to produce CNS effects. However, because of its greater penetrance of the blood–brain barrier than water-soluble drugs, it cannot be assumed that the same is true if atracurium is given by repeated bolus or prolonged infusion.

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**REFERENCES**