

Title: PHARMACOLOGY OF LAUDANOSINE IN DOGS

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Introduction. Atracurium, a recently approved nondepolarizing neuromuscular blocking drug, is metabolized primarily to laudanosine via Hofmann elimination.(1) Recently, Fahey *et al.*(2) found that significant amounts of laudanosine were detected in the plasma following a single 0.5 mg/kg dose of atracurium in man. Studies performed many years ago indicated that laudanosine may cause convulsions in animals.(3,4) We, therefore, determined the pharmacokinetics, including transfer into the cerebrospinal fluid (CSF), and the cardiovascular and convulsant effects of laudanosine in anesthetized dogs.

Methods. Mongrel dogs (n=7) were anesthetized with thiopental (10-15 mg/kg iv), their tracheae intubated and ventilation controlled. Anesthesia was maintained with 0.6 to 0.8% end-tidal halothane in oxygen. P_{CO}₂ was maintained between 30 and 40 mm Hg; temperature at 36.5 to 37.0°C with surface warming. Metal screws were positioned in the skull and connected to a Grass EEG pre-amplifier so that a single lead fronto-occipital EEG tracing was obtained. A femoral artery was cannulated for measurement of blood pressure (BP) and sampling of blood. Catheters were placed in a femoral vein, the cisterna magna, urinary bladder, and common bile duct for injection of laudanosine, sampling of CSF and sampling of urine and bile, respectively. In the first part of the study, an iv bolus of laudanosine, 1 mg/kg, was injected, and arterial blood, CSF, urine and bile were collected repetitively for 6 h. Laudanosine was quantified using a modified liquid chromatographic technique.(5) A three-compartment pharmacokinetic model was fitted to the plasma concentration data using standard formulas. After sampling was completed, repetitive doses of laudanosine (1-2 mg/kg) were injected every 5 min until grand mal seizures developed. EEG, heart rate (HR), and BP were monitored throughout. Once seizures developed, a muscle relaxant was injected to eliminate electromyographic artifacts in the EEG recording, and thiopental iv was used to control seizure activity.

Results. The pharmacokinetic variables of laudanosine are shown in Table 1. Laudanosine concentrations in CSF were maximal at 3-10 min after injection, and ranged from 210 to 640 ng/ml; corresponding plasma concentrations ranged from 500 to 1050 ng/ml (CSF/plasma ratio: 0.3-0.6). Although 0.5-12% of the injected dose of laudanosine was recovered unchanged from urine, none was recovered from bile. The remaining laudanosine was recovered in the urine and bile in the form of more polar glucuronide metabolites, which will be described. In two of seven dogs, we observed signs of awakening within 2-10 min after injection of laudanosine, 1 mg/kg. HR and BP were not changed. With repetitive doses of laudanosine, we found an increasing

frequency of signs of awakening, until, at 13-22 mg/kg cumulative dose, grand mal seizures developed. Systolic and diastolic BP decreased transiently 40 to 60% after doses of 2-7 mg/kg of laudanosine, while HR was not changed. 11

Discussion. This study reconfirms the investigations of previous authors and documents the transfer into CSF of laudanosine. Though the elimination half-life of atracurium in the dog was not determined in this study, it is likely that the elimination half-life of laudanosine at 112 min is considerably longer than that for atracurium. The use of atracurium in repeated doses or by infusion could lead to levels of laudanosine in man which could have central nervous system effects. This study suggests that further human studies are needed to allay the clinical concerns that this study generates.

References.

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Table 1: Pharmacokinetic Variables for Laudanosine *

| $t_{1/2} \pi$ (min) | $t_{1/2} \alpha$ (min) | $t_{1/2} \beta$ (min) | V_1 (L/kg) | $V_{d_{ss}}$ (L/kg) | Clearance (ml·kg ⁻¹ ·min ⁻¹) |
|------------------------|---------------------------|--------------------------|-----------------|------------------------|--|
| 0.8 | 15 | 112 | 0.20 | 2.7 | 24.5 |
| ±0.2 | ±2 | ±25 | ±0.07 | ±0.9 | ±8.3 |

* = values are mean ± SD