Title : PLASMA LEVELS OF LAUDANOSINE, BUT NOT OF ATRACURIUM, ARE INCREASED DURING THE ANHEPATIC PHASE OF ORTHOTOPIC LIVER TRANSPLANTATION IN PIGS

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Introduction: The effects of impaired hepatic function on the metabolism of atracurium is not entirely clear since contradictory results have been reported in the literature (1-3). Laudanosine, a major metabolite of atracurium is metabolized by the liver and excreted by the kidney (4). At high plasma levels, it has been shown to induce vagal block, tachycardia, and seizure-like activity (5). Laudanosine plasma levels achieved during impaired renal function are well below those associated with adverse central nervous system effects (6). Whether laudanosine plasma levels reach toxic values in patients with hepatic failure is not clear. The purpose of the present study was to quantify the changes in plasma concentration of atracurium and laudanosine induced by the lack of hepatic function during orthotopic liver transplantation in pigs.

Materials and Methods: Nine pigs (suus scrofa domesticus), weighing 22 to 25 kg, were premedicated with azaperon 4 mg/kg, ketamine 7.5 mg/kg and fentanyl 2 ug/kg i.m. and anesthetized with isoflurane 2-3%. The trachea was intubated without the use of a muscle relaxant and anesthesia was maintained with isoflurane (0.5% in oxygen) and fentanyl (2 ug/kg/hr). Ventilation was controlled to keep end-tidal PCO_2 at 30-40 mm Hg and body temperature was maintained at 35-37°C with thermoblankets. Normal saline was infused intravenously through the jugular vein at 6 ml/kg/hr. Mean systemic arterial pressure and central venous pressure were measured using a carotid arterial cannula and a central venous catheter, respectively, connected to calibrated quartz pressure tranducers (1290A HP), positioned at the mid-axillary line, and recorded on a chart recorder (78172A HP). During the whole investigation, arterial pH was maintained within the range of 7.35-7.45 with a $NaHCO_3$ infusion. The sciatic nerve was surgically prepared, isolated, and directly stimulated with a nerve stimulator Laubscher P1 NS-2B delivering a single twitch at 0.1 Hz with 0.2 msec duration, at supramaximal stimulation. The corresponding evoked muscle contraction was continuously recorded by a Grass FT-10 force-displacement transducer on a one-channel recorder. After a stable anesthetic level was established, a single i.v. bolus injection of atracurium (2 mg/kg) was given to obtain a 90% twitch depression, followed five minutes later by a constant rate intravenous infusion of atracurium at 120 ug/kg/min during the whole investigation. In preliminary studies, we found that this dosage resulted in a stable > 90% twitch depression. Blood samples for atracurium and laudanosine levels were drawn every 15 minutes, from 30 minutes after the beginning of atracurium infusion until the end of operation. Immediately following centrifugation, the plasma was separated, acidified and stored at -20°C within 30 seconds. Samples were analyzed with a HPLC assay (detection limits, 10 ng/ml for both substances) according to Simmonds (7). Mean ± SE values of data at the different time intervals were calculated. Statistical comparison over time was conducted by a one-way analysis of variance followed by a Duncan's test, taking a P value of < 0.05 as statistically significant.

Results: Figure 1 shows plasma levels of atracurium and laudanosine during the different periods of liver transplantation. Plasma levels of atracurium remained unchanged during the whole investigation, with and without hepatic circulation and function. In contrast, plasma levels of laudanosine significantly increased during the cross-clamping of liver vessels and remained at elevated levels after restoration of circulation to the transplanted liver. Temperature and mean systemic arterial pressure remained within 20% of baseline values during the whole transplantation. Arterial pH decreased significantly during the liver clamping period (from 7.46 ± 0.01 to 7.36 ± 0.01) and heart rate increased significantly after cross-clamping of the liver vessels (from 131 ± 7 to 165 ± 5 beats/min).

Discussion: The results of this study demonstrate that plasma levels of atracurium are not influenced by the lack of hepatic function during orthotopic liver transplantation in pigs, indicating that hepatic excretion and retention do not play an important role in the plasma clearance of atracurium. However, plasma laudanosine levels increased more than 2-fold after cross-clamping of the portal vein, indicating that toxic levels of laudanosine could possibly be achieved with the application of long-term atracurium infusions in patients with severe hepatic or multiorgan failure.

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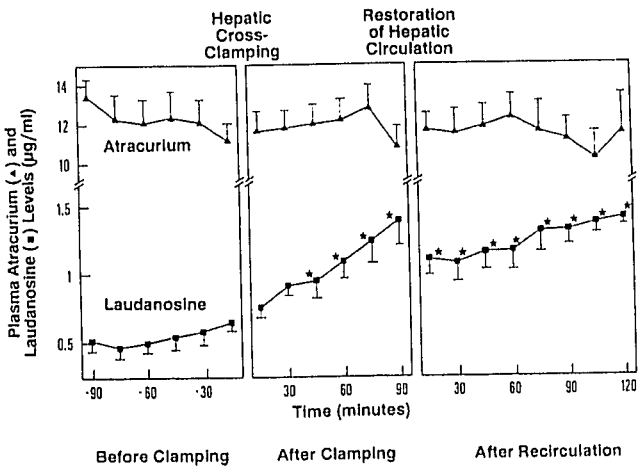

FIGURE 1: Plasma atracurium and laudanosine levels during the three periods of liver transplantation
* $P<0.05$ different from -15 min data point; $\bar{x}$ ± SE, n = 9