Title : ELEVATED PLASMA LEVELS OF LAUDANOSINE ARE ASSOCIATED WITH HIGH PLASMA CONCENTRATIONS OF NOREPINEPHRINE DURING ORTHOTOPIC LIVER TRANSPLANTATION IN PIGS

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Introduction: Laudanosine, a main metabolite of atracurium, is metabolized by the liver and excreted by the kidneys (1). Recent *in vitro* studies reported that laudanosine releases norepinephrine from guinea pig atrial tissues (2). In a previous study, we observed that plasma levels of laudanosine were significantly increased using a continuous infusion of atracurium during the anhepatic phase of liver transplantation in pigs (3). The purpose of the present study was to determine plasma levels of catecholamines during orthotopic liver transplantation in pigs and to evaluate their relationship to the increased levels of laudanosine measured in this situation.

Materials and Methods: Sixteen 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 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; body temperature was maintained at 35-37°C with thermoblankets. Arterial pH was maintained within the range of 7.30-7.45 with a $NaHCO_3$ infusion. The sciatic nerve was surgically prepared, isolated, and directly stimulated with a nerve stimulator Laubscher PI 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. Two groups of pigs subjected to an identical orthotopic liver transplantation protocol were investigated. In group I (n=8), the pigs were paralyzed with atracurium. In group II (control group, n=8), pipecuronium was used as muscle relaxant, a drug which has been shown to be devoid of significant cardiovascular effects (4). In group I, after a stable anesthetic level was established, a single i.v. bolus of atracurium (2 mg/kg) was given to obtain a 90% twitch depression. Five minutes later, a constant rate intravenous infusion of atracurium at 120 ug/kg/min was started to maintain surgical muscle relaxation during the whole operation. Blood samples for the determination of atracurium and laudanosine levels were drawn each 15 minutes, from 30 minutes following the start of atracurium infusion until the end of operation. Immediately following centrifugation of blood samples, 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 subtances) according to Simmonds (5). In group II, 50 ug/kg cumulative i.v. doses of pipecuronium were given during the first ten minutes until a 90% twitch depression was obtained, followed five minutes later by a constant rate intravenous infusion of pipecuronium at 8 ug/kg/min to maintain surgical muscle relaxation. Blood samples for plasma catecholamines determination were drawn every 60 minutes from the start of surgery. After centrifugation, plasma was separated on activated aluminium oxide. Epinephrine and norepinephrine were eluted by 0.1M perchloric acid, analyzed by a reverse phase HPLC and measured by amperometric detection. Mean ± SE values of data at the different time intervals were calculated. Statistical comparison over time was conducted within each group by a one-way analysis of variance, followed by a Duncan's test, and between both groups, by an unpaired Student's t-test, taking a P value of < 0.05 as statistically significant.

Results: Data of this study are summarized in Table 1. In the atracurium group (group I), norepinephrine plasma levels were significantly increased after the crossclamping of liver vessels. The increase of norepinephrine levels significantly correlated with simultaneous increases in laudanosine plasma concentrations ($r = 0.67$, $P < 0.001$, Fig. 1). In contrast, in the pipecuronium group (group II), plasma catecholamine levels were significantly lower than those in group I during each of the operating periods, and did not significantly increase over time. In addition, heart rate increased significantly after crossclamping in group I (from 131 ± 7 to 165 ± 5 beats/min), but not in group II (from 124 ± 5 to 125 ± 6 beats/min). Temperature and mean systemic arterial pressure remained within 20% of baseline values, fluid and blood requirements were similar in both groups, and arterial pH was maintained within the range of 7.30-7.45 during the whole study.

Discussion: The results of this study demonstrate that using an identical anesthetic technique, muscle relaxation with atracurium, but not with pipecuronium, induces a more than 2-fold increase in plasma norepinephrine levels during the anhepatic period of liver transplantation. Furthermore, the use of atracurium, but not of pipecuronium, is associated with significant tachycardia during this period. A close correlation between increases of plasma norepinephrine and laudanosine levels was observed, confirming the *in vitro* observation that laudanosine increases the release of norepinephrine (2). Our data suggest that the clinical use of atracurium may be limited by the norepinephrine release caused by elevated laudanosine levels that may occur in patients with severe hepatic or multiorgan failure.

References: 1. Ward S, et al. *Br J Anaesth* 58:6S-10S, 1986
2. Nagashima H, et al. *Anesthesiology* 65:A413, 1986
3. Pittet JF, et al. *Anesthesiology* (abstract submitted) 1988
4. Tassonyi E, et al. *Anesthesiology* 65:A284, 1986
5. Simmonds RJ *J Chromatography* 343:431-6, 1985

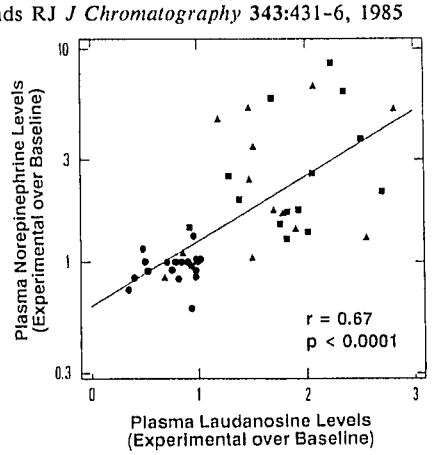

FIGURE 1: Correlation between individual changes of plasma norepinephrine and laudanosine levels measured before (●), during (▲) and after (■) crossclamping of liver vessels

Table 1: Plasma Levels of Epinephrine and Norepinephrine (nmol/ml)

	Epinephrine			Norepinephrine		
	Before Crossclamping	During Crossclamping	After Recirculation	Before Crossclamping	During Crossclamping	After Recirculation
Atracurium	4.4 ± 1.9	6.9 ± 1.4	7.5 ± 1.3	7.5 ± 1.0	16.0 ± 2.7*	18.0 ± 2.6*
Pipecuronium	3.5 ± 0.7	1.8 ± 0.5*	5.3 ± 1.1	3.9 ± 0.7	5.1 ± 2.3	9.1 ± 2.6
P†	NS	< 0.001	NS	0.01	0.001	0.001

Data are mean ± SE values of 1-3 catecholamine determinations from each of the 8 pigs
† statistical comparison between drugs
* $P < 0.05$ significantly different from before cross-clamping values