DRUG DISPOSITION I — MUSCLE RELAXANTS

A304

TITLE: **ATRACURIUM AND ITS METABOLITES IN THE ISOLATED PERFUSED RAT LIVER: BIOCHEMICAL AND MORPHOLOGICAL OBSERVATIONS.**

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INTRODUCTION: Due to its unique degradation pathway - by temperature and pH dependent Hofman decomposition and ester hydrolysis - the pharmacokinetics of atracurium are not altered by impaired hepatic function. For this reason, atracurium should be the ideal neuromuscular blocking agent for patients with hepatic failure (1) and is now widley used in clinical practice. In contrast, Nigrovic et al reported considerable hepatotoxicity, i.e. massive LDH leakage from isolated rat hepatocytes, of atracurium and especially of its breakdown products (2). So the purpose of this work was to study in an isolated perfused rat liver model the biochemical and morphological changes after application of either atracurium, laudanosine and atracurium preincubated in vitro for 120 min at 37 degree celsius to support the hypothesis that spontaneous degradation results in generation of hepatotoxic, reactive electrophilic esters.

MATERIALS AND METHODS: Livers were harvested from male Louvain rats (n=5 in each group). After anesthesia with thiopental sodium and cannulation of the portal vein and inferior vena cava, livers were excised and perfused via portal vein with oxygenated Krebs-Henseleit bicarbonate buffer (KHB) as described previously (3). After 20 min of normothermic perfusion for equilibration, 12.5 mg of atracurium, laudanosine or incubated atracurium (120 min at 37 degree celsius) per 10 g liver were applicated over 10 min, followed by KHB perfusion for additionally 60 min. Livers perfused for the same time with KHB only served as control. Aliquots of perfusate were collected at indicated times for enzyme (sGOT, LDH), lactate and electrolyte determination. At the end of perfusion, liver samples for light microscopy (HE, CAB, Goldner, PAS) and determination of hepatic high energy phosphates by HPLC were taken.

RESULTS: In comparison with control livers, no increase of either sGOT or LDH liberation into the perfusate was observed. Enzyme values remained constant within the whole test periode, ranging between 15-35 U/l (LDH) and 2-6 U/l (sGOT), respectively. Also lactate formation was comparable. Concerning potassium, a slight increase of perfusate potassium levels under laudanosine infusion and a decrease in the two other test groups were observed. Morphologically, all biopsis showed normal hepatic architecture, regular portal tracts with only minimal dilatation of sinusoides and central veins. Both, sinusoidal lining cells and hepatocytes could not be distinguished from controls. There was no evidence of increase in single cell necrosis or apoptosis. Concerning hepatic high energy phosphates, no difference in ATP values between the atracurium and the incubated atracurium group was seen in comparison with the control group. The highest ATP concentrations were observed in the laudanosine treated livers.

DISCUSSION: Although using extremly high concentrations of atracurium and laudanosine, we could not detect neither biochemically nor histologically any signs of liver cell damage in our isolated perfused rat liver model. Also, the application of incubated atracurium did not lead to any impairment of liver function. But work is in progress to investigate the effects of atracurium and its metabolites also in livers which were preserved in different protecting solutions prior to normothermic reperfusion to imitate liver transplantation conditions.

REFERENCES: 1. Ward S, et al. Br J Anaesth 55:1169-72, 1983
2. Nigrovic V, et al. Anesth Analg 65:1107-11, 1986
3. Reckendorfer H, et al. Transplant Proc (in press)

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TITLE: THE PHARMACOKINETICS OF TWO ISOMERS OF MIVACURIUM IN THE CAT

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INTRODUCTION: Mivacurium is a new short-acting non-depolarizing neuromuscular blocking (NMB) agent[1]. The trans-trans (T-T, 1309U83) and cis-trans (C-T, 1333U83) isomers comprise approximately 95% of the mivacurium formulation. The cis-cis (C-C, 1217U84) isomer accounts for 5% of mivacurium. Mivacurium undergoes rapid hydrolysis in cat and human plasma by pseudo-cholinesterase[2]. In vivo pharmacokinetic and pharmacodynamic profiles of the two potent isomers were individually determined to ascertain their relative contributions to the kinetic and dynamic profiles of mivacurium.

METHODS: Mongrel cats were anesthetized with chloralose (80mg/kg) and pentobarbital (10mg/kg) i.p. and mechanically ventilated. The twitch of the tibialis anterior was elicited at 0.15 Hz. A total of nine cats were randomly given 0.165 mg/kg ($4xED_{95}$) i.v. of either isomer and blood samples were taken at 13 time points between 0.5 and 11.5 minutes after the dose. Two groups of four cats each received continuous infusions of T-T or C-T to maintain 95-99% NMB. Blood samples were taken at 20, 40, and 60 minutes. Plasma levels were determined using HPLC with UV detection at 210 nm. Pharmacokinetic parameters were calculated using nonlinear regression analysis. Statistical analysis was performed using unpaired t-tests.

RESULTS: Results are summarized in Table 1. Both isomers have short distribution ($t_{\frac{1}{2}\alpha}$) and elimination ($t_{\frac{1}{2}\beta}$) half-lives, and small volumes of distribution (Vc). During continuous infusion, mean plasma levels of each isomer were not significantly different (T-T: 166 ± 21ng/ml vs. C-T 109 ± 19ng/ml; p value >0.05) and remained constant over 60 minutes. The results shown in Table 2 indicate that the NMB profiles are not significantly different.

CONCLUSION: The data show no significant differences in the pharmacokinetic or pharmacodynamic profiles of the two potent isomers of mivacuium. The short $t_{\frac{1}{2}\beta}$ is consistent with the short pharmacologic effect of these isomers. The short $t_{\frac{1}{2}\alpha}$ and small mean V_c are consistent with the polar quaternary structure which does not allow wide tissue distribution. Both the T-T and C-T isomers likely contribute equally to the brief kinetic and dynamic profiles of mivacurium.

REFERENCES: [1]Anesthesiology 68:723-732, 1988
[2]Anesth Analg 68:452-456, 1989

TABLE 1: Pharmacokinetic Parameters

Compound	n	$t_{\frac{1}{2}\alpha}$ (min)	$t_{\frac{1}{2}\beta}$ (min)	Vc (L/kg)	Vdss (L/Kg)	Cl (ml/min/kg)
1309U83	5	0.46	3.35	0.050	0.113	40.6
1333U83	4	0.40	3.05	0.061	0.140	65.0
p value		0.59	0.67	0.70	0.68	0.18

TABLE 2: Pharmacodynamics*

Compound	n	Onset (min)	100% Block (min)	Duration (min)**
1309U83	5	0.71 ± .05	10.4 ± 1.1	17.5 ± 1.0
1333U83	5	0.80 ± .04	9.5 ± 0.9	16.8 ± 0.6
p value		0.46	0.54	0.55

*Values = mean ± S.E. **Time from injection to 95% recovery.