Title: PHARMACOKINETICS OF ATRACURIUM AND METABOLITES IN NORMAL AND RENAL FAILURE PATIENTS

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Introduction: Atracurium, a non-depolarizing neuromuscular blocking agent of intermediate duration, decomposes spontaneously by Hofmann elimination and is hydrolyzed by non-specific esterases to form four metabolites, one of which, laudanosine, is known to act as CNS stimulant. In this study the pharmacokinetics and urinary excretion of atracurium, laudanosine and that of another metabolite, the quaternary alcohol, have been compared in normal and in renal failure patients (creatinine clearance <5 ml/min).

Methods: After giving informed consent, 23 adult patients participated in this study, which was approved by the local Medical Ethical Committee. Of these patients, 17 had normal renal function and 6 patients suffered from severe renal failure. Following premedication with diazepam 0.15 mg/kg orally, anesthesia was induced with thiopentone 4-6 mg/kg i.v. and fentanyl 5-7 µg/kg i.v. Anesthesia was maintained by ventilation with 40% oxygen in nitrous oxide, with 0.5-1.0% halothane in the gas mixture and incremental doses of fentanyl. Atracurium 500 µg/kg (2x ED90) was given by bolus injection to facilitate intubation. The ulnar nerve was stimulated at the wrist via surface electrodes with supramaximal, square wave impulses of 0.2 msec duration at a frequency of 0.1 Hz. The resultant contraction of the adductor pollicis muscle was measured by a Statham UC3 force-displacement transducer and continuously recorded. Before atracurium administration and up to 420 mins thereafter, blood samples were withdrawn from an antecubital vein, the plasma separated within 30 secs, acidified with sulphuric acid to a pH of 3.5 and immediately frozen to -20°C. From all patients with normal renal function total urine was collected in fractions up to 18 hrs after atracurium administration. Plasma and urine concentrations of atracurium, laudanosine and the quaternary alcohol were analyzed by HPLC. The plasma concentrations of the three compounds were fitted to equations with a varying number of exponential terms by means of an iterative linear least square regression analysing computer program. Differences between the results of both groups were determined by Students' t-test.

Results: The pharmacokinetic parameters of atracurium, laudanosine and the quaternary alcohol of both groups of patients are listed in Table 1. None of the parameters of atracurium differ significantly from each other. Only in patients with renal failure the plasma concentration of laudanosine suddenly increased, after an initial decrease, with a wide variation among the patients, approximating 20 mins after injection of atracurium and thereafter decreased. The terminal half-life of the quaternary alcohol and laudanosine differed significantly between the two groups. The total recovery of atracurium in the urine amounted to 32±15% of the administered dose. 11% was excreted in unchanged form and the rest mainly as the quaternary alcohol. In Table 2 the features of the neuromuscular blockade are listed: the onset (time from the end of injection to maximum effect), total duration (time from the end of injection to 90% return of control twitch height) and the recovery rate (time required for recovery of twitch height from 25 to 75% of control value). Total duration and recovery rate are significantly shortened in patients with renal failure.

Discussion: Renal failure causes no statistically significant differences of the kinetic parameters of atracurium. Similar observations were reported by Fahey et al. However, the significant increase of the terminal half-life of laudanosine and the quaternary alcohol as well as the increase of laudanosine plasma concentrations in patients with renal failure, indicates that the kidney plays an important role in the elimination of laudanosine and, to a lesser extend, of the quaternary alcohol. Due to the ten-fold difference in the elimination t 1/2 between atracurium and laudanosine, which is even greater in renal failure patients, cumulation of laudanosine will evidently occur after repeated bolus doses of atracurium or after administration of atracurium by long-lasting intravenous infusion. Consequently, the administration of atracurium by i.v. infusion should be discouraged, particularly in patients with impaired renal function. As total duration and recovery rate are significantly shortened, it would appear that there is a tendency towards resistance against atracurium in patients with renal failure.

Reference:
Fahey MR, Rupp SM, Fisher DM et al: The pharmacokinetics and pharmacodynamics of atracurium in patients with and without renal failure. Anesthesiology 61:699-702, 1984.

Table 1. Mean ± standard deviation.

ATRACURIUM		NORMAL	RENAL FAILURE	SIGNIF.
Cl	µg/l	3070±1453	4072±3280	n.s.
C2	µg/l	1540± 791	1531± 576	n.s.
t1	mins	2.5± 1.1	3.7± 1.7	n.s.
t2	mins	17.3± 3.8	19.7± 2.7	n.s.
Vl	ml/kg	129± 88	93± 55	n.s.
Vdss	ml/kg	280± 153	165± 69	n.s.
Cl	ml/kg/mins	10.8± 3.8	7.9± 2.2	n.s.
LAUDANOSINE				
t 1/2		176± 84	516± 262	p < .05
QUATERNARY ALCOHOL				
t 1/2		27.1± 8.3	42.5± 8.3	p < .05

Table 2. Mean ± standard deviation.

		NORMAL (n=9)	RENAL FAILURE (n=6)	SIGNIF.
Onset	mins	2.5±0.2	3.0± 0.6	n.s.
Duration	mins	64.1±7.2	51.8±11.5	p < .05
Recovery rate	mins	16.7±4.1	9.6± 2.0	p < .05