Title: PHARMACOKINETICS OF VECURONIUM IN MAN

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Introduction: Vecuronium (Org NC45) has a shorter time-course of action and less cumulative effects with repeat administrations as compared with its bisquarternary homologue, pancuronium.[1,2] The shorter duration of effect has been explained by a shorter elimination half-life;[3,4] however, such explanation has been inconclusive because the kinetic parameters were determined by a method limited by: (1) an insensitive assay, (2) mere application of a two-compartment mammillary model, and (3) lack of consideration of mode or rate of elimination of the compound from the body. We studied the kinetics and dynamics of vecuronium in a homogeneous group of subjects, utilizing a sensitive fluorimetric assay and defining an appropriate pharmacokinetic model. We also measured the urinary excretion rate of vecuronium and its metabolites.

Methods: Eleven adult patients (21-53 yrs, 61-90 kg, ASA Class I), with informed consent, were studied. Subjects were premedicated with Pantopon and atropine IM. Anesthesia was induced with thiopental IV and maintained with halothane 0.5% and N_2O 65% via non-rebreathing system, supplemented with IV fentanyl. Ventilation was controlled to maintain normocapnia. Neuromuscular blockade was monitored recording the thumb adductor twitch tension elicited by ulnar nerve stimulation at the rate of 0.1 Hz. Vecuronium 0.15 mg/kg was administered by 2 min infusion. Eight ml heparinized venous blood samples were drawn from 6 male subjects who underwent ear or nose surgery, at 1,3,5,7,10,15,20,30,45,60,90,120, 180,240 and 300 min after the end of the infusion, and immediately buffered to pH 6 in test tubes containing 2 ml of 1 N NaH_2PO_4. Additional multiple blood samples were taken during recovery from paralysis. Blood samples were centrifuged and the plasma samples were then frozen until analysis. Urine samples were collected from 5 female subjects who had urethral catheter for gynecological procedure, 1,2,3,4,6,8,12,16,20 and 24 hrs after the drug administration. Samples were checked for pH, buffered to pH 6 if needed, and frozen for later analysis. The assay was a fluorimetric, total determination of vecuronium and its hydrolyzed products followed by thin-layer chromatography to separate the metabolites and estimate their proportion. The sensitivity of the fluorimetric method was 5 ng/ml using 2 ml plasma sample and the precision was 3-10% coefficient of variation in the 5-1000 ng/ml range. Kinetic models consisting of up to 5 exponentials were fitted to the plasma concentration-time data by a computer program designed for iterative peeling, a least-square regression analysis on the log scale, and statistical comparisons of kinetic parameters.[5] The plasma concentration-effect relationship during the recovery from paralysis was examined by plotting the data on a Hill graph.

Results: A triexponential equation with the following parameter estimates appeared to fit appropriately the exprimental plasma concentration-time data.

	Mean	%CV		Mean	%CV
A ($\mu g\ ml^{-1}$)	1.64	55	α (min^{-1})	0.405	78
B	0.807	87	β	0.0545	31
C	0.0643	64	γ	0.00762	31

The half-lives for α, β and γ phases were respectively 1.71, 12.7 and 90.9 min, and these appeared to be not different from the values for pancuronium. The plasma clearance of 4.78 ml/kg/min appeared to be about 3 times that for pancuronium. None of the possible metabolites of vecuronium, 3-OH, 17-OH and 3,17-OH compounds, could be detected in plasma. Recovery of 10% neuromuscular activity was seen at 35.1±4.0 min (mean S.D.), and 50% at 45.5±5.8 min, and corresponding plasma concentrations (ED_{90} and ED_{50}) were 0.173 and 0.111 µg/ml. The recovery rate from 25 to 75% twitch tension was 12.6±2.7 min, and the rapid recovery course corresponded to the rapid decline of plasma concentration in the distribution phase. Vecuronium and its 3-OH metabolite were excreted in urine of 4 subjects at following rates:

	% of administered dose (mean S.D.)			
	1 hr	2 hrs	4 hrs	24 hrs
Vecuronium	2.1 ±1.7	10.6 ±3.8	14.1 ±6.8	18.4 ±4.5
3-OH	0.1 ±0.1	0.3 ±0.3	1.8 ±1.2	4.8 ±2.2

In one other subject, urinary excretion rate of vecuronium and its 3-OH metabolite was respectively 32 and 13.4% in 4 hrs and 35.7 and 17.5% in 24 hrs, which was considerably larger than above figures.

Discussion: The shorter time-course of vecuronium paralysis appears to be due to a high total plasma clearance which results in a very low concentration of C, the zero intercept of the terminal elimination phase. This high clearance occurs despite a low urinary excretion rate and is due to a large volume of distribution (3rd compartment) in organ tissues such as liver and a large biliary excretion. Bile samples taken from the common bile duct 60-120 min after administration of vecuronium 0.15 mg/kg in 9 patients undergoing cholecystectomy contained 20-80 µg/ml concentrations of vecuronium. Biliary excretion of 27-45% of the administered dose in 18 hrs was observed in 5 patients who had a T-tube choledochostomy, a major portion being excreted in 4-6 hrs.[6]

References:

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