Title : HEPATIC EXTRACTION AND CLEARANCE OF VECURONIUM IN HUMANS.

Authors : G. Goldfarb, M.D., P. Gauneau, M.D., E.T. Ang, M.D.
B. Lassale, M.D., P. Jolis, M.D.

Affiliation : Departement d'anesthesie-reanimation chirurgicale, hopital Beaujon, UER Xavier Bichat, université Paris 7, 92118 Clichy Cedex, France and departement d'anesthesie-reanimation chirurgicale, hopital Ambroise Pare, 92100 Boulogne, France

Though it is commonly thought that liver is the main route of elimination of vecuronium, hepatic elimination of this drug is not well-documented in man. In a recent study[1], vecuronium was found to appear early in bile of patients after a bolus injection; however, only 12,5% of the injected dose were recovered in bile and estimation of the hepatic storage of vecuronium was based upon liver biopsies dosages. The aim of the present study was to measure hepatic extraction and hepatic clearance of vecuronium in anesthetized patients.

Methods

After obtaining informed consent and approval by human studies committee, 6 adult patients (ASA I-II) with normal hepatic and renal function, aged (mean ± SEM) 34 ± 7 yrs and weighing 69 ± 4 kg were studied. All of them were scheduled for orthopedic surgical procedures presumed to be long lasting and hemorrhagic. After premedication with diazepam (10 mg PO), induction of anesthesia was done with thiopental and fentanyl. Tracheal intubation was performed after local anesthesia of the larynx with lidocaine. Anesthesia was maintained with a mixture of N_2O, 60% in oxygen delivered by controlled ventilation and increments of fentanyl. A catheter was advanced in an hepatic vein, via the internal jugular vein, under fluoroscopic visualization. After a bolus IV (100 $\mu g.kg^{-1}$), a continuous infusion of vecuronium was started (100 $\mu g.kg^{-1}.h^{-1}$) for one hour. Simultaneous hepatic and contrololateral arm venous samples were intermittently collected, immediately centrifugated and buffered. Hepatic blood flow (HBF) was measured by the indocyanine green clearance and extraction method. The plasma concentration of vecuronium was determined using a minor modification of the Rose Bengale fluorometric method for pancuronium assay[2]. Total plasma clearance (Cl_{tot}) of vecuronium was calculated as: Cl ($ml.min^{-1}$) = Delivery Rate / Peripheral plasma steady state concentration (Css_{per}). Hepatic extraction (HE) of vecuronium was calculated as: $1-Css_{hep}/Css_{per}$ (Css_{hep}: hepatic plasma steady state concentration). hepatic clearance (Cl_{hep}) of vecuronium was calculated as: HE x HBF. Force of thumb adduction elicited by supramaximal ulnar nerve stimulation at a frequency of 0.1 Hz, was recorded. During recovery of paralysis, the time elapsing during 25 and 75% of control twitch (T_{25-75}) was measured. Statistical analysis was done with ANOVA and correlation coefficient.

Results

100% suppression of the evoked twitch response was obtained in every patient after the bolus IV and maintained during the infusion time. A 40 min steady state period of peripheral and hepatic plasma concentrations of vecuronium was observed. Results are summarized in table 1. The HE of vecuronium was low and the hepatic clearance of vecuronium accounted only for 18 to 35% of Cl_{tot} in 4 out of the 6 patients. T_{25-75} and Cl_{hep} were not correlated.

Discussion

To the authors' knowledge, hepatic extraction and clearance of vecuronium has never been measured in man. The present study shows that vecuronium has a low hepatic extraction and has an elimination that does not depend on HBF. More surprising is the low hepatic clearance of vecuronium observed in 4 out of the 6 studied patients. This is in contradiction with both animal[3] and human studies[1]. Two hypothesis can be sustained: 1) The method used for the vecuronium dosage could be non-specific for the unchanged compound; thus the extraction and the hepatic clearance could be underestimated; 2) Alternatively, the liver could not be the major pathway of elimination. Further studies seem necessary to assess the validity of these assumptions.

References

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TABLE 1
Pharmacokinetics of vecuronium during the steady state period.

Patients N°	HBF (l/min)	Cssper (µg/ml)	Csshep (µg/ml)	Cltot (ml/min/kg)	HE %	Clhep (ml/min/kg)
1	0.940	0.407	0.344	4.10	11.5	2.52
2	0.996	0.494	0.470	3.37	4.9	0.59
3	1.090	0.362	0.273	4.60	24.6	4.12
4	0.942	0.582	0.548	2.86	5.8	0.92
5	1.070	0.503	0.404	3.31	19.7	1.15
6	0.994	0.353	0.312	4.72	11.6	1.53

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