Title: DOES THE INDEPENDENT MEASUREMENT OF 3-DESACETYLVECURONIUM INFLUENCE THE PHARMACOKINETICS OF VECURONIUM?

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Introduction. In studies of the pharmacokinetics of vecuronium, several analytical techniques have been used to determine plasma concentration of the drug. High performance liquid chromatography (HPLC)[1] and chemical ionization mass spectrometry (CIMS)[2] measure parent compound only. The fluorimetric technique measures a 'total' concentration which includes any deacetylated metabolites[3]; subsequent determination of these deacetylated compounds may be achieved by thin layer chromatography but this technique has insufficient sensitivity to measure the plasma concentration of these metabolites following normal clinical doses of vecuronium in humans.[4] We are interested in how the pharmacokinetic parameters may be influenced by whether or not the 3-desacetyl metabolite (3-desVEC) is included in the measurement of plasma vecuronium concentration. We have developed a gas chromatographic assay which permits the simultaneous and independent measurement of vecuronium and this metabolite. We have determined the pharmacokinetics of vecuronium with and without the inclusion of the metabolite and compared the resulting values in three patient groups; normal (i.e. with no significant disease), renal failure and severe hepatic dysfunction.

Methods. Following approval by our Committee for Human Research a total of 32 patients were studied. Anesthesia was induced with thiopental 2-6 $mg \cdot kg^{-1}$ i.v. and maintained with nitrous oxide 60% and isoflurane 0.9 -1.1% (end-tidal concentrations). End-tidal PCO_2 was maintained between 35 and 40 mm Hg, and esophageal temperature above 35.5° C. Heparinized blood samples were collected, prior to, and 2,4,6,8,10,15,20, 25, 30, 45, 60, 90, 120, 180, and 240 min following a bolus injection of vecuronium (100 $\mu g \cdot kg^{-1}$). Following separation and acidification of the plasma, concentrations of VEC and 3-desVEC were obtained by organic ion-pair extraction of the compounds and quantification via capillary gas chromatography with nitrogen sensitive detection. Plasma concentration *vs* time data for VEC alone and for VEC plus 3-desVEC (VEC_{tot}) were fit to a two compartment model by least-squares nonlinear regression. The following parameters were derived:-

Distribution half life - $t_{1/2}\alpha$ (min)
Elimination half life - $t_{1/2}\beta$ (min)
Volume of the central compartment - V_1 $(ml \cdot kg^{-1})$
Volume of distribution at steady state - Vd_{ss} $(ml \cdot kg^{-1})$
Plasma Clearance - Cl $(ml \cdot kg^{-1} \cdot min^{-1})$
Mean residence time -*MRT* (min)

The kinetic parameters derived using VEC or VEC_{tot} concentrations were compared within each group by paired t test. Comparisons between the groups were made by Student's t test for unpaired data. Differences were considered significant at $P < 0.05$.

Results. The results of the kinetic analysis and comparison are detailed in the table.

Discussion. We have demonstrated that the inclusion of the 3-desacetyl metabolite in the estimate of plasma vecuronium concentration will significantly alter the values derived for the pharmacokinetic parameters, within each patient group. This is a result primarily of a decreased terminal elimination slope and an increased area under the plasma concentration *vs* time curve. The putative 17-desacetyl and 3,17-*bis*desacetyl metabolites have not been detected in human plasma. We feel, therefore, that it is unlikely these metabolites would contribute significantly to the estimation of 'total' VEC. Our data provide a partial explanation for the different pharmacokinetic values for vecuronium reported by different investigators. It is important to note that when comparisons were made between the patient groups the same qualitative differences were found regardless of whether VEC or VEC_{tot} data were used. It appears, therefore, that the inclusion of the metabolite will significantly alter the absolute values of the derived kinetic parameters but will not affect the results of comparisons made between groups, under the conditions we describe.

Table. Kinetic parameters for vecuronium derived from plasma concentrations of parent drug alone (VEC) and parent plus the 3-desacetyl metabolite (VEC_{tot}). All results are mean ± standard deviation.

Group	Parameter	VEC	VEC_{tot}
Normal (n=10)	$t_{1/2}\alpha$	7.9 ± 2.4	7.7 ± 2.4
	$*t_{1/2}\beta$	55 ± 18	66 ± 23
	$*V_1$	92 ± 21	87 ± 20
	Vd_{ss}	200 ± 53	215 ± 56
	$*Cl$	5.0 ± 1.9	4.3 ± 1.9
	*MRT	45 ± 17	56 ± 21
Renal (n = 11)	$t_{1/2}\alpha$	11.9 ± 5.2	12.2 ± 5.0
	$*t_{1/2}\beta$	84 ± 26	148 ± 112
	$*V_1$	110 ± 36	107 ± 35
	$*Vd_{ss}$	236 ± 66	295 ± 126
	$*Cl$	2.9 ± 0.7	2.1 ± 0.6
	*MRT	84 ± 28	167 ± 147
Liver (n = 11)	$t_{1/2}\alpha$	7.2 ± 4.5	7.3 ± 3.8
	$*t_{1/2}\beta$	49 ± 16	70 ± 24
	V_1	94 ± 45	89 ± 39
	$*Vd_{ss}$	203 ± 79	232 ± 76
	$*Cl$	4.5 ± 1.6	3.6 ± 1.5
	*MRT	46 ± 17	71 ± 28

* $P < 0.05$ VEC *vs* VEC_{tot}

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