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Pharmacokinetics of vecuronium during acute isovolaemic haemodilution

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Summary

To evaluate the effect of acute isovolaemic haemodilution on the pharmacokinetics of vecuronium, we studied 13 patients undergoing haemodilution during surgery and 13 control patients. General anaesthesia was induced with thiopentone 4–6 mg kg^{-1} and fentanyl 2–4 μg kg^{-1}, and maintained with enflurane and 60% nitrous oxide in oxygen. The haemodilution patients underwent major elective plastic surgery with an anticipated surgical loss of more than 600 ml. Haemodilution was achieved by drainage of venous blood and i.v. infusion of lactated Ringer's solution and 6% dextran, during which the packed cell volume and haemoglobin concentration decreased from 45% to 28.1% and from 14.7 g dl^{-1} to 9.1 g dl^{-1}, respectively. After administration of a bolus of vecuronium 100 μg kg^{-1}, an improved fluorimetric assay was used to measure the plasma concentrations of vecuronium for 5 h. The results showed that the disposition kinetics of vecuronium were best described mathematically by a three-compartment open model in the two groups. The mean volume of the central compartment and volume of distribution at steady state were 42.3 (SD 11.8) ml kg^{-1} and 168.4 (31.5) ml kg^{-1}, respectively, in control patients, and significantly greater (55.2 (13.4) ml kg^{-1} and 225.9 (53.3) ml kg^{-1}) in the haemodilution patients ($P<0.05$). The elimination half-life was 50.3 (11.5) min in control patients and significantly greater (68.2 (15.1) min) in the haemodilution patients ($P<0.05$). The half-lives of fast distribution and distribution, mean residual time, area under the plasma concentration curve and plasma clearance were unchanged in patients who underwent haemodilution compared with the control group. (*Br. J. Anaesth*. 1997; **79**: 612–616).

Key words
Neuromuscular block, vecuronium. Pharmacokinetics, vecuronium. Blood, haemodilution.

Vecuronium is a non-depolarizing neuromuscular blocking agent with an intermediate clinical duration of action. In recent years, the possible factors influencing the pharmacokinetics of vecuronium, such as age,[1,2] hepatic[3] and renal[4,5] insufficiency, pregnancy[6] and hypothermia,[7] have been studied extensively. Preoperative isovolaemic haemodilution, which is an effective method of reducing homologous blood transfusion during surgery, is often associated with haemodynamic changes, changes in regional organ blood flow, blood chemistry, blood volume and body fluid distribution.[8–13] Previous studies have shown that the potencies of suxamethonium, pancuronium and tubocurarine are increased and the duration of action prolonged, after preoperative normovolaemic haemodilution.[14,15] However, there are no studies on the pharmacokinetics of vecuronium during acute isovolaemic haemodilution in adult patients. In this study, we have measured plasma concentrations of vecuronium using an improved fluorimetric technique and observed the effect of acute isovolaemic haemodilution on the pharmacokinetics of vecuronium.

Patients and methods

After obtaining informed consent and approval from the hospital's Ethics Committee, we studied 13 patients undergoing acute isovolaemic haemodilution during surgery and 13 patients not receiving haemodilution. All patients were ASA I, aged 18–39 yr and were undergoing elective plastic surgery. The haemodilution patients underwent major plastic surgery with an anticipated surgical loss of more than 600 ml. Three patients underwent breast reconstruction with a free flap, five patients received extensive head and face plastic surgery, four patients had an abdominoplasty and one patient a maxillectomy. Patients with cardiac and respiratory diseases were excluded. None suffered any disease or were receiving any drug known to alter neuromuscular function. Those with anaemia (haemoglobin concentration <12 g dl^{-1}) were also excluded.

Patients were premedicated with diazepam 0.2 mg

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kg^{-1} and atropine 0.01 mg kg^{-1} i.m., 1 h before anaesthesia. On arrival in the operating room, an i.v. catheter was inserted and general anaesthesia was induced with thiopentone 4–6 mg kg^{-1} and fentanyl 2–4 μg kg^{-1}. After topical anaesthesia with 2% lignocaine, the trachea was intubated without the aid of a neuromuscular blocking agent, and general anaesthesia was maintained with enflurane (1.5–2% expired concentration) and 60% nitrous oxide in oxygen. Fentanyl 2 μg kg^{-1} i.v. was supplemented as required. The lungs were ventilated ($V_T = 8$–10 ml kg^{-1}, $f = 8$–10 bpm) during surgery and $P_{E'CO_2}$ was maintained within normal limits.

After stable anaesthesia had been achieved in the haemodilution patients, 12–15 ml kg^{-1} of blood (approximately 20% of blood volume) were obtained from a cubital vein over a period of 15–20 min before the start of surgery and stored in a reservoir bag containing ACD solution. Simultaneously, a volume of Ringer's lactate solution, double or triple that of the withdrawn blood, and an equal volume of 6% medium molecular dextran (molecular weight 70 000 Da) were infused rapidly via a separate venous cannula. The packed cell volume (PCV) target after haemodilution was 25–30%. During surgery, blood loss was measured by swab and drape weighing and from suction bottles, and was replaced with Ringer's lactate solution and medium molecular dextran. Blood was reinfused only after major surgical loss was complete in the reverse order of collection through non-filtered infusion sets. Control patients only received Ringer's lactate solution 10–12 ml kg^{-1} h^{-1} during surgery. Haemodynamic variables remained stable throughout the study in all patients.

During surgery ECG, arterial pressure, heart rate, temperature and Sp_{O_2} were monitored continuously (Cardiocap, Datex Instrumentarium, Helsinki, Finland). Inspired and end-tidal concentrations of oxygen, carbon dioxide and nitrous oxide were measured and displayed digitally by an anaesthetic gas monitor (anaesthesia gas monitor type 1304, Bruel and Kjaer, Denmark). A cannula was placed in the radial or femoral artery for sampling. Arterial pH, Pa_{O_2}, Pa_{CO_2}, PCV and haemoglobin concentration were measured with a blood-gas electrolyte analyser (Model-5, Nova Biomedical Company, Hoboken, USA) before and during anaesthesia. Total plasma protein (TPP) and albumin (Alb) concentration were also measured using an automatic biochemical analyser (Type-550, Corning Medical Company, Oberlin, Ohio, USA). Body core temperature was maintained at 36–37 °C.

PLASMA SAMPLING

When anaesthesia was stable or haemodilution was complete, an i.v. bolus of vecuronium 100 μg kg^{-1} was administered. Blood samples (4 ml) were collected from an antecubital vein before and at 1, 3, 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240 and 300 min after administration of vecuronium. Each blood sample was centrifuged within 5 min, and 1 ml of plasma was acidified immediately by adding 150 μl of NaH_2PO_4 1 mol $litre^{-1}$ to prevent hydrolysis of vecuronium. Spontaneous hydrolysis of vecuronium in plasma occurs at body pH and room temperature at a rate of 0.35% when determined in our laboratory. The samples were then frozen at −20 °C until subsequent analysis. Plasma concentrations of vecuronium were measured by a modified fluorimetric assay described originally for pancuronium by Kersten, Meijer and Agoston.[16] The fluorescent intensity of the sample was measured by a spectrofluorophotometer (model RF450; Shimadzu Corporation, Japan). The lower limit of sensitivity of this technique was 5 ng ml^{-1} for vecuronium. The coefficients of variation at concentrations of 10 ($n = 8$), 250 ($n = 10$) and 1000 ng ml^{-1} ($n = 10$) were 9.7%, 4% and 0.5%, respectively, in our laboratory. None of the drugs used during anaesthesia interfered with assay of vecuronium.

PHARMACOKINETICS ANALYSIS

Individual data points from the time–plasma concentration curve of vecuronium were stored on a computer and analysed with a $3P_{87}$ program edited by the Chinese Association of Mathematical Pharmacology (Beijing, People's Republic of China). Plasma vecuronium concentration–time data were fitted to both two- and three-compartment mammillary pharmacokinetic models using non-linear, least-squares regression. Models were compared statistically using the F test to determine the simplest model which accounted for the data of each patient. In all patients, a three-compartment pharmacokinetic model was preferred statistically to a two-compartment model, using the technique of Boxenbaum, Riegelmann and Elashoff.[17] Therefore, the following variables were calculated using standard formulae from the $3P_{87}$ program: half-lives of rapid distribution ($T_{1/2}^{\pi}$), distribution ($T_{1/2}^{\alpha}$) and elimination ($T_{1/2}^{\beta}$), volume of the central compartment (V_c), volume of distribution at steady state (V^{ss}), area under the plasma concentration curve (AUC), mean residual time (MRT) and plasma clearance (Cl).

A POMS statistical software version 2.00 (Shanghai Scientific and Technical Publishers, Shanghai, People's Republic of China) was used for statistical analysis of the data. A chi-square test was used to compare sex distribution between the two groups. Other statistical analyses were made with the two-tailed non-parametric Mann–Whitney U test. $P < 0.05$ was considered significant.

Results

There was no statistically significant difference between the two groups in age, body weight, height, preoperative temperature or duration of operation. Compared with preoperative values, concentrations of haemoglobin, PCV, total plasma protein and albumin during surgery decreased significantly in patients who had haemodilution but remained stable in the control group (table 1). Changes in arterial pH, Pa_{O_2} and Pa_{CO_2} in all the patients remained within normal limits throughout the study.

Compared with controls, plasma concentrations

Table 1 Patient characteristics of those who underwent ($n=13$) or did not have ($n=13$) haemodilution before and during surgery. Hb = Haemoglobin; PCV = packed cell volume; TPP = total plasma protein; Alb = albumin. Data are mean (SD). $*P<0.05$, compared with preoperative data; $\dagger P<0.05$, compared with controls

	Control		Haemodilution	
	Before op.	During op.	Before op.	During op.
Sex (M/F)	6/7		7/6	
Age (yr)	22		24	
Weight (kg)	58.7 (10.2)		60.1 (11.4)	
Height (cm)	168.5 (6.1)		170.1 (5.9)	
Rectal temperature (°C)	36.5 (0.05)		36.6 (0.07)	
Duration of surgery (h)	5.2 (1.4)		4.9 (1.7)	
Hb (g dl^{-1})	14.8 (1.2)	14.5 (1.0)	14.7 (1.0)	9.1 (1.2)*†
PCV (%)	45.2 (5.2)	43.8 (6.3)	45.0 (3.8)	28.1 (5.9)*†
TPP (g $litre^{-1}$)	70.1 (6.8)	69.4 (5.5)	69.5 (4.9)	48.5 (8.9)*†
Alb (g $litre^{-1}$)	40.1 (3.2)	39.3 (5.5)	41.2 (5.1)	29.2 (4.7)*†

Table 2 Vecuronium pharmacokinetics in controls and haemodilution patients during surgery. $T_{1/2}^{\pi}$ = Half-life of fast distribution; $T_{1/2}^{\alpha}$ = distribution half-life; $T_{1/2}^{\beta}$ = elimination half-life; V_c = volume of the central compartment; V^{ss} = volume of distribution at steady state; AUC = area under the plasma concentration curve; MRT = mean residual time; *Cl* = plasma clearance (mean (SD)). $*P<0.05$ compared with controls

	Controls ($n=13$)	Haemodilution ($n=13$)
$T_{1/2}^{\pi}$ (min)	1.5 (0.58)	1.6 (0.9)
$T_{1/2}^{\alpha}$ (min)	12.1 (4.8)	14.1 (3.8)
$T_{1/2}^{\beta}$ (min)	50.3 (11.5)	68.2 (15.1)*
V_c (ml kg^{-1})	42.3 (11.8)	55.2 (13.4)*
V^{ss} (ml kg^{-1})	168.4 (31.5)	225.9 (53.3)*
AUC (μg ml min)	33.3 (8.4)	30.4 (8.9)
MRT (min)	56.8 (13.4)	63.4 (18.2)
Cl (ml kg^{-1} min^{-1})	3.1 (1.0)	3.7 (1.5)

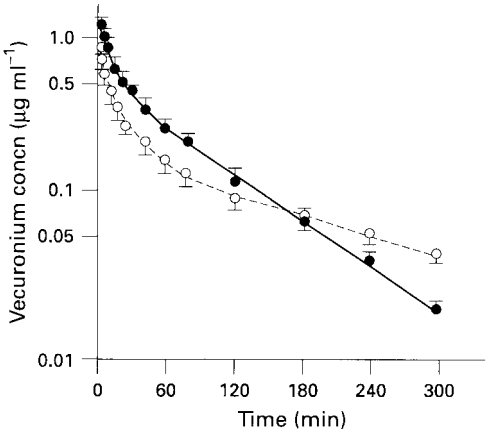

Figure 1 Plasma concentration–time curves for vecuronium in controls (●) and in patients who underwent acute isovolaemic haemodilution (○) after a single i.v. injection of vecuronium 100 μg kg^{-1} (mean, SEM).

of vecuronium in the haemodilution patients were lower during the initial 120 min after administration of the drug, but were higher from 120 to 300 min (fig. 1). Mean plasma concentrations of vecuronium were significantly different between the two groups at each time, except at 120, 180 and 240 min.

The concentration–time data for all patients were well described by a three-compartment open model. The pharmacokinetics of vecuronium for the two groups are summarized in table 2. In the haemodilution patients, V_c and V^{ss} were greater ($P<0.05$) and the elimination half-live ($T_{1/2}^{\beta}$) was longer ($P<0.05$) compared with controls. The half-lives of rapid distribution ($T_{1/2}^{\pi}$) and distribution ($T_{1/2}^{\alpha}$), AUC, MRT and *Cl* were not significantly different between the two groups.

Discussion

In this study, a classical fluorimetric assay was used to determine the plasma concentration of vecuronium: the lower limit of sensitivity of the method is 5 ng ml^{-1}, which is sufficient to detect vecuronium in plasma for up to 5 h after a bolus of 100 μg kg^{-1}. This fluorimetric assay had been used extensively to study the pharmacokinetics of vecuronium in children and adults,[14 18 19] but as it measures both vecuronium and its deacetylated metabolites, its lack of specificity could be criticized. In previous studies[14] thin layer chromatography was conducted after the assay to separate and estimate the proportion of metabolites. Even in adults with chronic renal failure,[4] none of the metabolites could be detected in plasma at any time. However, comparison between the fluorimetric and the more specific high-pressure liquid chromatography method (HPLC)[20] suggests that metabolites may account for 15% of the total plasma concentration of vecuronium over a range of 200–1000 ng ml^{-1}. But even if the presence of low concentrations of vecuronium metabolites slightly altered the pharmacokinetic data, there is no reason to suggest that such metabolites may be present in a greater proportion in haemodilution patients than in controls. Thus we believe that comparison of the pharmacokinetic data between the two groups is valid. Previous studies have suggested that the pharmacokinetics of vecuronium measured by fluorimetric assay were similar to those determined by HPLC or gas chromatography.[1 16] Furthermore, the pharmacokinetic data of vecuronium obtained in controls were within the range of those reported in previous studies.[5 6 18 19 21]

The most important difference between the control patients and those undergoing haemodilution was the greater volume of distribution of vecuronium in patients receiving haemodilution. Our data showed that in comparison with controls, the volume of the central compartment and volume of distribution of vecuronium at steady state in patients undergoing haemodilution increased by 33.4% and 25.5%, respectively. After administration

of vecuronium 100 μg kg^{-1}, mean plasma concentrations of vecuronium in controls were 1.78 μg ml^{-1} at 1 min and 1.05 μg ml^{-1} at 3 min respectively, which were significantly higher than those in the haemodilution patients (1.14 μg ml^{-1} and 0.89 μg ml^{-1}; $P<0.05$). Vecuronium is a water soluble non-depolarizing neuromuscular blocking agent. It distributes mainly in extracellular fluid after i.v. administration.[22] Possible explanations for our results include rapid infusion of large volumes of crystalloid and colloidal solutions markedly increasing blood volume.[8] Haemodilution also decreases blood viscosity, increases cardiac output and velocity of blood flow. Thus blood flow to vessel organs such as the liver, lungs, kidneys, heart and brain is increased, possibly increasing metabolism and excretion of drugs.[9–11] In addition, haemodilution decreases plasma colloid oncotic pressure because of a decrease in plasma protein concentration. A large quantity of infused crystalloid solution could therefore enlarge the extracellular fluid volume.[12]

Vecuronium is eliminated mainly by the liver, and to a lesser extent unchanged by the kidney.[4 18] In this study, plasma clearance of vecuronium in patients undergoing haemodilution increased by 16.2%. This may be a result of the increase in hepatic and renal blood flow during haemodilution.[10 13] In addition, decreased plasma protein concentration during haemodilution might increase the ratio of unbound to bound vecuronium in plasma. As only free drug is filtered at the glomerulus, renal elimination may be increased. However, the difference in plasma clearance between the two groups was not statistically significant, which might be related to the small sample size and large individual differences. Although the elimination half-life of a drug is inversely proportional to plasma clearance (which was increased in the haemodilution patients), the elimination half-life of vecuronium was markedly prolonged in the haemodilution patients. This may be related to their larger volume of distribution at steady state.

In this study, the decay in plasma concentrations of vecuronium occurred in a triexponential manner, in contrast with that described in earlier studies[5 21 23] where plasma concentrations declined biexponentially. Possible factors that may explain this discrepancy are differences in the methods used to measure drug concentrations, different doses of vecuronium or duration of plasma sampling. In one study,[23] plasma concentrations of vecuronium measured by a relatively insensitive HPLC method (lower limit of detection 50 ng ml^{-1}) were observed for only 90 min after injection of vecuronium. Consequently, the larger part of the slower, terminal elimination phase was probably not detected. In another study, also using HPLC,[5] a larger dose of vecuronium (0.28 mg kg^{-1}, five times the recommended ED_{95} dose) was used in order to measure plasma concentrations for a longer period. A large dose of a drug can, in principle, lead to non-linear pharmacokinetic processes, with a consequent shallow rate of decay in the early phases of plasma concentration decline, and the merging of the early and late distribution slopes. Perhaps for this reason Fahey and colleagues[5] selected a biexponential function to describe the plasma decay curve of vecuronium, even though they detected the plasma decay curve of vecuronium for 4 h. In the study of Lebrault and colleagues[21] using a fluorimetric assay with a lower limit of sensitivity of 25 ng ml^{-1}, not only was a larger dose of vecuronium administered (0.2 mg kg^{-1}, 3.6 times the recommended ED_{95} dose), but plasma concentrations were observed for a shorter period (210 min) compared with our study.

However, in studies using very sensitive mass spectral analysis (level of detection 2 ng ml^{-1})[23] or a modified fluorimetric assay (level of detection 5 ng ml^{-1})[19] to measure plasma concentrations after administration of vecuronium 25–50 μg kg^{-1} or 100 μg kg^{-1} for 5–8 h, the authors found that the disposition kinetics of vecuronium were best described by a model with three compartments and with pharmacokinetic variables that agreed closely with those generated in this study. Mass spectrometry is the most sensitive assay method available to date and it specifically measures only unchanged vecuronium (or any of its metabolites, if so desired). Therefore, the results of this study support the views of Bencini and co-workers[4] that vecuronium disposition kinetics are best described by a three-compartment open model.

Early studies showed that the duration of neuromuscular effect after moderate doses of vecuronium (100 μg kg^{-1}) is governed by the distribution phase rather than the elimination phase. However, after a large dose (200–300 μg kg^{-1}) or repeated doses, recovery from paralysis probably occurs during the elimination phase.[22] On the basis of our results, it was assumed that compared with controls, the larger distribution volume of vecuronium in the haemodilution patients would result in lower plasma concentrations and thus increased dose requirements to achieve comparable neuromuscular block. In addition, the clinical duration of a lower dose of vecuronium may be shorter in patients undergoing haemodilution than in controls because of the larger distribution volume at steady state and higher plasma clearance. But after large or repeated doses, the clinical duration of vecuronium in the haemodilution patients may be prolonged because of the longer elimination half-life.

However, it must be remembered that haemodilution may also be associated with significant changes in plasma protein concentrations. The pharmacological effect of a drug is highly dependent on its degree of plasma protein binding, as only unbound drug diffuses through membranes and is thus available for binding to receptors and exerting its pharmacological action. Schuh reported[14] that the potency of pancuronium was increased during haemodilution, which may be related to a decrease in plasma protein binding. As the protein-bound fraction of vecuronium (30%) is similar to that of pancuronium (29%),[24] any increase in the plasma concentration of unbound vecuronium during haemodilution may outweigh the influences of a larger volume of distribution and a higher plasma clearance on its neuromuscular blocking effects.

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