Vecuronium in renal failure

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Neuromuscular blockade during surgery was provided with vecuronium in 24 adult patients in end-stage renal failure and in 21 normal patients who served as controls. Dose response curves were constructed which showed that the effective doses required to produce 50, 90 and 95 per cent neuromuscular blockade in patients with renal failure were 27.5, 43 and 49 $\mu\text{g}\cdot\text{kg}^{-1}$ respectively. These were not significantly different from the doses of 31, 49 and 57 $\mu\text{g}\cdot\text{kg}^{-1}$ in the normal patients. Repeated small doses of 0.01 $\text{mg}\cdot\text{kg}^{-1}$ had a significantly longer duration of action and were associated with some cumulation in the renal failure group. Recovery from the block occurred rapidly after neostigmine, was no different in renal failure and was not associated with recurarization. It is concluded that, when given to subjects in renal failure, vecuronium offers advantages over established agents such as shorter duration of action and easy reversibility.

Key words

NEUROMUSCULAR RELAXANTS; vecuronium; RENAL FAILURE; anaesthesia.

All non-depolarizing neuromuscular blocking drugs are ionized quaternary ammonium compounds and, because they are water soluble, are excreted in the urine. Consequently, their duration of action is prolonged in renal failure unless they are metabolized rapidly. The degree to which renal impairment influences their duration of action depends on the presence of alternative routes of excretion. Vecuronium is a monoquaternary analogue of pancuronium which has been released recently for clinical use in the United States. Although the kidney is an important site of clearance, the liver is the major

route of excretion in animals.¹ In addition, vecuronium undergoes spontaneous deacetylation to hydroxy metabolites² which have minimal neuromuscular blocking effects.³ These alternative mechanisms probably explain why the duration of action of equipotent doses of vecuronium in normal subjects is only one-third that of pancuronium.⁴

Its action should be altered little by renal dysfunction although the available evidence is scanty. In rats, clamping of the renal arteries did not alter significantly the depth or duration of vecuronium blockade.⁵ In man, renal failure is associated with only small increases in the duration of neuromuscular block and recovery rate⁶ as a result of statistically insignificant alterations in the pharmacokinetic behaviour of vecuronium in renal failure.⁷ However, these observations are based upon small patient populations and there is no information of the potency, cumulative tendency, or reversibility of vecuronium in renal failure in man.

The present study was designed to compare the potency, duration of action, cumulative tendency of repeated doses and the reversibility of vecuronium in patients with normal renal function and with those in end-stage renal failure.

Methods

The protocol was approved by the hospital Ethics Committee. After informed consent had been obtained, 45 adult surgical patients were studied. Twenty-one of the patients had normal renal function, were ASA physical status class I–II, were without known or suspected neuromuscular disease, and were not taking medication known to interfere with neuromuscular transmission. These patients constituted the control group. Twenty four patients were in end-stage renal failure undergoing a variety of surgical procedures; renal transplantation (7), dialysis access (13), transplant nephrectomy (2), parathyroidectomy (1) and laparotomy (1).

Patients in both groups received premedication with a narcotic and atropine intramuscularly approximately 60 min before surgery. Anaesthesia

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was induced with thiopentone, 3–5 mg·kg⁻¹, and maintained with nitrous oxide, 50–70 per cent, in oxygen and supplemented with halothane (0.5–1 per cent inspired). The tracheas of all patients were intubated and the lungs ventilated to maintain an end-tidal PCO₂ of 32–35 mmHg (Hewlett Packard capnometer).

Neuromuscular transmission was measured, after induction of anaesthesia until the end of surgery, using train-of-four stimulation according to the method of Ali *et al.*⁸ The ulnar nerve was stimulated supramaximally at the elbow with subcutaneous needle electrodes. Four square wave impulses of 0.2 ms duration and 2 Hz frequency were administered every 12 seconds using a Grass S48 stimulator and SIU5 isolation unit. The hand and forearm were immobilized in a splint. The force of contraction of the adductor pollicis muscle was measured with a Grass FT10 force displacement transducer and the response recorded on a Grass Polygraph pen and ink recorder. The skin temperature over the thumb was monitored and maintained above 32°C.

After stabilization of muscle twitch had been obtained, vecuronium was injected as a single bolus of one of 11 doses between 10 and 60 µg·kg⁻¹. At least two patients received each dose which was chosen by random allocation. Twitch depression was measured after it had reached a stable level and these data points were used to construct a dose-response curve using log-probit paper.⁹ Additional doses, 10–20 µg·kg⁻¹, of vecuronium were given to produce twitch depression of at least 95 per cent. Neuromuscular blockade was maintained during surgery with repeated boluses of 10 µg·kg⁻¹ given whenever the force of the first stimulus of the train returned to ten per cent of control. Towards the end of surgery the neuromuscular block was antagonized with atropine, 1.2 mg·70 kg⁻¹, and neostigmine, 2.5 mg·70 kg⁻¹. Monitoring of neuromuscular transmission continued until the train of four ratio (T4/T1), defined as the force of contraction of

FIGURE 1 Single dose, vecuronium log-probit dose response curves in normal and renal failure patients. Data points for 0 and 100 per cent block were excluded from construction of regression lines.

the fourth twitch in each train divided by the force of contraction of the first, exceeded 0.7. Then the patients were extubated and returned to the recovery room where neuromuscular activity was assessed by the usual clinical criteria which included adequacy of respiration, hand grip and head lift.

Regression lines for dose response curves were constructed by the method of least squares excluding points of 0 and 100 per cent block. The curves in the normal and renal failure patients were compared graphically as a log-probit plot and analyzed for parallelism and potency. Mean values are presented with the standard error of the mean as the index

TABLE I Demographic data

	n	Sex		Age yrs	Wt kg	Duration min
		M	F			
Normal	21	13	8	50.6 ± 3.0	67.1 ± 2.1	109.0 ± 17.6
Renal failure	24	12	12	45.1 ± 3.2	65.5 ± 3.1	89.3 ± 14.9

TABLE II Laboratory data

	Hb g·dl ⁻¹	Na mmol·l ⁻¹	K mmol·l ⁻¹	Ca mmol·l ⁻¹	BUN mg·dl ⁻¹	Cr mg·dl ⁻¹	Albumen g·dl ⁻¹	Protein g·dl ⁻¹
Normal	14.1 ± 0.3	141.0 ± 0.6	4.2 ± 0.1	9.4 ± 0.1	13.4 ± 1.0	0.96 ± 0.04	4.1 ± 0.08	6.9 ± 0.1
Renal failure	8.9 ± 0.4	136.7 ± 1.0	4.7 ± 0.2	9.1 ± 0.2	83.4 ± 7.2	11.5 ± 0.9	3.7 ± 0.1	6.4 ± 0.1
p	< 0.0001	< 0.001	< 0.05	NS	< 0.0001	< 0.0001	< 0.01	< 0.05

TABLE III Pharmacodynamic data

	Potency			Duration of 0.01 mg·kg ⁻¹		T4/T1	
	ED 50 (μg·kg ⁻¹)	ED 90 (μg·kg ⁻¹)	ED 95 (μg·kg ⁻¹)	1st dose (min)	10th dose (min)	minutes after neostigmine	
						5	10
Normal	31	49	57	7.7 ± 0.8	8.3 ± 0.6	0.44 ± 0.05	0.67 ± 0.04
Renal failure	27.5	43	49	9.0 ± 0.8	13.8 ± 2.0	0.54 ± 0.03	0.69 ± 0.03

of dispersion. Probabilities were calculated from Student's *t* test, and chi-square analysis and the null hypothesis rejected when *p* < 0.05.

Results

There were no significant differences in the sex ratios (χ^2), ages, weights or severity and duration of surgery between the two groups (Table I). However, there were significant differences in the laboratory data (Table II). In particular, haemoglobin concentration was lower and blood urea and serum creatinine concentrations were increased in the renal failure group.

The log-probit dose response curves for the two groups are shown in Figure 1. The curves were parallel and not significantly different from each other. Doses which produced 50, 90 and 95 per cent were obtained by interpolation and are recorded in Table III.

The durations of action of "top-up" doses of 0.01 mg·kg⁻¹ are shown in Figure 2 and Table III. In those patients who received more than ten doses of vecuronium there was a progressive, significant increase in the duration of action in the renal failure group of approximately 50 per cent over two hours. This cumulation was not seen in the patients with normal renal function. Mean duration of action of "top-up" doses was greater in the renal failure group (12.0 ± 1.4) than in the control group (7.3 ± 0.7 ; *p* < 0.05) (Figure 2).

After antagonism of the block with neostigmine,

recovery occurred rapidly and at a similar rate in both groups (Table III). All patients were extubated at the end of surgery and no problems with ventilation were seen postoperatively.

Discussion

Until recently the choice of non-depolarizing neuromuscular blocking drugs to provide muscle relaxation for prolonged operations in patients with renal failure has been limited. Alterations in the pharma-

FIGURE 2 Durations of action of repeated small doses of vecuronium (0.01 mg·kg⁻¹) in patients receiving ten or more "top-ups." Significant differences between the mean values of the two groups are shown.

* = *p* < 0.05.

TABLE IV Pharmacokinetics of non-depolarizing relaxants

		$t_{1/2\beta}$ (min)	Vd_{ss} (l·kg ⁻¹)	Cl (ml·kg ⁻¹ ·min ⁻¹)
Gallamine ¹⁰	Normal	131	0.21	1.2
	Renal failure	752	0.29	0.24
Mecurine ¹¹	Normal	360	0.47	1.2
	Renal failure	684	0.35	0.38
Pancuronium ¹²	Normal	133	0.26	1.8
	Renal failure	257	0.3	0.9
d-tubocurarine ¹³	Normal	89	0.3	3.0
	Renal failure ¹⁴	↑		↓
Atracurium ¹⁵	Normal	10	0.12	7.6
	Renal failure	23	0.17	6.7
Vecuronium ⁷	Normal	80	0.19	3.0
	Renal failure	97	0.24	2.5

$t_{1/2\beta}$ = half-time of the terminal elimination phase.

Vd_{ss} = volume of distribution at steady state.

Cl = plasma clearance.

cokinetic behaviour (Table IV) of the established agents results in increased durations of action. The clearances of gallamine and metocurine are decreased considerably because the kidney is their predominant route of excretion and, thus, their use is contraindicated in renal failure. Pancuronium and d-tubocurarine have an alternative hepatic route of excretion but plasma clearance is still reduced by approximately half. Recently, Hunter *et al.*¹⁶ confirmed that the duration of action of single doses of atracurium was not prolonged and there was no evidence of cumulation. Limited studies with vecuronium suggested that the minimal pharmacokinetic alterations induced by renal failure were associated with only minor pharmacodynamic changes.

The present study confirmed these findings. Although the duration of action of repeated doses of vecuronium were significantly longer with non-functioning kidneys, the increases were of minimal clinical importance. More interesting was the observation that cumulative effects were seen after repeated doses in patients with renal failure but not in normal controls. The reason for this difference is not understood. Theoretically, cumulation occurs as a result of progressive increases in either the drug half-life or the sensitivity of the neuromuscular junction to circulating relaxant. Alternatively, cumulation may be seen if repeated doses are injected during the distributional phase of the previous dose. Whatever the aetiology the effect

was to prolong the duration of action by about 50 per cent after ten doses, or two hours. This cumulation is less than that observed by Fahey *et al.*⁴ following repeated doses of pancuronium but they gave the drug for over six hours. Studies with the newer agents will need to be repeated for similar durations before it can be concluded that cumulative effects are absent.

The potency of vecuronium in normal patients in the present study was similar to that reported by Gramstad and Lilleaasen¹⁷ but less than that reported by others^{4,18} using either different methods of measurement or different anaesthetic combinations. No alteration in potency could be detected in patients with renal failure despite differences in electrolyte and plasma protein concentrations and possible fluid volume shifts from recent dialysis. In particular, the anephric patient for parathyroidectomy demonstrated normal sensitivity to vecuronium but her serum calcium concentration after haemodialysis was within the normal range.

Recovery of neuromuscular function after neostigmine proceeded as rapidly in the renal failure group as in normals. The rate of recovery was similar to or faster than that described previously for pancuronium¹⁹ in renal failure. In normal patients it has been demonstrated that recovery of neuromuscular function after neostigmine antagonism was quicker with vecuronium than pancuronium.²⁰ There was no evidence of reparation in either group confirming that if a non-depolarizing neuro-

muscular block is adequately antagonized fears of postoperative recurarization in renal failure are unfounded.²¹

In conclusion, vecuronium has suitable neuromuscular blocking effects to be used as a muscle relaxant in patients in renal failure. In these patients, the potency and reversibility of the drug are not affected by renal dysfunction. Although the duration of action of small repeated doses is slightly longer and demonstrates some cumulation, it is unlikely that these will be associated with difficulty in clinical management. When these properties are combined with the absence of cardiovascular activity, vecuronium represents a considerable advantage over existing agents in the provision of muscle relaxation to the patient in renal failure.

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Résumé

Le bloc neuromusculaire a été effectué avec du vécuronium chez 24 patients en défaillance rénale terminale et chez 21 patients normaux qui ont constitué le groupe contrôle. Les courbes de réponse qu'on a établies ont montré que les doses nécessaires pour produire un bloc neuromusculaire de 50, 90 et 95 pour cent étaient respectivement de 27.5, 43 et 49 $\mu\text{g}\cdot\text{kg}^{-1}$. Ces doses ne diffèrent pas sensiblement des doses nécessaires chez les patients normaux qui sont respectivement de 31, 49 et 57 $\mu\text{g}\cdot\text{kg}^{-1}$.

Des petites doses répétées de 0.01 $\text{mg}\cdot\text{kg}^{-1}$ provoquaient un bloc neuromusculaire de plus longue durée possiblement relié à un certain degré d'accumulation dans le groupe en défaillance rénale. La disparition du bloc s'est effectuée rapidement à la suite de néostigmine dans l'un et l'autre groupes et on n'a pas observé de récurarisation chez les insuffisants rénaux. On conclut que le vécuronium, administré à des patients en défaillance rénale possède certains avantages sur les autres agents connus, en particulier une durée d'action plus courte et une réponse assurée à la néostigmine.