Secondary hyperparathyroidism shortens the action of vecuronium in patients with chronic renal failure

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The authors studied the duration of action of vecuronium in 15 patients with normal renal function and 40 patients with chronic renal failure to evaluate the effect of secondary hyperparathyroidism on the action of vecuronium. The patients were divided into four groups: 15 patients with normal renal function (Group A); nine patients with chronic renal failure who did not need haemodialysis (Group B); 15 anephric patients who did not require parathyroidectomy (Group C); and 16 anephrenic patients who underwent parathyroidectomy because of severe secondary hyperparathyroidism (Group D). The ratio of the height of the first twitch (T_1) to the baseline value before vecuronium administration was measured by an electromyogram. Baseline T_1 was obtained after anaesthesia induction with thiamylal iv. The time to 10% recovery of the first twitch (REC 10) after administration of vecuronium 0.12 mg · kg^{-1} iv was measured in each group. Anaesthesia was maintained with isoflurane and nitrous oxide in oxygen, and supplemented with fentanyl iv. Patients in Group D showed shorter REC 10 (51 ± 4 min) than those in Groups B (71 ± 6 min) and C (80 ± 10 min) ($P < 0.05$), but similar REC 10 to patients in Group A (37 ± 4 min). These results suggest that the duration of action of vecuronium in anephric patients with secondary hyperparathyroidism is shorter than in those without secondary hyperparathyroidism.

Key words
NEUROMUSCULAR RELAXANTS: vecuronium;
HORMONES: parathyroid;
KIDNEY: failure.

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Presented in part at the 68th Clinical and Scientific Congress of the International Anesthesia Research Society in Orlando, FL, March 5–9, 1994.

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Accepted for publication 8th January, 1995.

Les auteurs étudient la durée d'action du vécuronium auprès de 15 patients avec une fonction rénale normale et de 40 patients avec une insuffisance rénale chronique afin d'évaluer l'effet d'une hyperparathyroïdie secondaire sur l'action du vécuronium. Les patients sont répartis en quatre groupes: quinze patients avec une fonction rénale normale (Groupe A); neuf patients avec une insuffisance rénale chronique non hémodialysés (Groupe B); 15 patients anéphriques qui n'ont pas besoin d'une parathyroïdectomie (Groupe C) et 16 patients anéphriques qui subissent une parathyroïdectomie à cause d'une hyperparathyroïdie secondaire grave (Groupe D). Le rapport de la hauteur de la première contraction (T_1) à la contraction de base avant l'administration de vécuronium est mesurée par un électromyogramme. Le T_1 de base est obtenu après l'induction de l'anesthésie avec du thiamylal iv. Le temps de récupération à 10% dès la première contraction (REC 10) après l'administration iv de 0,12 mg · kg^{-1} de vécuronium est mesuré dans chaque groupe. L'anesthésie est maintenue avec de l'isoflurane et du protoxyde d'azote dans l'oxygène et des suppléments de fentanyl iv. Les patients du groupe D montrent un plus court REC 10 (51 ± 4 min) que ceux du groupe B (71 ± 6 min), et du groupe C (80 ± 10 min) ($P < 0,05$), mais un REC 10 semblable aux patients du groupe A (37 ± 4 min). Les résultats suggèrent que la durée d'action du vécuronium chez les patients anéphriques est plus courte avec que sans hyperparathyroïdie secondaire.

Vecuronium is considered to be a desirable neuromuscular relaxant for patients with renal failure because its elimination depends mainly on metabolism by the liver.[1,2] Whereas some studies demonstrated that the duration of action of vecuronium was the same in patients with normal renal function and those with chronic renal failure (CRF),[3,4] others showed that the plasma clearance of vecuronium was decreased and the duration of action prolonged in CRF.[5,6] Further, wide inter-patient variability exists both in patients with normal renal function[7] and in patients with CRF.[8,9] Although altered responses of muscle relaxants in primary hyperparathyroidism have

TABLE I Patient characteristics

	Group A	*Group B*	*Group C*	*Group D*
Number	15	9	5	16
Male	5	6	9	7
Female	10	3	6	9
Age (yr)	52.3 ± 3.5	58.7 ± 5.2*	45.1 ± 3.5	49.9 ± 3.2
Weight (kg)	54.3 ± 2.8	60.8 ± 3.1*	52.9 ± 2.5	50.1 ± 2.3*
Creatinine ($mg \cdot dl^{-1}$)	0.9 ± 0.04	3.0 ± 0.6*	9.5 ± 0.7*†	10.0 ± 0.5*†
BUN ($mg \cdot dl^{-1}$)	13.3 ± 1.2	36.3 ± 5.7*	66.6 ± 8.4*†	67.1 ± 3.4*†
History of haemodialysis (yr)			7.3 ± 1.2	11.8 ± 1.1‡

(Mean ± SEM).
*($P < 0.05$) compared with Group A.
†($P < 0.05$) compared with Group B.
‡($P < 0.05$) compared with Group C.

been reported,[10,11] there is no report that describes this phenomenon in secondary hyperparathyroidism.

Accordingly, in this study, we evaluated the effect of severe hyperparathyroidism, one of the uraemic syndromes, on the duration of action of vecuronium.

Methods

Fifty-five surgical patients were enrolled in the study after institutional approval and informed consent. They were divided into four groups: Group A had 15 patients with normal renal function; Group B had nine patients with CRF who did not need haemodialysis therapy; Group C had 15 anephric patients who did not require parathyroidectomy; and Group D had 16 anephric patients who underwent parathyroidectomy because of severe secondary hyperparathyroidism. The indications for parathyroidectomy for patients with CRF are as follows: (1) severe symptoms of hyperparathyroidism including, itching, bone pain, and ectopic calcification; and (2) high plasma concentration of parathyroid hormone or hypercalcaemia in spite of medical treatment.

All patients in Groups C and D had been dialyzed within 48 hr before surgery. Patients were premedicated with diazepam 10 mg or rilmazafone 1 mg 90 min *po* before induction of anaesthesia which was induced with thiamylal 5 $mg \cdot kg^{-1}$ *iv* and the trachea was intubated following vecuronium 0.12 $mg \cdot kg^{-1}$ *iv*. Anaesthesia was maintained with isoflurane 1.0 to 1.5% (inspired) and nitrous oxide 60% in oxygen, and fentanyl 0.1 to 0.2 mg *iv*. Standard monitors during anaesthesia were used in all patients.

Neuromuscular function was monitored using an electromyogram monitor (NMT-100-31-01, Datex, Helsinki, Finland). The adductor pollicis twitch was elicited by ulnar nerve stimulation with supramaximal 2 Hz train-of-four square wave impulses (0.2 msec duration) every 20 sec at the wrist. Neuromuscular function was evaluated by determining the ratio of the height of the first twitch (T_1) to the baseline value before vecuronium administration. Baseline T_1 before vecuronium was obtained after anaesthesia induction with thiamylal and vecuronium 0.12 $mg \cdot kg^{-1}$ was administered. The time to 10% recovery of T_1 (REC 10) after vecuronium was measured. Data were expressed as mean ± SEM. The one-way analysis of variance (ANOVA), with Scheffe's F post hoc test was used for statistical analysis and $P < 0.05$ was deemed significant. Sperman's regression analysis was used for relationship between the history of haemodialysis and REC 10 in Groups C and D.

Results

The patients' characteristics are shown in Table I. There were differences between Groups B and C in age ($P < 0.05$), and Groups B and D in body weight ($P < 0.05$). Preoperative creatinine and BUN were normal in Group A, and were higher in other groups, in particular Groups C and D ($P < 0.01$). The history of haemodialysis therapy in Group D was longer than in Group C ($P < 0.05$). The patients' laboratory data during surgery are shown in Table II. There was a difference in base excess between the patients of Group A and Groups C and D ($P < 0.05$). Serum potassium concentrations in Group D were higher than those in other groups ($P < 0.05$). Although there was a difference in serum ionized calcium concentrations between Groups B and D, there was no difference between Groups C and D. Haemoglobin values in Groups B, C and D were lower than in Group A ($P < 0.05$).

The differences in the duration of action of vecuronium in patients of each group are shown in Table III. Patients in Group D showed shorter REC 10 than those in Groups B and C ($P < 0.05$). However, REC 10 in Group A was similar to that in Group D. There was no correlation between the duration of action of vecuronium (REC 10) and a history of haemodialysis therapy in anephric patients (Groups C and D) ($r^2 = 0.082$).

TABLE II Patient data during surgery

	Group A	*Group B*	*Group C*	*Group D*
pH	7.44 ± 0.01†‡	7.40 ± 0.02	7.39 ± 0.02†	7.40 ± 0.01‡
BE ($mEq \cdot L^{-1}$)	0.2 ± 0.6†‡	−2.7 ± 1.4	−3.2 ± 0.9†	−3.8 ± 0.6‡
K($mEq \cdot L^{-1}$)	3.8 ± 0.1*‡	4.3 ± 0.2*§	4.4 ± 0.3¶	5.2 ± 0.2‡§¶
Ca^{++} ($mmol \cdot L^{-1}$)	1.03 ± 0.03	0.98 ± 0.02§	1.08 ± 0.06	1.11 ± 0.05§
Hb ($g \cdot dl^{-1}$)	12.0 ± 0.4†‡	9.7 ± 0.6*	9.0 ± 0.3†	9.0 ± 0.3‡
Temperature (°C)	36.4 ± 0.1	36.6 ± 0.2	36.2 ± 0.1	36.9 ± 0.1

(Mean ± SEM).
*($P < 0.05$): Groups A vs B.
†($P < 0.05$): Groups A vs C.
‡($P < 0.05$): Groups A vs D.
§($P < 0.05$): Groups B vs D.
¶($P < 0.05$): Groups C vs D.

TABLE III Duration of action of vecuronium

	Group A	*Group B*	*Group C*	*Group D*
REC 10 (min)	37 ± 4*† ($n = 15$)	71 ± 6*‡ ($n = 9$)	80 ± 10†§ ($n = 15$)	51 ± 4‡§ ($n = 16$)

(Mean ± SEM).
*($P < 0.05$): Groups A vs B.
†($P < 0.05$): Groups A vs C.
‡($P < 0.05$): Groups B vs D.
§($P < 0.05$): Groups C vs D.

Discussion

In the present study we found that the duration of action of vecuronium in CRF patients, both with and without haemodialysis therapy, who did not require parathyroidectomy was longer than in patients with normal renal function. This prolongation of the duration of action of vecuronium may be due to delayed elimination of vecuronium and its active metabolite (3-desacetylvecuronium) as reported by Lynam *et al.*[5] Prolonged duration of action of vecuronium in CRF patients was also confirmed by a meta-analysis of eight clinical studies by Beauvoir *et al.*[12]

Our study showed that the duration of action of vecuronium in the anephric patients with severe hyperparathyroidism was shorter than in the patients with CRF who did not require parathyroidectomy. This result is inconsistent with the hypothesis that delayed renal elimination of vecuronium and its metabolite due to CRF may prolong the duration of action of vecuronium, because the renal elimination of vecuronium in anephric patients with severe hyperparathyroidism should be less than that in the CRF patients who did not need the haemodialysis therapy. The duration of action of vecuronium in patients with CRF exhibits wide inter-patient variability both in this study and in previous reports.[8,9] Patients with no renal function showed REC 10 ranging from 21 min to 143 min in our study. This interpatient variability is, in part, why the duration of action of vecuronium in patients with no renal function has never been adequately defined. Anephric patients are regarded as the homogenous group in terms of their renal elimination of vecuronium but may be regarded as the heterogeneous group in terms of the degree of the uremic syndromes and the history of CRF and hemodialysis therapy. This heterogeneity in CRF patients may relate to this wide interpatient variability in the duration of action of vecuronium.

Primary hyperparathyroidism was reported to hasten the recovery of atracurium.[10] However, there are few studies on the relationship between the action of vecuronium and parathyroid function in CRF. It has been reported that the action of vecuronium is shortened in patients with primary hyperparathyroidism and this was thought to be due to hypercalcaemia.[11] However, secondary hyperparathyroidism does not usually cause hypercalcaemia because the decrease in serum ionized calcium concentration associated with CRF leads to secondary hyperparathyroidism. In our study there was no difference in serum ionized calcium concentration between the anephric patients with or without severe secondary hyperparathyroidism. Although secondary hyperparathyroidism with CRF does not usually cause

hypercalcaemia, it enhances entry of calcium into some tissues such as skin, cornea and blood vessels.[13] Accordingly, it is possible that this increase in the tissue content of calcium may have some effect on the action of vecuronium. It has also been suggested that hyperparathyroidism may change the sensitivity of skeletal muscle itself to vecuronium.[14]

In our study patients with severe secondary hyperparathyroidism had received haemodialysis for longer than patients without severe secondary hyperparathyroidism and other effects of long history CRF or haemodialysis therapy may also reduce the sensitivity of vecuronium in CRF patients. However, there was no correlation between the history of haemodialysis therapy and the duration of action of vecuronium in the anephric patients in our study. Further, the duration of action of vecuronium was not different between CRF patients who did not need haemodialysis therapy and those who needed haemodialysis therapy. Accordingly, our data suggest that haemodialysis per se did not affect the duration of action of vecuronium.

Although we did not measure blood concentrations of guanidine derivatives, it has been reported that CRF alters sensitivity to muscle relaxants through nicotinic receptor down-regulation as a result of the chronically increased release of acetylcholine induced by some guanidine compounds.[15]

We evaluated hyperparathyroidism mainly from clinical symptoms and we did not measure plasma parathyroid hormone concentrations in patients without evident symptoms of hyperparathyroidism. In spite of this potential fault, our results indicate that severe secondary hyperparathyroidism reduces the duration of action of vecuronium in CRF patients through a mechanism that is unclear. Accordingly, further evaluation of the effect of parathyroid function on muscle relaxants by pharmacokinetic-dynamic relations is needed in patients with CRF.

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