Pharmacodynamic behaviour of vecuronium in primary hyperparathyroidism

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This study evaluated the potency and time course of action of vecuronium in patients with primary hyperparathyroidism (HPT) and marked hypercalcaemia during nitrous oxide-opioid anaesthesia. Twenty ASA physical status I and II patients were studied by measuring the force of contraction of the adductor pollicis in response to stimulation of the ulnar nerve: ten control patients and ten patients with HPT and ionized calcium concentration over $2.80 \text{ mEq} \cdot \text{L}^{-1}$. After induction of anaesthesia with thiopentone and maintenance with $\text{N}_2\text{O}/\text{O}_2$ and fentanyl, vecuronium was administered to determine cumulative dose-response curves. When maximum block had been obtained, twitch height was maintained at 10% of baseline value over 20 min by adjusting the infusion rate of a syringe-pump containing vecuronium and vecuronium plasma concentration ($\text{EC}_{90\text{ss}}$) was determined. During spontaneous recovery, after termination of infusion, the recovery index, the time from 25 to 75% recovery, was measured. The dose to produce 90% block was greater in the HPT than in control group: $69 (24) \text{ vs } 54 (18) \mu\text{g} \cdot \text{kg}^{-1}$ ($P < 0.02$). The calculated ED_{50} was also greater in HPT: $42 (4) \text{ vs } 31 (5) \mu\text{g} \cdot \text{kg}^{-1}$ in controls ($P < 0.001$). (Values are given as mean and coefficient of variation). The slope of the dose-response curve, the dose necessary to maintain 90% block, and the $\text{EC}_{90\text{ss}}$ did not differ. The RI_{25-75} was slower in the HPT group although the difference did not reach statistical significance. It is concluded that hyperparathyroidism

with hypercalcaemia increases vecuronium requirement; only during the onset of neuromuscular blockade.

Cette étude évalue la puissance et le déroulement temporel, pendant une anesthésie au protoxyde d'azote-morphinique, du vécuro-nium chez des patients souffrant d'hyperparathyroïdie primaire (HPT) avec hypercalcémie importante. Vingt patients ASA I et II sont étudiés par la mesure de la force de contraction de l'adducteur du pouce en réponse à une stimulation du nerf cubital: dix patients servent de contrôles à dix patients souffrant d'HPT et dont la concentration de calcium ionisé dépasse $2,80 \text{ mEq} \cdot \text{L}^{-1}$. Après induction au thiopentone et entretien au $\text{N}_2\text{O}/\text{O}_2$ avec fentanyl, on administre du vécuro-nium pour déterminer les courbes cumulatives doses-effets. Après l'obtention d'un bloc maximal, la hauteur du twitch est maintenue à 10% au-dessus de la ligne de base pendant plus de 20 min en ajustant la vitesse de perfusion d'un pousse-seringue contenant du vécuro-nium; on détermine à ce moment la concentration plasmatique de vécuro-nium ($\text{ED}_{90\text{ss}}$). Pendant la récupération spontanée, après l'arrêt de la perfusion, l'index de récupération, la durée requise pour une récupération de 25 à 75% est mesuré. La dose requise pour produire un bloc à 90% est plus élevée dans l'HPT que dans le groupe contrôle: $69 (24) \text{ vs } 54 (18) \mu\text{g} \cdot \text{kg}^{-1}$ ($P < 0,02$). L' ED_{50} calculée est aussi plus élevée dans l'HPT: $42 (4) \text{ vs } 31 (5) \mu\text{g} \cdot \text{kg}^{-1}$ dans le groupe contrôle ($P < 0,001$). (Les valeurs reproduites sont la moyenne et le coefficient de variation). La pente de la courbe dose-effet, la dose nécessaire au maintien du bloc à 90% et l' $\text{EC}_{90\text{ss}}$ sont identiques. Le RI_{25-75} est plus lent dans le groupe HPT mais sans différence statistique. En conclusion, l'hyperparathyroïdie associée à une hypercalcémie importante n'augmente les besoins en vécuro-nium que pendant l'installation du bloc neuromusculaire.

Key words

NEUROMUSCULAR RELAXANTS: vecuronium;
INTERACTIONS: hyperparathyroidism, hypercalcaemia;
PHARMACOKINETICS: dose-response relationships.

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The calcium ion plays an important role in neuromuscular transmission.¹ Acute changes in concentrations of ionized calcium have been shown to interact on the action of muscle relaxants. Increases in ionized calcium concentrations (Ca^{++}) *in vitro* produce decreases in the sensitivity of a nerve muscle preparation to both d-tubocurarine and pancuronium.² In *in vivo* animal

experiments, increased Ca^{++} was shown to antagonize the blocking effects of atracurium and vecuronium.³

Patients with primary hyperparathyroidism (pHPT) have chronically elevated plasma ionized calcium and decreased phosphate concentrations. The increased extracellular calcium concentration is related to a hypersecretion of parathormone. This hypersecretion may be due to a reduced sensitivity of pathological parathyroid cells to calcium or an increase of the PTH-secreting parathyroid mass.⁴ Patients with neuropathy or neuromuscular disease due to severe pHPT have been described⁵ but the usual presentation of pHPT is an asymptomatic patient, or one with few symptoms, and a moderate hypercalcaemia.^{6,7} In asymptomatic pHPT, neither consistent abnormality of neuromuscular transmission nor abnormal muscle structure were found.^{6,8} However, Al-Mohaya's case report described that the duration of action of atracurium was reduced in a patient with pHPT and high total calcium concentration.⁹ A recent study showed that the magnitude of vecuronium-induced twitch depression was less for patients with pHPT than for control patients.¹⁰

The effects of prolonged disturbances of calcium homeostasis on vecuronium block are insufficiently known. The present study was designed to examine the hypothesis that the hypercalcaemia induced by hyperparathyroidism would modify vecuronium neuromuscular block.

Methods

After informed consent and the University Ethics Committee's approval, 20 adult patients aged 21–64 yr, ASA physical status I or II were studied: ten patients had primary hyperparathyroidism with plasma ionized calcium concentration $>2.80 \text{ mEq} \cdot \text{L}^{-1}$ and were scheduled for removal of an adenoma or subtotal parathyroidectomy. Ten patients with normal parathyroid function, scheduled for minor surgical procedures served as controls. The study was not blinded. All patients were free from medications or conditions known to affect neuromuscular transmission.

Premedication consisted of $3 \text{ mg} \cdot \text{kg}^{-1}$ hydroxyzine *po*. Anaesthesia was induced with thiopentone $6\text{--}8 \text{ mg} \cdot \text{kg}^{-1}$, and fentanyl $2\text{--}3 \mu\text{g} \cdot \text{kg}^{-1}$. Tracheal intubation was performed after topical anaesthesia (3 ml lidocaine 5%) without the use of muscle relaxants. Anaesthesia was maintained by inhalation of nitrous oxide 70% in oxygen and supplemental doses of $1\text{--}2 \mu\text{g} \cdot \text{kg}^{-1}$ fentanyl as required. No volatile agents were used. Ventilation was controlled to maintain an end-tidal carbon dioxide tension in the range of 30–35 mmHg. Core temperature was kept $>36^\circ\text{C}$. Skin temperature was recorded from the studied thenar region and maintained $>34.5^\circ\text{C}$.

Cutaneous electrodes were placed at the wrist and neu-

romuscular blockade was assessed by measuring the evoked response of the adductor pollicis muscle to supramaximal stimulation of the ulnar nerve by a current constant stimulator. The force of contraction was measured isometrically by a force displacement transducer and recorded on line using the Curametre® (Bio Industry-France). Square-wave pulses of 0.2 ms duration (single twitch) were delivered every ten seconds during the onset of neuromuscular block. During spontaneous recovery TOF (TOF, four stimuli with a frequency of 2 Hz) impulses were applied every 20 sec. Resting thumb adductor tension was maintained between 200 and 300 g throughout the study.

After stabilization of the control twitch height for at least 10 minutes, arterial blood samples were collected for blood gas analysis, plasma ionized and total calcium, phosphate, potassium, magnesium, plasma proteins and haematocrit. The ionized calcium concentration was measured by an analyzer with a calcium specific electrode (Radiometer®-Copenhagen). Then, the dose-response part of the study was performed using a cumulative technique. Initially, vecuronium $20 \mu\text{g} \cdot \text{kg}^{-1}$ were given as a bolus. Once the maximum effect of the selected initial dose was reached, additional doses of $10 \mu\text{g} \cdot \text{kg}^{-1}$ were given when the maximum effect had been obtained until approximately 95% twitch height depression was obtained. In case no effect was obtained within 2.5 min after the initial dose – that is when no decrease in evoked twitch height occurred after at least 15 consecutive single twitches – a supplementary dose of $10 \mu\text{g} \cdot \text{kg}^{-1}$ vecuronium was administered as a divided initial dose.

Hereafter twitch height was maintained at 10% of baseline value by manually adjusting the infusion rate of a syringe-pump containing vecuronium $0.1 \text{ mg} \cdot \text{ml}^{-1}$ in saline (NaCl 0.9%). The dose requirement was noted and vecuronium plasma concentration ($\text{EC}_{90\text{ss}}$) was determined after at least 20 min of unchanged block and infusion rate. During spontaneous recovery, after termination of infusion, the time interval between 75 and 25% block (RI_{25-75}) was measured.

For the determination of plasma concentration of vecuronium, 4 ml blood samples were withdrawn into lithium heparinized tubes from an arterial line after the end of the infusion period. Samples were immediately acidified by the addition of 1 ml NaH_2PO_4 , 1 M. The plasma was separated within one hour and deep frozen until analysis by high performance liquid chromatography (HPLC).⁵ The concentrations of vecuronium and its putative metabolites has been determined by an HPLC method described for rocuronium, modified and validated for vecuronium.¹¹ After extraction from plasma, compounds were separated by HPLC followed by post-column ion-pair extraction and fluorometric detection.

The method shows a linear relationship between the logarithm of the response ratio (peak height compound/peak height interval standard) ranging from 5–1000 ng for vecuronium and its metabolites, showing an intra-day variability of 4.7–1.5%, 2.6–2.7%, and 9.7 and 2.8% for vecuronium, 3-desacetyl vecuronium and 3,17-didesacetyl vecuronium respectively, whereby 100–1000 μl plasma can be processed. The accuracy, expressed as percentages found of the added amount are 105%, 99%, 104% and 95% for 10, 100, 500, 1000 $\text{ng} \cdot \text{ml}^{-1}$ vecuronium respectively. For 3-desacetyl vecuronium the accuracy amounts to 112%, 105%, 99%, and 87%, whereas for 3,17-didesacetyl vecuronium the accuracy amounts to 115%, 108%, 85%, and 105% for the afore-mentioned concentrations respectively. The lower limit of quantification, defined as the minimum concentration, which can be determined with an accuracy and precision better than 15% is 5 $\text{ng} \cdot \text{ml}^{-1}$ for all three compounds.

A log-logit analysis of the dose-response data during onset of block was performed for each patient. Individual dose-response regression lines were calculated. These lines were characterized by the effective doses at 50% block (ED_{50}) calculated by interpolation, and the corresponding slopes.

All values are given as mean values with the coefficient of variation (%) in brackets [$\text{CV} = (\text{SD}/\text{mean}) 100\%$]. The results were analyzed using the Mann-Whitney U-test. Differences were considered significant at $P < 0.05$.

Results

The age of the patients ranged from 18 to 61 yr and 24 to 54 yr in the control and HPT groups respectively. Both groups were comparable with respect to age, male/female distribution, weight, body surface area, plasma proteins, blood gases, haematocrit and plasma concentrations of magnesium and potassium. Plasma phosphate (normal range: 0.75–1.25 $\text{mmol} \cdot \text{L}^{-1}$) and plasma ionized calcium (normal range: 2.2–2.6 $\text{mEq} \cdot \text{L}^{-1}$) and total calcium concentrations (normal range: 2.2–2.6 $\text{mmol} \cdot \text{L}^{-1}$) were different between the two groups (Table I).

The cumulative dose-response curves were completed in 20 (25) and 18 (16) min for the HPT and control group respectively (NS). More dose increments were required to produce equivalent block, 5.9 (27) vs 4.4 (21) ($P < 0.02$), in the HPT group than in the control group. Consequently the total cumulative dose of vecuronium to achieve 90% block was higher in the HPT group than in the control group, 69 (24) vs 54 (18) $\mu\text{g} \cdot \text{kg}^{-1}$ respectively ($P < 0.02$).

The dose-response curve for patients with hyperparathyroidism showed a shift to the right compared with that for the control group, as can be deduced from the

TABLE I Characteristics of the two groups of patients. Data are presented as mean values and coefficients of variation (%) in parentheses (CV)

	HPT group	Control group	P
<i>n</i>	10	10	
M/F	2/8	3/7	NS
Age (yr)	44 (36)	39 (33)	NS
Weight (kg)	54.7 (19)	58.5 (10)	NS
Body surface area (m^2)	1.58 (11)	1.56 (6)	NS
Ca^{++} ($\text{mEq} \cdot \text{L}^{-1}$)	3.18 (11)	2.45 (3)	<0.01
Total calcium ($\text{mmoles} \cdot \text{L}^{-1}$)	3.05 (9)	2.34 (5)	<0.01
PO_4 ($\text{mmoles} \cdot \text{L}^{-1}$)	0.72 (19)	1.19 (18)	<0.01

TABLE II Summary of data obtained in the study. Results are presented for the group of patients with hyperparathyroidism (HPT) and for the control group. Data are presented as mean values and coefficients of variation (%) in brackets (CV). For the abbreviations of the variables see the explanation in the Results section

Parameter	HPT group	Control group	P
ED_{90} ($\mu\text{g} \cdot \text{kg}^{-1}$)	69 (24)	54 (18)	<0.02
ED_{50} ($\mu\text{g} \cdot \text{kg}^{-1}$)	42 (04)	31 (05)	<0.001
Slope_{dr}	4.96 (17)	4.41 (17)	NS
$\text{Inf. rate}_{90\text{ss}}$ ($\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$)	112 (26)	108 (20)	NS
$\text{EC}_{90\text{ss}}$ ($\mu\text{g} \cdot \text{L}^{-1}$)	298 (09)	299 (06)	NS
RI_{25-75} (min)	12.3 (39)	9.8 (19)	NS

increase of the calculated value of the dose producing 50% block (ED_{50}). The parallelism of the curves is suggested by the absence of a difference in the slopes of the line of the log-logit dose-response relationship of both groups (Table II).

Drug infusion requirements for maintaining a block of 90% for at least 40 min after the first administration of vecuronium and following 20 min at an unchanged rate of infusion were not different between the two groups. ($\text{Inf. Rate}_{90\text{ss}}$, Table II). The mean values of the plasma vecuronium concentrations at the end of the constant infusion period, corresponding to a 90% twitch height depression, were almost identical ($\text{EC}_{90\text{ss}}$, Table II). In one patient we failed to obtain a plasma sample at 90% block and this patient was consequently excluded from the $\text{EC}_{90\text{ss}}$ determination.

In the HPT group, a higher mean value and a wider range of recovery indices were obtained but the difference did not reach the level of significance (Table II).

Discussion

This study was designed to evaluate the influence of primary hyperparathyroidism with chronic hypercalcaemia on the potency and the time course of action of vecur-

onium. The results showed that, initially, a higher dose is needed to obtain a similar degree of block in HPT patients. The dose-response relationships were established in the absence of inhalational agents – which are known to potentiate the effect of vecuronium.¹² The parallel shift to the right of the dose-response curve is in accordance with the findings of Caldwell *et al.*, who showed that the magnitude of vecuronium-induced twitch depression was less for the patients with primary HPT than for control patients.¹⁰

In the present study, the cumulative dose technique was used to assess the potency of vecuronium. The last dose of vecuronium was administered more than 12 min after the first dose. D'Hollander *et al.*, using a similar cumulative dose technique, found an ED₅₀ and an ED₉₀ at 37 and 56 $\mu\text{g} \cdot \text{kg}^{-1}$ respectively.¹³ These findings are comparable with the results obtained in the control patients in the present study. For muscle relaxants with an intermediate time-course of action, it is known that this cumulative method may lead to overestimation of the effective dose, when given as a bolus, due to redistribution taking place during the determination of the dose-response curve. Nevertheless the method remains valid when used to compare neuromuscular blocking effects between two groups.^{14,15}

Plasma concentrations at the end of infusion were almost identical for similar degrees of neuromuscular block. During pseudo steady-state conditions, as reached in our study at the end of the infusion period, plasma concentrations should reflect the concentration of vecuronium in the effect compartment. This was shown earlier by d'Hollander *et al.*¹⁶ and could be confirmed by pharmacokinetic simulation of our study design using the pharmacokinetic data of Sohn *et al.*¹⁷ Based on these results it is difficult to explain differences in potency (ED_{90cum}) by differences in sensitivity (EC_{90ss}). Pharmacokinetic factors, associated with simultaneous increases of the ED_{90cum} dose and the recovery index, may be involved, such as an increase in the (initial) volume of distribution in patients with hyperparathyroidism. Further pharmacodynamic-kinetic modelling studies may be helpful to elucidate the mechanisms involved, since modelling enables us to discriminate between pharmacodynamic and pharmacokinetic factors.

The recovery was somewhat slower in the HPT group although the difference did not reach statistical significance. The absence of a statistical difference in recovery index between the two groups may probably be based on a type II error. This could be the consequence of a larger variation of recovery indices in the HPT group, which hampered detection of statistical differences between groups with a limited number of patients.

The only differences in electrolyte values between the

two study groups were hypercalcaemia and hypophosphataemia in the HPT group. In both groups, electrolyte status and intravascular volume – as assessed by plasma proteins, urea concentrations, and by haematocrit – were normal. Low concentrations of phosphate in plasma may impair neuromuscular function, although interactions with neuromuscular blockers are unknown.¹⁸ The effects of varying calcium concentration on a vecuronium-induced block have been reported previously. Using an isolated guinea-pig nerve-lumbrical muscle preparation, Waud has shown that increases in concentration of ionized calcium decrease the sensitivity of the preparation to d-tubocurarine and pancuronium.² In another study, Gramstad *et al.* have determined the neuromuscular blocking effects of vecuronium at high plasma concentrations of ionized calcium in the cat *in vivo*: an acute increase in Ca⁺⁺ (2.42 meq · L⁻¹ to 3.18 meq · L⁻¹) antagonized an already established vecuronium neuromuscular block of vecuronium, but the size of interaction (increased ED₅₀ by 7–13%) was considered clinically insignificant.³

These laboratory data were obtained following acute changes of calcium ion concentration in other species. In contrast, in primary HPT, the chronic hypercalcaemia might also lead to other processes aimed at counteracting the effects of the increased calcium levels to maintain homeostasis.

In conclusion, this study shows that patients with primary HPT are more resistant to an initial dose of vecuronium than normal patients and that the effective doses to obtain 50 and 90% block (ED₅₀ and ED₉₀) in these patients are respectively 1.35 and 1.3 times higher than in patients with normal parathyroid function. The resistance of patients with primary HPT cannot be explained fully by pharmacodynamic differences, since the concentration of vecuronium at 90% neuromuscular block (EC_{90ss}) in these patients is similar to that in control patients with normocalcaemia.

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