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Does cyclosporine affect the duration of action of vecuronium in renal transplant recipients?

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Abstract: The duration of action of vecuronium was tested in 41 surgical patients to evaluate whether cyclosporine modulates the action of vecuronium. The patients were divided into three groups: 12 patients with normal renal function (group A); 14 renal transplant recipients who had received cyclosporine before surgery (group B); and 15 patients with chronic renal failure undergoing surgery other than renal transplantation and who did not receive cyclosporine (group C). The times to 10% and 20% recovery of the first twitch (REC 10 and REC 20) after intravenous administration of vecuronium 0.12 mg·kg^{-1} were measured using an electromyogram in each group. REC 10 and REC 20 were significantly prolonged in the patients of group B (REC 10: 93 ± 18 min, REC 20: 110 ± 14 min) and group C (REC 10: 80 ± 10 min, REC 20: 89 ± 12 min) than in the patients of group A (REC 10: 39 ± 5 min, REC 20: 45 ± 5 min) ($P < 0.01$). There was no significant difference in the duration of action of vecuronium between the patients of groups B and C. In summary, cyclosporine did not prolong the duration of action of vecuronium in the renal transplant recipients when the same dose was administered compared with the patients with chronic renal failure who did not receive cyclosporine.

Key words: Cyclosporine, Renal transplantation, Vecuronium

Introduction

We previously reported that the duration of action of vecuronium was prolonged in renal transplant recipients compared with patients with normal renal function [1]. We speculated that this prolonged duration of vecuronium in renal transplant recipients was most likely due to cyclosporine, an immunosuppressive drug [2]. Although cyclosporine was reported to potentiate the action of vecuronium in cats [2], these are no prospective clinical reports evaluating its effect on the duration of action of vecuronium. Cyclosporine is usually given to patients with organ failure, and therefore it is difficult to determine whether the prolongation of the action of vecuronium is due to the cyclosporine or the organ failure. In the present study, we evaluated the duration of action of vecuronium in renal transplant recipients who had received cyclosporine before surgery, and compared them with those of patients with chronic renal failure (CRF) who were not given cyclosporine, to evaluate whether cyclosporine prolongs the duration of action of vecuronium.

Methods

Forty-one surgical patients were studied after institutional approval and informed consent were obtained. They were divided into three groups: group A, 12 patients with normal renal function; group B, 14 renal transplant patients who received cyclosporine before surgery; and group C, 15 patients with CRF undergoing surgery other than renal transplantation and who did not receive cyclosporine.

All patients in groups B and C had been dialyzed within 48 h before surgery. In group B, all patients had received oral cyclosporine 6.0–8.3 mg·kg^{-1}·day^{-1} for 5 days before surgery. In addition to cyclosporine, ten patients had received azathioprine 50–100 mg·day^{-1} orally before surgery. Although all patients received intravenous methylprednisolone 500 mg during surgery, no patients received any antibiotics before or during surgery.

All of the patients were premedicated with diazepam 10 mg or rilmazafone 1 mg orally 90 min before the induction of anesthesia. Anesthesia was induced in all patients with intravenous thiamylal 5 mg·kg^{-1}

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and the trachea was intubated following vecuronium 0.12 mg·kg^{-1} i.v. and maintained with isoflurane 0.9–1.2 MAC and 60% nitrous oxide in oxygen, and fentanyl 0.1–0.2 mg i.v. The standard monitors, including an anesthesia gas monitor, were used in all patients during anesthesia. Normothermia and normocapnia were maintained in all patients during anesthesia and surgery.

Neuromuscular function was monitored using an electromyogram monitor (NMT—100-31-01, Datex, Helsinki, Finland). The abductor pollicis twitch was elicited by ulnar nerve stimulation with supramaximal 2-Hz train-of-four square wave impulses (0.2 ms duration) every 20 s at the wrist. Neuromuscular function was evaluated by determining the ratio of the first twitch (T1) to the baseline value before vecuronium administration. The baseline T1 before vecuronium administration was obtained after anesthesia induction by thiamylal and then vecuronium 0.12 mg·kg^{-1} i.v. was administered. The times to 10% and 20% recoveries of T1 (REC 10 and REC 20) after vecuronium administration were measured. REC 20 is thought to be a useful clinical determinant of the duration of action of muscle relaxants. REC 10 was also compared among groups because surgery was over before REC 20 was achieved in some anephric patients. Data are expressed as mean ± SEM. One-way analysis of variance (ANOVA) and the Student's *t*-test were used for statistical analysis of the data and $P < 0.05$ was taken as significant.

Results

The patient's characteristics are shown in Table 1. The patients in group B were significantly younger than in the other two groups ($P < 0.01$). Creatinine and blood urea nitrogen levels in groups B and C were significantly higher than those in group A ($P < 0.01$). The history of hemodialysis therapy in group C was significantly longer than that in group B ($P < 0.01$). Liver function was within normal limits in all patients.

The patients' data during surgery are shown in Table 2. There was a significant difference in base excess between the patients in groups B and C and those in group A ($P < 0.05$), but the pH in all groups was within normal limits. There were no differences among the groups in serum potassium and ionized calcium concentrations. Hemoglobin values in groups B and C were lower in those in group A ($P < 0.01$). Group B received about four times the amount of fluid that group C, received and twice the amount of fluid that group A received ($P < 0.01$). Blood cyclosporine levels in group B ranged from 150 to 200 ng·kg^{-1} on the morning of surgery.

REC 10 and REC 20 after intravenous administration of vecuronium 0.12 mg·kg^{-1} are shown in Table 3. Surgery was over before REC 20 measurement in three patients of group C. In all patients in group B, T1 had recovered to 20% of the baseline value before the transplanted kidney started to function. REC 10 and REC 20 were significantly longer in patients in groups B and C than those in group A ($P < 0.01$). There were no significant differences in these values between groups B and C. There were no significant differences in these values between the patients who received azathioprine preoperatively (REC 10: 87 ± 20 min, REC 20: 111 ± 26 min, $n = 10$) and those who did not (REC 10: 107 ± 4 min, REC 20: 145 ± 10 min, $n = 4$).

Table 1. Patient characteristics

	Group A	Group B	Group C
Number	12	14	15
Male	5	11	9
Female	7	3	6
Age (years)	49.1 ± 3.6[a]	25.6 ± 2.6[a,b]	45.1 ± 3.5[b]
Weight (kg)	55.7 ± 2.8	53.7 ± 3.1	52.9 ± 2.5
Creatinine (mg·dl^{-1})	0.93 ± 0.07	14.02 ± 0.69[c]	9.46 ± 0.67[c]
BUN (mg·dl^{-1})	13.6 ± 4.4	46.2 ± 3.4[c]	66.6 ± 8.4[c]
History of hemodialysis (years)		3.0 ± 0.6[b]	7.3 ± 1.2[b]

(mean ± SEM)
[a] $P < 0.01$ groups A *vs* B.
[b] $P < 0.01$ groups B *vs* C.
[c] $P < 0.01$ *vs* Group A.
BUN, blood urea nitrogen.

Table 2. Patient data during surgery

	Group A	Group B	Group C
pH	7.44 ± 0.02	7.42 ± 0.02	7.39 ± 0.02
BE (mEq·l^{-1})	0.2 ± 0.7	−1.7 ± 0.9*	3.2 ± 0.9*
K (mEq·l^{-1})	3.7 ± 0.1	3.8 ± 0.2	4.4 ± 0.3
Ca^{++} (mmol·l^{-1})	1.02 ± 0.04	1.08 ± 0.04	1.08 ± 0.06
Hb (g·dl^{-1})	12.2 ± 0.4	9.3 ± 0.2**	9.0 ± 0.3**
Temperature (°C)	36.4 ± 0.2	35.9 ± 0.1	36.2 ± 0.1
Fluid (ml·kg^{-1}·h^{-1})	6.6 ± 1.0	11.9 ± 0.6*	3.2 ± 0.6**

(mean ± SEM)
* $P < 0.05$ *vs* group A.
** $P < 0.01$ *vs* group A.
Hb, hemoglobin; BE, base excess.

Table 3. Time to 10% and 20% recoveries of the first twitch (REC10 and REC20)

	Group A	Group B	Group C
REC 10 (min)	39 ± 5 ($n = 12$)	93 ± 18* ($n = 14$)	80 ± 10* ($n = 15$)
REC 20 (min)	45 ± 5 ($n = 12$)	110 ± 20* ($n = 14$)	89 ± 12* ($n = 12$)

(mean ± SEM)
* $P < 0.01$ *vs* group A.

Discussion

In some previous studies, it was reported that cyclosporine could potentiate the action of vecuronium. Gramstad et al. showed that vecuronium blockade was increased by 50%–95% following intravenous administration of cyclosporine 0.8 $mg \cdot kg^{-1}$, less than the standard clinical dose, and from 50% to 78% by vehicle alone [2]. Sidi et al., who performed a prospective study, showed that cyclosporine was related to prolonged neuromuscular blockade and respiratory failure after renal transplantation [3]. There are case reports indicating that the duration of action of vecuronium was prolonged in patients receiving cyclosporine [4,5]. Cyclosporine is usually administered to patients undergoing organ transplantation or who already have transplanted organs. Accordingly, it is difficult to determine whether the prolongation of action of vecuronium is due to cyclosporine itself or to the effect of organ failure. In this study, we compared the duration of action of vecuronium in patients who had received cyclosporine before surgery with that in patients who did not receive cyclosporine. Renal function was impaired in groups B and C, and there was no difference in renal function between these two groups. Our results showed that the duration of action of vecuronium was significantly longer in patients with CRF than in patients with normal renal function. This is in accordance with our previous report [1]. However, the duration of action of vecuronium in patients who had received cyclosporine before surgery did not differ from that in patients who did not receive cyclosporine when the same dose of vecuronium was administered intravenously after anesthesia induction.

In the previous reports of the interaction between cyclosporine and vecuronium, cyclosporine was administered intravenously, but in our renal transplant recipients, it was administered orally before surgery. The blood cyclosporine levels in our patients on the morning of surgery were within the therapeutic ranges. The intravenous preparation of cyclosporine was dissolved in an ethanol-cremophor vehicle. The vehicle itself was reported to potentiate the neuromuscular blockade of vecuronium and pancuronium [2,6,7], but to a lesser degree and for a shorter period than the combination of cyclosporine and vehicle [2].

We should consider other factors besides cyclosporine to explain the duration of action of vecuronium in this study. First, the renal transplant patients received almost four times as much fluid as the patients with CRF, who did not receive cyclosporine. Due to the hydrophilic nature of vecuronium, as with all neuromuscular blocking drugs, this factor would alter the effective plasma vecuronium concentration. Although we did not measure the plasma vecuronium concentrations in this study, we speculate that the effective concentration was lower in the renal transplant patients. It is possible that cyclosporine increases the recovery time after vecuronium administration, but due to fluid administration and the potential decrease in the effective vecuronium concentration, recovery may be observed sooner than in patients receiving less fluid (i.e., comparable to group C). This may explain why the duration of action of vecuronium in the renal transplant patients was more prolonged than in patients with CRF who had not received cyclosporine, when compared at the same effective concentration. The serum vecuronium concentrations should be evaluated in this type of clinical study. Further, ten renal transplant recipients received azathioprine orally before surgery. However, there were no significant differences in REC 10 and REC 20 between those patients who received azathioprine and those who did not. Although azathioprine was reported to attenuate the action of *d*-tubocurarine in cats [8], it was thought to produce a relatively weak and transient antagonizing effect on vecuronium [9]. No antagonizing effect of azathioprine was observed in our study. Vanacker and van be Walle showed that the time until 25% T1 twitch recovery from vecuronium was significantly longer in renal transplant patients than in other patients with CRF, and the prolongation was speculated to be mainly due to the tobramycin which the renal transplant recipients had received before surgery [10]. In the present study, no patients received antibiotics before or during surgery.

In conclusion, our results indicate that cyclosporine does not prolong the duration of action of vecuronium when the same dose is administered to CRF patients not receiving cyclosporine.

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