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Dose requirements of continuous infusion of rocuronium and atracurium throughout orthotopic liver transplantation in humans

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Abstract: Objective: To compare the dose requirements of continuous infusion of rocuronium and atracurium throughout orthotopic liver transplantation (OLT) in humans. Methods: Twenty male patients undergoing liver transplantation were randomly assigned to two comparable groups of 10 patients each to receive a continuous infusion of rocuronium or atracurium under intravenous balanced anesthesia. The response of adductor pollicis to train-of-four (TOF) stimulation of unlar nerve was monitored. The infusion rates of rocuronium and atracurium were adjusted to maintain T1/Tc ratio of 2%~10%. The total dose of each drug given during each of the three phases of OLT was recorded. Results: Rocuronium requirement, which were (0.468±0.167) mg/(kg·h) during the paleohepatic phase, decreased significantly during the anhepatic phase to (0.303±0.134) mg/(kg·h) and returned to the initial values at the neohepatic period ((0.429±0.130) mg/(kg·h)); whereas atracuruim requirements remained unchanged during orthotopic liver transplantation. Conclusions: This study showed that the exclusion of the liver from the circulation results in the significantly reduced requirement of rocuronium while the requirement of atracurium was not changed, which suggests that the liver is of major importance in the clearance of rocuronium. A continuous infusion of atracurium with constant rate can provide stable neuromuscular blockade during the three stages of OLT.

Key words: Rocuronium, Atracurium, Orthotopic liver transplantation
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INTRODUCTION

Rocuronium bromide is a new steroidal nondepolarizing neuromuscular blocking drug that has a faster onset of action than other nondepolarizing neuromuscular blocking drugs. The liver is the major route for its elimination. On the other hand, impaired liver function does not alter either atracurium's elimination or plasma clearance (Ward and Neill, 1983; Pitter *et al*., 1990). The exclusion of the hepatic circulation and function during the anhepatic phase of orthotopic liver transplantation (OLT) did not alter requirements of atracurium significantly in humans (Farman *et al*., 1986). We have therefore compared the dose requirements of continuous infusion of rocuronium and atracurium throughout OLT in humans.

METHODS

After obtaining institutional ethics approval and informed consent, 20 male patients (aged 27~65 years) undergoing liver transplantation with severe liver dysfunction (Child-Pugh Class C) due to liver cirrhosis were included in this study. The etiology of liver cirrhosis was hepatitis B in all patients. They were randomly assigned by random number table to two groups of 10 patients each to receive rocuronium or atracurium as the only neuromuscular blocking

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drug during the procedure. Patients were excluded if they had cardiac, pulmonary, renal, muscular, or electrolyte disorders, as were patients with recent exposure to medications known to interfere with neuromuscular transmission.

On arrival in the operation room, the electrocardiogram, heart rate, pulse oximetry, end-tidal P_{CO_2} and invasive blood pressure were monitored continuously in all patients. Anesthesia was induced with intravenous midazolam 0.05~0.1 mg/kg, etomidate 0.3 mg/kg and fentanyl 3~5 μg/kg. Controlled ventilation of the lung was conducted with O_2-enriched air to maintain normocapnia, and skin temperature over the adductor pollicis was maintained greater than 32 °C. Body temperature was monitored by nasopharyngeal probe and maintained at 35.0~37.5 °C with a warming blanket.

When stable anesthesia was achieved, neuromuscular function was assessed using an accelograph. The ulnar nerve was stimulated at the wrist with a nerve stimulator in train-of-four (TOF) mode at 2 Hz every 12 s through surface electrodes. After stabilization of control responses (Tc) over a period of about 10 min, 0.6 mg/kg of rocuronium or atracurium was given to facilitate tracheal intubation. Anesthesia was maintained with a continuous infusion of propofol (4 mg/(kg·h)) and intermittent bolus injection of fentanyl 3~5 μg/kg and midazolam 0.05~0.1 mg/kg as necessary. The total dosage of fentanyl and midazolam were controlled within 30 μg/kg and 0.3 mg/kg, respectively. The height of the first twitch in the TOF with respect to the Tc (T1/Tc) was recorded continuously. When recovery from the initial bolus dose was evident by a single twitch depression (T1/Tc) of more than 5%, an infusion of rocuronium or atracurium was started. The initial rate of these infusions was 0.4 mg/(kg·h) for rocuronium and 0.6 mg/(kg·h) for atracurium. The rates of these infusions were adjusted by an increase or decrease of 25% every 6~15 min to maintain T1/Tc of 2%~10%. The total dose of each drug given during each of the three phases of OLT was recorded. To calculate the requirements during a phase, the dose given during that phase was divided by the duration of that phase and body weight.

Repeated analysis of variance followed by Fisher's test was used. Statistical significance was inferred if $P<0.05$.

RESULTS

The two groups of patients were comparable in age, weight, preoperative values of creatinine, preoperative values of potassium, Child-Pugh score, the duration of each phase of OLT, red blood cell and fresh frozen plasma replacements, and the total doses of fentanyl and midazolam (Table 1 and Table 2). All patients were normothermic throughout the observation.

Rocuronium requirement, which were (0.468±0.167) mg/(kg·h) during the paleohepatic phase, decreased significantly during the anhepatic phase to (0.303±0.134) mg/(kg·h) and returned to the initial values at the neohepatic period ((0.429±0.130) mg/(kg·h)); whereas atracurium requirements remained unchanged during the three stages ((0.602±0.111), (0.507±0.096), and (0.534±0.101) mg/(kg·h)) (Table 3).

Table 1 Clinical characteristics of the patients (*n*=20, mean±*SD*)

Characteristics	Rocuronium	Atracurium
Age (years)	47.1±7.0 (38~62)	48.6±10.8 (27~65)
Weight (kg)	68.0±9.2 (54~80)	65.4±9.5 (52~82)
Child-Pugh score	10.6±0.52	10.6±0.84
Preoperative values of creatinine (mmol/L)	88±25	84±19
Preoperative values of potassium (mmol/L)	4.19±0.63	4.23±0.44

Table 2 Intraoperative data of the two groups (*n*=20, mean±*SD*)

Group	Duration (min)			Red blood cell (u)	Fresh frozen plasma (ml)	Fentanyl (μg/kg)	Midazolam (mg/kg)
	Paleohepatic	Anhepatic	Neohepatic				
Rocuronium	92±24	53±8	196±35	17.4±7.0	2395±814	22.1±5.4	0.22±0.08
Atracurium	85±32	52±6	184±52	18.9±7.5	2513±1260	20.8±7.8	0.25±0.07

Table 3 Doses of two drugs during each period (mg/(kg·h))

Phase	Rocuronium	Atracurium
Paleohepatic phase	0.468±0.167	0.602±0.111
Anhepatic phase	0.303±0.134*	0.507±0.096
Neohepatic phase	0.429±0.130	0.534±0.101

*$P<0.05$, compared with that of paleohepatic and neohepatic phases

DISCUSSION

In the present study, we observed reduced dose requirements for rocuronium during the anhepatic period while achieving stable neuromuscular blockade throughout the OLT procedure, whereas the dose requirement of atracurium was unchanged.

Rocuronium bromide is eliminated primarily via the liver. When the liver is excluded from the circulation in cat, rocuronium's clinical duration of action increases almost threefold (Khuenl-Brady *et al.*, 1990) and Gao *et al*.(2002) showed that patients undergoing liver transplantation had a 7%~50% decrease in rocuronium concentration during the neohepatic phase compared with the anhepatic phase. These findings suggested that the pharmacokinetics and pharmacodynamics of rocuronium might be altered by liver disease. After giving a single bolus of 0.6 mg/kg rocuronium to patients with liver disease, Magorian *et al*.(1995) observed that hepatic impairment prolonged the elimination half-life of rocuronium, which might result in a longer duration of action in patients with liver disease, particularly after prolonged administration. A recent study using continuous infusion of rocuronium during OLT in humans showed that the rocuronium infusion requirements was decreased by 24% during the anhepatic phase and rocuronium requirement during the neohepatic phase was increased when the grafted liver started functioning after revascularization (Gao *et al.*, 2003). Our results are therefore accorded with these findings. However, in the study of Gao *et al*.(2002) there was no change in the plasma rocuronium concentration during the anhepatic phase compared with the paleohepatic phase. In the present study, we have found that rocuronium requirement during the paleohepatic phase decreased significantly during the anhepatic phase, which do not totally support the kinetic data of Gao *et al*.(2002). We noticed that in that paper, venovenous bypass was used for all patients during the anhepatic period and loss of rocuronium to the venovenous bypass circuit may be the possible reason for lack of change in plasma rocuronium concentration (Fisher *et al.*, 1997). On the other hands, atracurium is hydrolyzed by nonspecific esterases and spontaneously decomposes at physiological pH and temperature by Hofmann elimination (Fisher *et al.*, 1986). No increase in plasma concentration of atracurium was found during the anhepatic period of OLT in pigs (Pitter *et al.*, 1990), which suggested that the liver does not play a important role in the clearance of atracurium. Two further studies during OLT in humans supported the point, showing no significant changes in atracurium requirements during the three stages of OLT (Farman *et al.*, 1986; O'Kelly *et al.*, 1991). Our results are also accorded with these findings.

Several nonhepatic factors that can influence the doses of neuromuscular blocking drugs may be encountered during OLT. Our results were controlled for renal function and other factors such as age, weight, anesthetic drugs, hypothermia and blood loss. No significant difference between groups was found for any of these factors.

In summary, this study showed that the exclusion of the liver from the circulation results in significantly reduced requirement of rocuronium while the requirement of atracurium is not changed, which suggests that the liver is of major importance in the clearance of rocuronium. A continuous constant rate infusion of atracurium can provide stable neuromuscular blockade during the three stages of OLT.

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