enteric traction during anesthesia that indicate the response to be an occasional decrease in systemic blood pressure due to venous pooling with decreased return to the heart and subsequent decrease in CO. Our data indicate that the response is a nearly universal decrease in MAP secondary to marked systemic vasodilation accompanied by a compensatory increase in CO. Changes in HR, CVP, and PCWP varied, and there seemed to be no significant effect on the pulmonary vascular system.

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Failure of Metronidazole to Alter a Vecuronium Neuromuscular Blockade in Humans

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Neuromuscular blocking effects of muscle relaxants can be enhanced by some antibiotics, especially aminoglycosides, polymixins, and tetracyclines.[1–4] Recently, in the last few years, prophylactic administration of large doses of nitroimidazole-type drugs have protected patients against systemic gram-negative bacterial infections during and after elective colonic surgery.[5] Recently, McIndewar and Marshall found a marked potentiation of a neuromuscular blockade from vecuronium by metronidazole in α-chloralose/pentobarbital-anesthetized cats.[6] Using routine neuromuscular monitoring procedures, we sought to determine whether a vecuronium neuromuscular blockade is enhanced in patients receiving a preoperative iv administration of metronidazole.

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Key words: Neuromuscular relaxants: vecuronium. Antibiotics: metronidazole.

MATERIALS AND METHODS

The present study was approved by the Ethical Committee of Human Research of the Brussels Free University. Cumulative dose–effect curves were determined for vecuronium following metronidazole administration. Adult patients of both sexes (ASA Class I–II) were selected after their informed consent had been obtained. None of these patients had any clinical or biochemical evidence of renal or liver function abnormalities. The patients were free of neurologic abnormalities. One hour before anesthesia, all the patients received diazepam 200 $\mu g \cdot kg^{-1}$ orally.

Before the start of anesthesia, a displacement transducer (UC3 cell Statham), fitted with tension attenuator

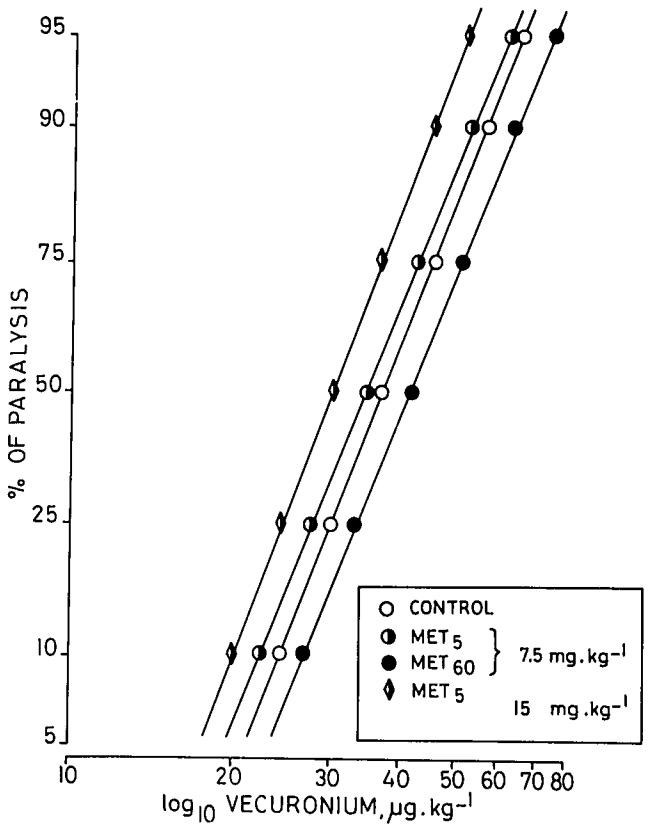

FIG. 1. Logit transform of the per cent of paralysis *versus* cumulative dose ($\mu g \cdot kg^{-1}$) of vecuronium in the presence of different doses of preoperative iv administration of metronidazole. ◑ MET 5 = patients receiving 7.5 $mg \cdot kg^{-1}$ of metronidazole 5 min before vecuronium administration; ● MET 60 = patients receiving 7.5 $mg \cdot kg^{-1}$ of metronidazole 60 min before the vecuronium administration; ◊ MET 5 = patients receiving 15 $mg \cdot kg^{-1}$ of metronidazole 5 min before the vecuronium administration; O CONTROL = patients receiving saline 5 min before the vecuronium administration.

(UL4-20, Statham) incorporated in a hand-grip was secured with adhesive strips to the right hand of the patient to measure isometric thumb displacement. Two 25-gauge needles were placed subcutaneously close to the ulnar nerve at the wrist, and contraction of the adductor pollicis muscle was induced by square-wave pulses lasting 0.2 ms and delivered at 0.1 Hz from a Grass S88® stimulator. The stimulation voltage equaled 1.5 times that required to evoke a maximal twitch response. Anesthesia was induced with methohexital 1,000 $\mu g \cdot kg^{-1}$ iv and fentanyl 5 $\mu g \cdot kg^{-1}$ iv and maintained by supplementary doses of 100 $\mu g \cdot kg^{-1}$ of methohexital if necessary. When the patient was unconscious, ventilation was controlled until intubation of the trachea which was performed after the cumulative dose-effect study had been completed and before the start of surgery.

When a consistent control tension was obtained, the patients of Group 1 (n = 5) received 7.5 $mg \cdot kg^{-1}$ iv metronidazole diluted in 150 ml of saline, in a 10-min period, 5–10 min after induction of anesthesia; in Group 2 (n = 5) −15 $mg \cdot kg^{-1}$ iv metronidazole was given, in a 10-min period, 5–10 min after the start of anesthesia; in Group 3 (n = 5) 7.5 $mg \cdot kg^{-1}$ iv metronidazole was administered over a 10-min period 1 h before the start of anesthesia. In Group 4 (n = 5), 150 ml of saline was given iv in a 10-minute period, 5–10 min after the start of anesthesia. At the end of metronidazole or saline infusions, the cumulative dose–effect curve of vecuronium was established according to Donlon *et al.*[7] by giving a 20 $\mu g \cdot kg^{-1}$ bolus of vecuronium followed by supplementary doses of 10 $\mu g \cdot kg^{-1}$ until twitch tension was completely obliterated. The temperature of the body core and exposed arm was kept within normal limits by the use of a water warming blanket and surgical sheets. The ventilation was adjusted to maintain normocapnic conditions controlled by regular checks of the p_{CO_2} of peripheral venous blood as previously described.[8]

Linear regression analysis between the logit transform of twitch tension and the log cumulative dose of vecuronium were performed with the SPSS programs.[9] Differences between the control series and the metronidazole series were analysed statistically using Wilcoxon rank test. Statistically significant differences were assumed at $\alpha \leq 0.05$.

In the second part of the study, 30 patients (ASA Class I–II) scheduled for abdominal surgery were selected as described above. Fifteen patients undergoing colorectal surgery received 7.5 $mg \cdot kg^{-1}$ iv of metronidazole over a 10-min period after the start of anesthesia; the other 15 patients received no prophylactic preoperative antibiotics.

In these 30 patients, vecuronium was given as a loading dose of 100 $\mu g \cdot kg^{-1}$, followed by supplementary injection of 20 $\mu g \cdot kg^{-1}$ each time the twitch tension recovered to 25% of its initial value. In these series the time intervals between five successive vecuronium reinjections were compared. The results were expressed as percentage of the duration of the first maintenance dose of 20 $\mu g \cdot kg^{-1}$ of vecuronium. Differences between the control and the metronidazole series were analyzed by analysis of variance. Statistically significant differences were assumed at $P < 0.05$.

RESULTS

The results determined for all the series investigated are illustrated in figure 1. Under the conditions of the study, differences were noted between the control group (Group 4)—ED_{50}: 37 ± 1 $\mu g \cdot kg^{-1}$; and ED_{90}: 56 ± 1

$\mu g \cdot kg^{-1}$ (mean ± SD)—and the series of patients receiving 15 $mg \cdot kg^{-1}$ at the start of anesthesia (Group 2)—ED_{50}: 30 ± 1 $\mu g \cdot kg^{-1}$; and ED_{90}: 45 ± 1 $\mu g \cdot kg^{-1}$ (Wilcoxon rank test: $2\alpha = 0.10$). No statistically significant differences were noted between the control group and either the patients receiving 7.5 $mg \cdot kg^{-1}$ of metronidazole iv immediately after the start of anesthesia (Group 1) or those receiving metronidazole 60 min before the start of anesthesia (Group 3).

The time intervals, noted for five reinjections of 20 $\mu g \cdot kg^{-1}$ of vecuronium once twitch height returned to 25% of the control value, in patients receiving metronidazole 7.5 $mg \cdot kg^{-1}$ at the start of anesthesia in comparison to patients receiving no prophylactic antibiotherapy is illustrated in figure 2. No significant (variance analysis) intergroup differences were observed.

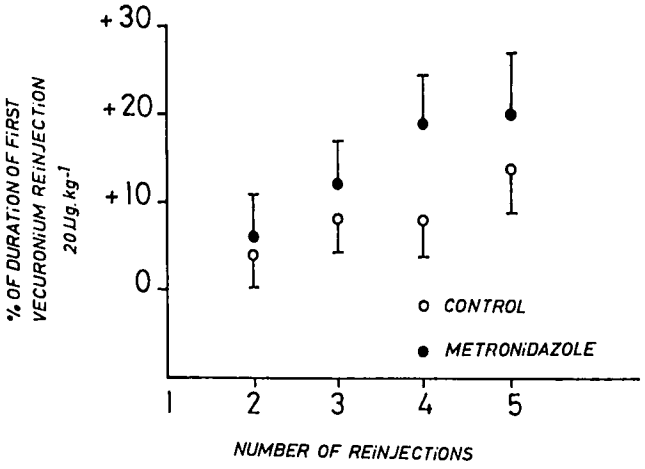

FIG. 2. Evolution of the time intervals observed after five vecuronium reinjections (20 $\mu g \cdot kg^{-1}$) in patients receiving either 7.5 $mg \cdot kg^{-1}$ metronidazole (n = 15, ●) or saline as placebo (n = 15, ○). The results are expressed as a percentage of the duration of the first reinjection of 20 $\mu g \cdot kg^{-1}$ of vecuronium. No statistically significant differences between the two series are observed. Results are presented as mean + SEM.

DISCUSSION

For precise quantitative comparison of the potency of different muscle relaxants, two different techniques have been proposed: single bolus dose and cumulative dose responses.[8,10] Strict agreement between the results obtained by these two techniques has been documented for *d*-tubocurarine and pancuronium[10] but not for the muscle relaxants of medium to short duration of action, such as vecuronium.[11] With vecuronium, the start of paralysis recovery occurs before the whole cumulative dose response study is achieved, leading to dosage overestimation. In these conditions, this technique cannot be used to deduce, for example, the exact 50% bolus blocking dose. However, the cumulative dose response technique remains valid and particularly useful to compare neuromuscular blocking effects in presence and absence of potential interacting agents as illustrated by McIndewar and Marshall.[6]

Although the action of metronidazole upon mechanical activity of striated muscle induced by acetylcholine or by nerve stimulation has been studied in animals, the experimental results remain difficult to interpret.[6,12] In *in vitro* observations, bath concentration of about 1 $mg \cdot ml^{-1}$ of metronidazole increased the contractile force of frog and rat striated muscles in the absence and in the presence of *d*-tubocurarine.[9] In alpha-chloralose–pentobarbital anesthetized cats, *in vivo* potentiation of the effects of vecuronium-induced neuromuscular blockade, assessed by the cumulative doses method, was only observed with some delay—1 h—after the termination of a 20 $mg \cdot kg^{-1}$ iv metronidazole administration.[6] No potentiation was seen when pancuronium is used instead of vecuronium. McIndewar and Marshall explained the slow onset of action of metronidazole upon vecuronium myorelaxant properties in cats as a hypothetical effect of metronidazole metabolites.

In view of the present results, the clinical situation appears somewhat different: delayed—1 h—potentiation of vecuronium blockade was not observed in patients receiving acute 7.5 $mg \cdot kg^{-1}$ iv metronidazole administration. The sole potentiation observed in the cumulative doses study occurred rapidly—10 min—after metronidazole administration and was dose dependent. The ED_{90} values of vecuronium for Group 1 (7.5 $mg \cdot kg^{-1}$ iv metronidazole) and Group 2 (15 $mg \cdot kg^{-1}$ iv metronidazole) were 53 and 45 $\mu g \cdot kg^{-1}$, respectively, whereas the ED_{90} of the control group was 56 $\mu g \cdot kg^{-1}$. The absence of a delayed potentiation of the neuromuscular blocking effects of vecuronium by metronidazole shown by the cumulative dose experiments was confirmed by data obtained in the second part of the study using the reinjections technique, *i.e.*, no increase in the time interval between supplementary doses of vecuronium was observed following preoperative administration of 7.5 $mg \cdot kg^{-1}$ iv metronidazole.

To conclude, under the conditions of this study, the delayed metronidazole–vecuronium interaction seen previously in the cat could not be demonstrated. In anesthetized patients, the neuromuscular blocking effects of vecuronium appear to be very slightly enhanced only shortly after the rapid infusion of higher than usual doses of metronidazole. As evidenced in the first part of this study, the slight potentiation of the neuromuscular blocking effect of vecuronium was only noted in the patients—Group 2—receiving in 10 min 15 $mg \cdot kg^{-1}$ of metronidazole. This dose represents actually twice

the usual iv preoperative dose of metronidazole necessary to obtain therapeutic blood levels. In humans, the therapeutic metronidazole blood level of 4 $ng \cdot ml^{-1}$ already is attained and maintained for 6–8 h after slow—20 min—iv administration of 7.5 $mg \cdot kg^{-1}$ of metronidazole.[13,14] Therefore, it is unlikely that following the administration of one usual iv clinical dose of metronidazole a potentiation of vecuronium induced neuromuscular block will occur in normal subjects.

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Persistent Phrenic Nerve Paresis Following Interscalene Brachial Plexus Block

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Accidental, temporary blockade of the phrenic nerve occurs in 36% of patients having interscalene brachial plexus block,[1] but long-lasting injury to the phrenic nerve has not been reported. We describe a phrenic nerve paresis that has persisted more than 3 years following an interscalene brachial plexus block.

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Key words: Complications: nerve injury; Anesthetic techniques: regional; interscalene brachial plexus block.

Report of a Case

A 64-year-old man, 180 cm tall, weighing 95.5 kg, and in good health except for well-controlled hypertension, was hospitalized for elective shoulder surgery. Admission physical examination was unremarkable except for decreased strength and limited range of motion of the right shoulder. His preoperative chest roentgenogram was normal except for basilar fibrosis.

Premedication was with fentanyl 25 μg, droperidol 1.25 mg, pentobarbital 50 mg, and scopolamine 0.4 mg, all intramuscularly. After establishing an iv infusion, electrocardiograph, and (cuff) blood pressure monitoring, the nerve block was attempted using the technique described by Winnie.[2] A 22-gauge, short-bevel needle was oriented with the bevel parallel to the nerve fibers, and after some difficulty, a paresthesia to the shoulder was elicited. Within 30–45 s following injection of bupivacaine, 50 ml 0.5% solution with epinephrine, 1:200,000, the patient had a generalized seizure develop. He was promptly treated with an oropharyngeal airway, positive-pressure oxygen via mask, and sodium thiopental 125 mg iv. Further details about the performance of the block or the resulting spread of anesthesia are not available from the written medical record.

Surgery was canceled, and the patient was taken to the recovery