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Influence of carbamazepine on the dose–response relationship of vecuronium†

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SUMMARY

We have determined the cumulative dose–response relationship for vecuronium from the evoked compound electromyogram of the hypothenar muscles in eight patients who were receiving carbamazepine. The ED_{50}, ED_{90} and ED_{95} were 29, 52 and 64 μg kg^{-1}, respectively, and were significantly different ($P < 0.05$) from those of a control group (ED_{50}, ED_{90} and ED_{95} 21, 36 and 44 μg kg^{-1}, respectively). (Br. J. Anaesth. 1994; **72**: 125–126)

KEY WORDS

Pharmacology: interaction, vecuronium, carbamazepine. Neuromuscular relaxants: vecuronium.

It has been shown that the dose requirements of patients receiving dimethyltubocurarine, pancuronium and vecuronium are increased when phenytoin or carbamazepine is given concurrently [1–3], despite earlier *in vitro* work which demonstrated enhanced block induced by tubocurarine in the presence of a wide variety of anticonvulsant drugs [4].

Ornstein and colleagues have described dose–response curves for vecuronium and atracurium in patients taking phenytoin; there was no significant alteration with atracurium, but with vecuronium there was a parallel shift of the curve to the right by approximately 50% compared with that of a control group of patients not taking phenytoin [2]. Roth and Ebrahim have demonstrated previously resistance to pancuronium in patients receiving carbamazepine who underwent neurosurgery for excision of seizure foci, and have reported a shorter time to recovery and shorter recovery index for vecuronium, but not atracurium [3].

The present study was designed to determine the dose–response relationship for vecuronium in patients chronically receiving carbamazepine. In addition, our control group was sufficiently large for us to compare dose–response curves for patients whose mean age differed by approximately 20 yr.

METHODS AND RESULTS

With institutional Ethics Committee approval and informed consent, we studied 24 patients, eight of whom were receiving carbamazepine in a daily dose of 1200–1600 mg and were undergoing craniotomy for excision of seizure foci (group 1). In addition to carbamazepine, the patients in group 1 were receiving clorazepate (three patients), valproic acid (two), perphenazine (one) and sulfasalazine (one). The remaining 16 patients (group 2) were not receiving anticonvulsants and were undergoing a variety of general surgical procedures. Patients in group 2 were receiving dexamethasone (two patients), famotidine (two), fluoxetine (one), sucralfate (one), hydrocodone (one), propoxyphene (one), diclofenac (one), indomethacin (one), chlorpromazine (one), amitriptyline (one), allopurinol (one), hydrochlorothiazide (one) and oestrogen (one). Patients were admitted into the study with ASA physical scores I–III, but were excluded if they had cardiac, hepatic, renal or neuromuscular disease. On that morning of surgery, patients in group 1 received carbamazepine (eight), chlorazepate (three), valproic acid (two) and perphenazine (one) and those in group 2 received dexamethasone (two), amitriptyline (one) and chlorpromazine (one) together with premedication of midazolam 1–3 mg i.m. 1–2 h before surgery.

Neuromuscular function was monitored by a Puritan Bennett-Datex NMT Monitor 221 using a supramaximal stimulus of the ulnar nerve at the wrist of four square-wave impulses of 100 ms in duration, delivered at a frequency of 2 Hz every 10 s. The integrated electromyogram (EMG) was recorded from the evoked response of the muscles of the hypothenar eminence. The monitor was applied before induction of anaesthesia with thiopentone 3–5 mg kg^{-1} and sufentanil 0.5 μg kg^{-1} i.v. Anaesthesia was maintained with 60% nitrous oxide in oxygen, and supplementary doses of thiopentone 1 mg kg^{-1} as required. Ventilation was provided with a face mask to maintain $P_{E'CO_2}$ in the range 4.0–4.7 kPa.

After stabilization of the EMG, cumulative doses of vecuronium were given until at least 95% first twitch (T1) depression was observed. Each drug increment was given only after the effect of the previous dose had reached a stable response as defined by three equal, consecutive first twitches. The initial dose of vecuronium was 10 μg kg^{-1}, but the incremental doses were either 5 μg kg^{-1}, 10 μg

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TABLE I. *Patient characteristics and ED_{50}, ED_{90} and ED_{95} values (mean (SD)) for the effect of vecuronium on neuromuscular transmission assessed by electromyogram. Patients in group 1 were receiving carbamazepine in addition to other drugs; those in group 2 were not receiving carbamazepine.* * $P < 0.05$, *group 1* vs *group 2*

	Group 1	Group 2
Age (yr)	27.5 (17–46)	38.8 (17–57)*
Height (cm)	170 (7.9)	164.6 (9.6)
Weight (kg)	71.6 (12)	68 (14.4)
BSA (m^2)	1.8 (0.2)	1.75 (0.2)
Sex (M/F)	4/4	3/13
ED_{50} ($\mu g\ kg^{-1}$)	29 (5)	21 (2)*
ED_{90} ($\mu g\ kg^{-1}$)	52 (10)	36 (5)*
ED_{95} ($\mu g\ kg^{-1}$)	64 (15)	44 (7)*

kg^{-1} or 20 $\mu g\ kg^{-1}$, depending on the response to the initial dose. Dose–response curves were constructed for each patient using regression analysis of the logit transformation of T1 depression and log dose.

Data were analysed using Student's *t* test, Fisher's exact chi-square test and ANOCOV where appropriate. $P < 0.05$ was considered significant.

Apart from age, the groups were similar in characteristics. The mean dose required to produce 50%, 90% and 95% depression of T1 was increased by approximately 40% in patients taking carbamazepine (table I).

COMMENT

We have demonstrated that the iminostilbene, carbamazepine, while structurally unrelated to phenytoin, induces resistance to vecuronium to a similar degree. The dose–response curve was moved to the right and parallel to that of the control group by approximately 40–50% in patients receiving anticonvulsants such that the ED_{50}, ED_{90} and ED_{95} for vecuronium were the same whether the anticonvulsant was phenytoin [2] or carbamazepine. The ED_{95} of vecuronium in patients receiving phenytoin is increased from 48 to 69 $\mu g\ kg^{-1}$ [2] and we have shown that in patients taking carbamazepine it is increased from 44 to 64 $\mu g\ kg^{-1}$.

The explanation for resistance to non-depolarizing neuromuscular blocking drugs during chronic anticonvulsant therapy has been the cause of much debate, although recent evidence suggests both pharmacokinetic and pharmacodynamic mechanisms. In their description of the interaction of phenytoin and dimethyltubocurarine, Ornstein and colleagues were unable to demonstrate differences from control in the plasma decay curve of dimethyltubocurarine, suggesting similar pharmacokinetics, but in that and later work, these investigators demonstrated shift of the dose–response curve to the right for both dimethyltubocurarine and vecuronium [1, 2]. However, despite similar decay curves for the plasma concentration of total drug, decreased duration and recovery index have both been described as typical of this interaction, suggesting that the pharmacokinetics of the neuromuscular blocker may, indeed, be altered. This has been confirmed by Kim and colleagues, who described the interaction of phenytoin and metocurine in a rat model [5]. These investigators demonstrated that chronic anticonvulsant therapy induced an increase in α-acid glycoprotein which correlated negatively with the free fraction of dimethyltubocurarine. Furthermore, they were able to demonstrate an increase in acetylcholine receptors on the muscle membrane of the treated rats, suggesting a pharmacokinetic and a pharmacodynamic explanation for the resistance to non-depolarizing neuromuscular blocking drugs.

The age range of our control patients (17–57 yr) enabled us to derive a dose–response relationship for two groups whose mean ages were 29 and 49 yr. This age difference of 20 yr had no influence on the potency of vecuronium. Despite using a cumulative dose–response technique, our method of determining potency yielded results similar to those described by Bell, Mirakhur and Clarke, who used a single dose method [6]. For adult patients with a mean age of 38 yr and elderly patients with a mean age of 74.3 yr, Bell's group described ED_{50} values of 23.1 and 25.7 $\mu g\ kg^{-1}$, respectively, and ED_{95} values of 39.6 and 43.1 $\mu g\ kg^{-1}$. These differed marginally from our results in that the ED_{50} we obtained (21 $\mu g\ kg^{-1}$ for younger patients and 20 $\mu g\ kg^{-1}$ for older patients) was slightly smaller and the ED_{95} (42 $\mu g\ kg^{-1}$ for younger patients and 46 $\mu g\ kg^{-1}$ for older patients) was slightly greater. These discrepancies could be explained by the different methodology: we used the evoked compound electromyogram derived from the muscles of the hypothenar eminence, whereas Bell's group transduced the force of contraction of the adductor pollicis muscle.

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