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FACTORS LIMITING THE RATE OF TERMINATION OF THE NEUROMUSCULAR BLOCKING ACTION OF FAZADINIUM DIBROMIDE

M.B. TYERS

Department of Pharmacology, Allen & Hanburys Research Ltd., Ware, Hertfordshire

1 Reasons for the termination of the neuromuscular blocking action of fazadinium dibromide have been investigated.

2 In the anaesthetized cat, maximum neuromuscular block of tibialis anterior muscle twitches following rapid intravenous injection of fazadinium was obtained as the injection bolus passed through the muscle, indicating that fazadinium very readily crosses capillary membranes.

3 The half-life of plasma clearance of fazadinium was about 1 min in both cat and man, despite a 10 fold difference in duration of action in these species. Plasma samples were bioassayed for neuromuscular blocking activity on an isolated, superfused phrenic nerve-diaphragm preparation of the rat.

4 In the anaesthetized cat, occlusion of the renal or hepatic circulations did not prolong the neuromuscular blocking action of single doses of fazadinium. Repeated doses accumulated slowly when the hepatic circulation was occluded but not when the renal circulation was occluded.

5 Fazadinium is eliminated from the body by both the liver and kidneys but the rates of these processes are insufficient to account for the initial rapid plasma clearance.

6 The rate-limiting step for the termination of the neuromuscular blocking action of fazadinium is most likely to be the rate of drug-receptor dissociation.

Introduction

Identification of the rate-limiting step for the termination of action of neuromuscular blocking drugs has important clinical implications. For example, in patients with renal insufficiency the paralysing actions of gallamine (Feldman & Levi, 1963; Churchill-Davidson, 1967), tubocurarine (Logan, Howie & Crawford, 1974) and pancuronium (Somogyi, Shanks & Triggs, 1977) are prolonged because elimination via the kidneys is a major determinant for the termination of the paralysing actions of these drugs and succinylcholine causes a prolonged apnoea in patients deficient in serum pseudocholinesterase. A further example is the recurarisation which occurs occasionally after apparently complete reversal of competitive neuromuscular block or by an anticholinesterase agent (Foldes, 1960; Hannington-Kiff, 1970). Recurarisation is probably a consequence of effective plasma concentrations of these drugs being sustained after the effect of the anticholinesterase agent has waned. Therefore, a drug which is not dependent upon a sustained plasma concentration for maintenance of neuromuscular block should be easier to reverse with anticholinesterase agents and safer in patients with renal or hepatic deficiencies because such recurarisation would not occur.

Fazadinium dibromide (AH 8165D), a new competitive neuromuscular blocking drug, has an onset time as rapid as that of succinylcholine (Blogg, Savage, Simpson, Ross & Simpson, 1973; Mehta, Lewin & Fidler, 1977) and is shorter-lasting than pancuronium or (+)-tubocurarine in animals and man (Brittain & Tyers, 1972; 1973; Blogg *et al.*, 1973). The duration of action of fazadinium, like that of most other bisquaternary, competitive neuromuscular blocking drugs, is longer in primates than in lower animal species.

The present study was undertaken following an observation made during initial clinical experiments with fazadinium (AH 8165D) in conscious human volunteers (Simpson, Strunin, Savage, Walton, Foley, Maxwell, Ross & Harris, 1972) using the ulnar nerve-adductor pollicis muscle preparation (Tyrell, 1969), that the neuromuscular block caused by fazadinium was sustained for some time after the circulation to

the forearm had been restored by releasing the tourniquet. The purpose of the present study was to investigate the reasons for, and the factors which affect, the rate of termination of the neuromuscular blocking action of fazadinium in anaesthetized animals and man.

Methods

Measurement of neuromuscular blockade

Cats (1.8–2.8 kg) were anaesthetized with chloralose, 80 mg/kg intravenously, following induction with 3% halothane in a N_2O:O_2 mixture (3:1). The tibialis anterior muscle of one hind limb was prepared for indirect stimulation via the peroneal nerve by the method of Brittain & Tyers (1973). The peroneal nerve was stimulated at a frequency of 1 Hz with square wave pulses of supramaximal voltage and 0.2 ms width. Drugs were given through a cannula inserted into a jugular vein. Blood samples were taken from the jugular vein or from the cannulated femoral artery of the contralateral leg to the nerve-muscle preparation. To determine the significance of hepatic or renal elimination on the duration of the neuromuscular blocking action of fazadinium in the anaesthetized cat, the circulation to the liver was occluded by ligation of the capsule of Glisson, which encloses the hepatic artery, portal vein and bile duct; the circulation to the kidneys was occluded by bilateral ligation of the renal artery and vein.

Bioassay of fazadinium in blood

Whole blood or plasma samples were bioassayed for neuromuscular blocking activity on the isolated phrenic nerve-diaphragm preparation of the rat (Bülbring, 1946). The tissue was suspended in a warm, moist and enclosed atmosphere. Warmed (36°C), oxygenated Krebs solution was superfused over the tissue at a rate of 1.5 ml/min such that the whole tissue, especially the nerve-muscle junction, was well bathed. Diaphragm muscle twitches were evoked by stimulation of the phrenic nerve with trains of square wave pulses of supramaximal voltage (45 Hz for 0.2 s and 0.2 ms pulse width) given once every 15 seconds. Standard concentrations of fazadinium were superfused to determine the sensitivity of the preparation. Neuromuscular blocking activities of the samples were determined by superfusion using a 3 + 1 bioassay procedure and expressed as concentrations of fazadinium. The maximum sensitivity of the preparation ranged from 0.12–0.5 μg/ml of fazadinium.

Plasma clearance rate in man

The plasma clearance rates of single intravenous doses of fazadinium were determined in consenting patients undergoing surgery at The London Hospital. Blood samples were taken from a central venous catheter and bioassayed for neuromuscular blocking activity on the superfused rat phrenic nerve-diaphragm preparation.

Drugs and materials

Fazadinium dibromide (AH 8165D; Allen & Hanburys Research Ltd.) was dissolved and diluted where necessary in 0.9% w/v NaCl solution (saline) and injected intravenously. Doses and concentrations of drugs refer to the free bases. The composition (g/l) of the Krebs solution used in the bioassay procedure was as follows: NaCl 6.92, $NaHCO_3$ 2.10, KCl 0.35, $MgSO_4$ $7H_2O$ 0.3, KH_2PO_4 0.16, D-glucose 2.00 and $CaCl_2$ 0.14, gassed with 95% O_2 and 5% CO_2.

Results

Plasma concentration of fazadinium and neuromuscular blockade

The relationship between the intensity of neuromuscular blockade and the plasma concentration of fazadinium was investigated during the onset phase of paralysis in the anaesthetized cat and during the recovery phase in the anaesthetized cat and in anaesthetized human patients. In the cat the mean (±s.e.) peak arterial plasma concentration of fazadinium in femoral arterial samples was 30.1 ± 1.5 μg/ml (n = 3), which was reached within the first 10 s following an intravenous injection of 1.0 mg/kg. The peak concentration was only transient and marked the passage of the injection bolus. Assuming that similar changes in plasma concentration occurred in both hind limbs, Figure 1 shows that the neuromuscular block of tibialis anterior muscle twitches coincided with the passage of the bolus through the muscle. Thus, fazadinium diffuses rapidly and freely across capillary membranes and axolemmae into the interstitial fluid environment of the motor endplate acetylcholine receptors. The absence of a second peak for the recirculation of the injection bolus indicates that the drug is rapidly removed from the plasma. The ability of fazadinium to move freely between plasma and interstitial fluid is also reflected in the clearance rate of the drug from venous blood in the cat for which the half-life was 45 s (Figure 2). In man also, fazadinium is very rapidly cleared from the plasma with a half-life of 50 seconds. The plasma clearance curves for fazadinium, 0.5 and 1.0 mg/kg, in the cat and man may be divided simply into two main phases. First, there is a rapid distribution phase in which the drug is widely diluted throughout the extracellular water

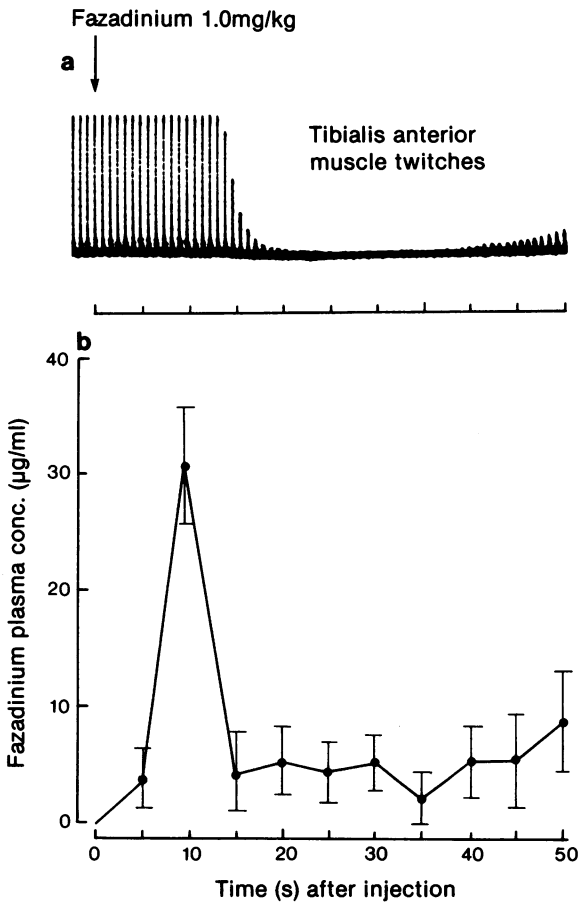

Figure 1 Relationship between arterial plasma concentration of fazadinium (b) and onset of neuromuscular blockade (a) in the anaesthetized cat. Tibialis anterior muscle twitches were evoked by stimulation of the peroneal nerve. Blood samples (2 ml) were taken continuously for 50 s from the contralateral femoral artery and bioassayed for neuromuscular blocking activity on the isolated, superfused phrenic nerve-diaphragm preparation of the rat.

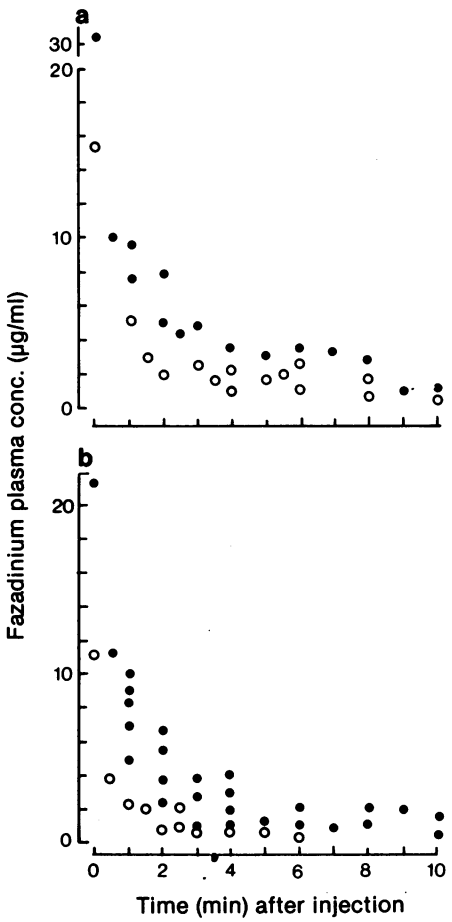

Figure 2 Plasma clearance curves for single intravenous doses of fazadinium, 0.5 (○) and 1.0 (●) mg/kg in the anaesthetized cat (a) and man (b). Blood samples were taken from intravenous catheters and bioassayed for neuromuscular blocking activity on the isolated, superfused phrenic nerve-diaphragm preparation of the rat.

(Martin, 1976) and, second, there is a much slower redistribution and excretion phase (Tyers, 1975). It is clear that since fazadinium is considerably longer acting in man than in the cat, the initial distribution phase cannot limit the rate of recovery from block. The second slower phase, however, requires further investigation.

Extent of renal and hepatic clearance of fazadinium in the cat

Experiments were carried out in the anaesthetized cat to determine the rate of elimination of fazadinium by the liver and kidneys. In these experiments the assumption is made that during a continuous intravenous infusion of fazadinium, which is adjusted to maintain a constant inhibition of tibialis anterior muscle twitches, the rate of infusion is equal to the rate at which the drug is being inactivated. The processes of inactivation may be several and may include metabolic or chemical degradation, uptake into tissues and excretion. The rates of clearance of the drug by the liver or kidneys can be determined by occluding the circulation to each of these organs in turn. If either route of elimination was significant for the clearance of fazadinium, the rate of infusion of the

drug would have to be reduced in order to maintain the same degree of inhibition of muscle twitches. The reduction in the rate of infusion would then equal the rate of hepatic or renal clearance.

In three cats anaesthetized with chloralose an 80% inhibition of tibialis anterior muscle twitches was maintained with a mean (±s.e.) intravenous infusion rate of fazadinium of 65.7 ± 2.7 μg kg^{-1} min^{-1}. A constant level of neuromuscular block was obtained within 10 min after starting the infusion. Plasma samples taken at this time and at 5 min intervals thereafter, were bioassayed on the superfused rat phrenic nerve-diaphragm preparation. The mean (±s.e.) plasma concentration of fazadinium was 5.1 ± 0.35 μg/ml ($n = 4$) indicating that a steady state had been reached. Following occlusion of the hepatic circulation neuromuscular blockade increased. By reducing the mean (±s.e.) rate of infusion of fazadinium to 20.7 ± 1.9 μg kg^{-1} min^{-1} the initial 80% neuromuscular block could be retained. The mean (±s.e.) rate of elimination of fazadinium by the liver was therefore 45.0 ± 1.7 μg kg^{-1} min^{-1}. Similar experiments in 3 further cats in which the renal circulations were occluded showed that the mean rate of renal clearance of fazadinium was 22.0 ± 2.7 μg kg^{-1} min^{-1}. These clearance rates do not allow for changes in total blood volume (<7%) caused by occlusion of the circulations to the liver or kidneys, but it is clear that the deactivation of fazadinium during continuous intravenous infusions is totally accountable in terms of hepatic and renal clearance. However, for single doses of fazadinium these rates of renal and hepatic clearance are insufficient to explain the initial rapid plasma clearance but could account for the slower, later phase.

Having demonstrated that both renal and hepatic excretion routes are important for the elimination of fazadinium from the body, experiments were carried out to investigate the influence of these routes of elimination on the duration of neuromuscular block produced by single and multiple injections of fazadinium and its rate of plasma clearance. In the anaesthetized cat occlusion of the hepatic circulation did not increase the duration of neuromuscular blockade produced by the first dose of fazadinium, 0.3 mg/kg intravenously, given after the occlusion. Further doses of fazadinium, 0.3 mg/kg, given at 30 min intervals, with the hepatic circulation still occluded caused progressively longer lasting block of tibialis anterior muscle twitches (Table 1). When higher doses of fazadinium (1 mg/kg) were given, the first dose after hepatic occlusion appeared to produce only a slightly longer lasting block than that produced by pre-occlusion control doses, but this was not significant ($P > 0.05$). The plasma clearance curves for each of these doses were also determined and Figure 3 shows that while the initial plasma clearance proceeded at about the same rate, the slower second phase started at progressively higher plasma concentrations. In similar experiments in which the renal circulation was occluded, fazadinium (0.3 mg/kg i.v.) produced the same duration of neuromuscular blockade after occlusion as it did for control doses. Further doses of fazadinium (0.3 mg/kg) accumulated but at a much slower rate than that obtained after hepatic occlusion (Table 1).

Discussion

Competitive neuromuscular blocking drugs are generally slow in onset of action compared with succinylcholine and are slowly cleared from the plasma. The results obtained for fazadinium show that it has a very rapid onset of action and is rapidly cleared from the plasma. On following the progress of an injection

Table 1 The influence of hepatic and renal elimination on the duration of neuromuscular blockade produced by repeated intravenous doses of fazadinium, 0.3 mg/kg, in the anaesthetized cat

	*Mean (± s.e.) duration (min) of neuromuscular blockade**		
Time after occlusion (min)	*Control*	*Hepatic circulation occluded*	*Renal circulation occluded*
Control (−15)	1.00 ± 0.10	1.60 ± 0.17	1.10 ± 0.11
15	1.10 ± 0.10	1.86 ± 0.29	1.10 ± 0.12
45	1.30 ± 0.16	2.17 ± 0.38	1.11 ± 0.12
75	1.25 ± 0.10	2.50 ± 0.50	1.32 ± 0.11
105	1.25 ± 0.08	3.66 ± 0.86†	1.50 ± 0.14

* On the peroneal nerve-tibialis anterior muscle preparation, $n = 3$ cats.
† $P < 0.05$ as compared with control (−15 minutes).

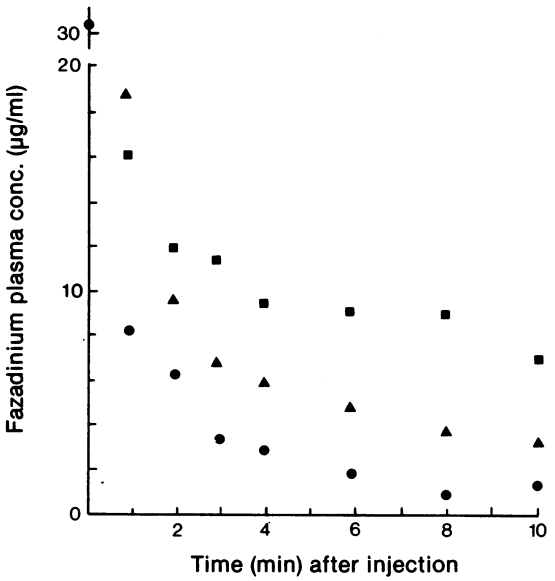

Figure 3 Effects of occluding the hepatic circulation on plasma clearance curves for fazadinium (1 mg/kg) in the anaesthetized cat. Symbols are the means of 2 experiments: control (●); 1st dose after occlusion (▲); 2nd dose after occlusion (■). Blood samples were taken from catheterized jugular veins and bioassayed for neuromuscular blocking activity on the isolated, superfused phrenic nerve-diaphragm of the rat.

bolus of fazadinium through the hind limb circulation in the anaesthetized cat, it was clear that the onset of neuromuscular block of tibialis anterior muscle twitches followed very soon after the arrival of the bolus in the muscle. Furthermore, peak neuromuscular blockade was attained during the first circulation of the drug through the muscle. Therefore, fazadinium, unlike most other competitive neuromuscular blocking drugs, is able to diffuse rapidly from the plasma into the interstitial fluid. In man also, fazadinium has a very rapid onset time for neuromuscular blockade (Blogg *et al.*, 1973; Mehta *et al.*, 1977) and is rapidly cleared from the plasma. The conditions following rapid intravenous injection of fazadinium have, therefore, the following similarities to those in the isolated forearm experiments. First, the injection bolus exposes the motor endplates to high concentrations of the drug and causes rapid muscle paralysis. Second, as the bolus passes the muscle and during its first circulation through the body, the concentration of fazadinium in the plasma falls rapidly to, and remains at, a level well below that necessary to sustain neuromuscular blockade. The rate-limiting step for the termination of drug actions cannot, therefore, be the rate at which fazadinium is cleared from the plasma but is probably the rate of dissociation of the drug from its receptors. Diffusional delays are unlikely to be important because fazadinium has a very rapid onset time to block and by definition passive diffusion barriers are bi-directional.

The prolonged neuromuscular blocking action of fazadinium, and some other competitive neuromuscular blocking drugs such as dacuronium (Norman & Katz, 1971) stercuronium (Wieriks, 1972; Admiraal, 1972) and N,N'-dimethylconessine (Busfield, Child, Clarke, Davis & Dodds, 1968) in primates compared with lower species requires further consideration if the rate of dissociation is to be the rate-limiting factor. A slower plasma clearance rate in man cannot be a limiting factor for fazadinium since the half-lives for plasma clearance in cat and man are very similar, despite the 10 fold difference in durations of action. However, N,N'-dimethylconnessine was shown to remain longer in the plasma of monkeys than in cats (Busfield *et al.*, 1968). Three possibilities may explain longer durations of action in primates. First, the acetylcholine receptors and their immediate chemical environments may differ structurally and provide exoreceptor sites which can bind antagonist molecules more strongly. Second, less acetylcholine is released from motor nerves, and third, the synaptic cleft is wider in primates so that less acetylcholine reaches the motor end-plates. Certainly an increased acetylcholine concentration at the motor endplate will increase the rate of recovery from neuromuscular block since, in the isolated forearm preparation in man, periodic tetanic stimulation of the ulnar nerve will accelerate the recovery of adductor pollicis muscle twitches blocked with gallamine or (+)-tubocurarine (Feldman & Tyrrell, 1970). Furthermore, the accumulation of endogenous acetylcholine plays a significant part in the reversal by neostigmine of competitive neuromuscular blockade. Changes in acetylcholine concentration at the motor endplate will also change the safety margin of transmission (Paton & Waud, 1967), i.e. the proportion of receptors which may be occupied by an antagonist before neuromuscular transmission is impaired. If the acetylcholine released from motor nerves is relatively less in primates than in lower species, in which neuromuscular blocking drugs are shorter-acting, the competitive displacement of the antagonist from the acetylcholine receptors would take longer and, perhaps more importantly, more receptors would have to become unoccupied by the antagonist before neuromuscular transmission could resume. Variation in the safety margin of neuromuscular transmission may therefore explain why most competitive neuromuscular blocking drugs are longer acting in primates than in lower species. It would of course be very interesting to measure the safety margin of transmission in the cotton-eared

marmoset, or another primate, in which fazadinium is longer acting.

For some competitive neuromuscular blocking drugs the durations of action are not longer in primates. For example, M&B 15944A, a monoquaternary compound has about the same short duration of action in man (Coleman, 1972) as it has in the cat (Banford, Biggs, Chaplen, Davis & Maconochie, 1972). Other drugs, such as pancuronium, gallamine and (+)-tubocurarine are only slightly longer-acting in primates than in lower animal species (Maclagan, 1976). The short duration of action of M&B 15944A in man is difficult to understand unless the drug is rapidly metabolized to inactive products or if the rate limiting step for termination of action is a rapid clearance from the plasma. For (+)-tubocurarine, termination of action correlates with its rate of plasma clearance (Matteo, Spector & Horowitz, 1974). The primary factor for determining the plasma clearance rate of (+)-tubocurarine appears to be a slow distribution throughout the extracellular fluid, since neuromuscular block is not prolonged when either renal or biliary excretion are available for the elimination of (+)-tubocurarine and a malfunction of one route is compensated for by an increase in the capacity of the other to excrete (+)-tubocurarine (Cohen, Brewer & Smith, 1967). Gallamine is dependent upon renal elimination for its plasma clearance and termination of action, and there is a risk of prolonged neuromuscular block in patients with renal insufficiency (Feldman & Levy, 1963; Cohen, 1968). The reliance of gallamine and (+)-tubocurarine upon plasma clearance probably explains the occasional reports of recurarisation which have occurred after the effect of the anticholinesterase agent has waned, i.e. there is a sustained effective plasma concentration of the drug after apparent neostigmine reversal. The duration of action of fazadinium does not correlate with plasma clearance rate, and neither renal nor biliary elimination is primarily important, although both routes are available and eventually one or other is essential for the elimination of fazadinium from the body. Recurarisation therefore is unlikely following use of fazadinium and in none of the patients who have received fazadinium has recurarisation been reported. Furthermore, because the plasma concentration of fazadinium falls very rapidly to ineffective levels the neuromuscular block produced by fazadinium is easier to reverse with neostigmine than that following drugs which remain at higher concentrations in the plasma (Buckley, Blogg, Simpson & Savage, 1974). In one clinical trial (Rowlands, personal communication) the relaxation produced by fazadinium was reversed even when neostigmine was given within 10 min of administration of the drug.

In conclusion, the rate limiting step in the termination of the neuromuscular blocking action of fazadinium is most likely to be the rate of drug-receptor dissociation. In animals the duration of action of fazadinium is unaffected by impairment of renal or biliary elimination, unless large repeated doses are given. These latter studies are being extended to man.

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