

A COMPARISON OF THE SKELETAL NEUROMUSCULAR AND AUTONOMIC GANGLION-BLOCKING POTENCIES OF FIVE NON-DEPOLARIZING RELAXANTS

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1 Results from *in vitro* experiments on the phrenic nerve–diaphragm and the hypogastric nerve–vas deferens preparations of the guinea-pig have been used to plot log concentration–effect curves for skeletal neuromuscular and ganglion blockade, respectively, for (+)-tubocurarine, pancuronium, alcuronium, gallamine and fazadinium (AH 8165).

2 From the log concentration–effect curves, EC_{50} s and equipotent ratios were calculated. The order of neuromuscular blocking potency was pancuronium = alcuronium > (+)-tubocurarine > fazadinium = gallamine. The ratio EC_{50} for ganglion blockade/ EC_{50} for neuromuscular blockade was 2.3 for fazadinium, 6.7 for (+)-tubocurarine, 22.9 for alcuronium, 24.3 for gallamine and 200.0 for pancuronium.

3 For pancuronium and gallamine there was a range of concentrations below those producing ganglion blockade at which the response of the vas deferens to hypogastric nerve stimulation was augmented.

4 The results are compared with some of those available in the literature, measured on other species by other methods.

Introduction

The non-depolarizing skeletal muscle relaxants produce other effects in addition to blockade of neuromuscular transmission (Paton, 1959). In clinical use, the most significant of these effects is manifested usually as a change in heart rate and blood pressure. An ability to block autonomic ganglia is one of the properties shared by the non-depolarizing compounds used as muscle relaxants. The potency of the compounds in blocking ganglia has been measured usually on anaesthetized cats (Marshall, 1973; Hughes & Chapple, 1976). It would be useful to be able to establish relative neuromuscular and ganglion blocking potencies on simple isolated tissue preparations in which effective concentrations would be known and the wide range of concentration from the absence of neuromuscular blockade to complete ganglion blockade could be covered easily. Ideally, this should be done on a skeletal muscle and a ganglion preparation from the same species.

We now describe measurements made *in vitro*, on tissues from a single species, of the neuromuscular and sympathetic ganglion blocking potencies of most of the non-depolarizing muscle relaxants in current clinical use. The phrenic nerve–diaphragm and the

hypogastric nerve–vas deferens preparations of the guinea-pig have been used. Potencies and potency ratios obtained from this species were compared with those available from measurements obtained by other methods on other species.

Methods

The guinea-pig isolated phrenic nerve–diaphragm preparation

One phrenic nerve–hemidiaphragm preparation was removed from male guinea-pigs (600 to 950 g) as described, for the rat, by Bülbbring (1946) and set up in 50 ml of Krebs solution at 37°C bubbled with 95% O₂ and 5% CO₂. The phrenic nerve was pulled through unshielded bipolar platinum ring electrodes and stimulated with supramaximal shocks at 0.2 Hz and 0.2 ms pulse duration. The muscle contractions were recorded on an ultraviolet recorder by means of an isometric transducer. Baseline recordings of control muscle twitches were made before the addition of a neuromuscular blocking drug to the bath, the drug

was allowed to act for 3 min, at the end of which time the preparation was washed in drug-free Krebs solution, three times in 20 min, to re-establish baseline-height contractions. The blocking effects of at least four concentrations of drug were established in this way. Hemidiaphragms from 5 guinea-pigs were used for each drug.

The guinea-pig isolated hypogastric nerve–vas deferens preparation

One hypogastric nerve–vas deferens preparation was removed by the method of Huković (1961) from male guinea-pigs (400 to 700 g) and set up in 50 ml of Krebs solution at 32°C bubbled with 95% O₂ and 5% CO₂. The hypogastric nerve was pulled into unshielded bipolar platinum ring electrodes and stimulated for 20 s with supramaximal shocks at 20 Hz and 0.2 ms pulse duration. There was a 4 min interval between trains of stimuli. The vas deferens was mounted between parallel platinum wire electrodes (Birmingham & Wilson, 1963) for transmural stimulation (supramaximal voltage, 20 Hz, 0.2 ms pulse width). The longitudinal contractions of the vas deferens were recorded on a potentiometric recorder by means of an isotonic transducer loaded at 0.75 g. Baseline recordings of control responses were made before the addition of the first concentration of drug which was allowed to act for four periods of stimulation of the hypogastric nerve. The bath concentration of drug was then repeatedly doubled for each of the succeeding four periods of stimulation, without changing the bath fluid, until complete blockade of the response to hypogastric nerve stimulation was obtained. In this way a cumulative concentration-effect curve was established. The response to transmural stimulation was tested between periods of hypogastric nerve stimulation or after complete blockade. Vasa deferentia from 5 guinea-pigs were used for each drug.

Drugs

These were (+)-tubocurarine chloride, gallamine triethiodide, pancuronium dibromide, alcuronium dichloride, fazadinium dibromide (AH 8165 D), pentolinium tartrate, trimetaphan camphorsulphonate and hexamethonium bromide. Bath concentrations are expressed in mol/litre. The composition of Krebs solution was as follows (mM): NaCl 119, KCl 4.7, MgSO₄ 1.2, NaH₂PO₄ 0.9, NaHCO₃ 25, CaCl₂ 2.5 and glucose 11.1.

Results

The effect of the skeletal muscle relaxants was measured as a percentage reduction in the diaphragm

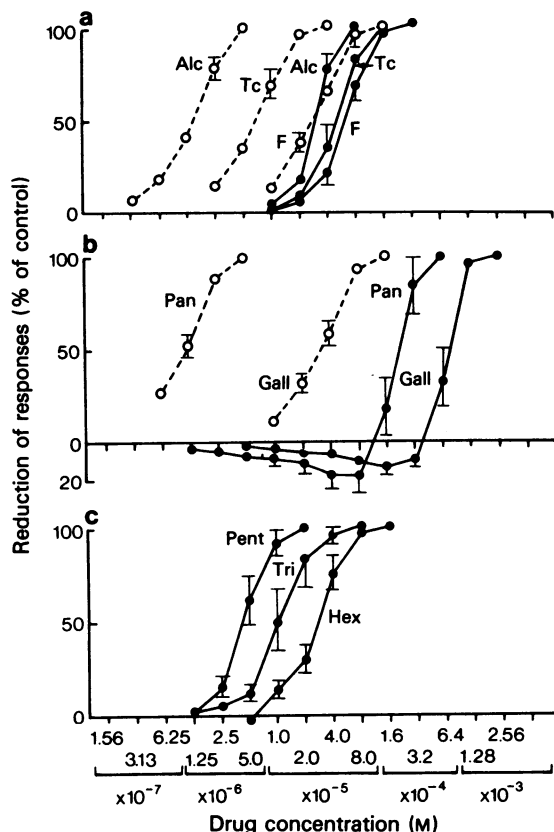


Figure 1 Log concentration-effect curves (a and b) for alcuronium (Alc), (+)-tubocurarine (Tc), fazadinium (F), pancuronium (Pan) and gallamine (Gall) on the response of the diaphragm to phrenic nerve stimulation (dotted lines) and the response of the vas deferens to hypogastric nerve stimulation (solid lines). In (c) log concentration-effect curves are shown for the effects of pentolinium (Pent), trimetaphan (Tri) and hexamethonium (Hex) on the response of the vas deferens to hypogastric nerve stimulation. Each point is the mean of measurements made on 5 guinea-pigs; vertical lines show s.e. mean. Ordinates: % reduction of control responses in absence of drugs. Abscissae: molar concentration of drugs on a log scale.

twitch response to phrenic nerve stimulation after 3 min exposure to each concentration of drug. The effect on ganglionic transmission was measured as a percentage reduction in the response of the vas to hypogastric nerve stimulation (preganglionic) after 15 min exposure to each concentration of drug: the responses to transmural stimulation (postganglionic) were not reduced. Three representative ganglion blocking agents were also tested on the vas preparation.

The effect of each drug concentration was expressed as a percentage reduction of the response compared

with the pre-drug control response. The means of these changes were plotted as log concentration-effect curves (Figure 1, dotted lines for diaphragm, solid lines for vas deferens). Regression lines for the concentrations of each drug which produced effects over the linear part of the log concentration-effect curve were used to calculate that concentration (with 95% confidence limits) which would produce a 50% blockade (EC_{50}). These EC_{50} s are shown in Table 1 together with, for the muscle relaxants, the ratio between the EC_{50} for ganglion blockade and the EC_{50} for neuromuscular blockade (the equipotent molar ratio, epmr).

The muscle relaxants, (+)-tubocurarine, alcuronium and fazadinium produced neuromuscular blockade at concentrations lower than those needed for ganglion blockade, but all were capable of producing complete blockade of ganglionic transmission. For this group of drugs, the difference between the neuromuscular blocking and ganglion blocking potencies was largest for alcuronium (epmr 22.9) and smallest for fazadinium (epmr 2.3).

A wider separation of neuromuscular and ganglion blocking potency was found for pancuronium (epmr 200.0). For pancuronium and gallamine the onset of ganglion blockade was delayed by the appearance, at lower concentrations, of an augmentation of the response of the vas deferens to hypogastric nerve stimulation (a maximum augmentation of the order of 12% for gallamine and 18% for pancuronium.)

The three ganglion blocking agents were each

capable of producing full blockade of ganglionic transmission with the order of potency being pentolinium > trimetaphan > hexamethonium.

Discussion

The results obtained in the present investigation allow a comparison to be made within one mammalian species of the relative potencies for neuromuscular blockade and sympathetic ganglion blockade of most of the non-depolarizing muscle relaxants in current clinical use.

The *in vitro* assay of ganglion blocking potency depended on the presence of a ganglionic relay in the hypogastric nerve innervating the vas deferens of the guinea-pig (Sjöstrand, 1962; Bentley & Sabine, 1963; Birmingham & Wilson, 1963). By separate stimulation of the preganglionic fibres of the hypogastric nerve and of the postganglionic nerve terminals within the wall of the vas deferens (Birmingham & Wilson, 1963) it is possible to localize the blocking effect of a drug to sympathetic ganglia. The experimental technique was validated by the measurement, *in vitro*, of the potency of three classic ganglion blocking agents, hexamethonium, trimetaphan and pentolinium; each was capable of producing complete blockade of the response to hypogastric nerve stimulation at a time when the response to transmural stimulation of intramural nerves was not reduced. In the same way, each

Table 1 Mean concentrations (calculated from regression lines fitted to log concentration-effect curves for measurements on 5 guinea-pigs for each drug) for 50% reduction of response of diaphragm (EC_{50} NMB) or vas deferens (EC_{50} GB)

Drug	EC_{50} for neuromuscular blockade (NMB) (95% confidence limits)	EC_{50} for ganglion blockade (GB) (95% confidence limits)	Equipotent molar ratio $\left(\frac{EC_{50} \text{ GB}}{EC_{50} \text{ NMB}}\right)$	NMB potency relative to pancuronium (Panc) $\left(\frac{EC_{50} \text{ Panc}}{EC_{50}}\right)$
(+)-Tubocurarine	$6.7 \times 10^{-6} \text{ M}$ ($5.7 \rightarrow 7.9 \times 10^{-6} \text{ M}$)	$4.5 \times 10^{-5} \text{ M}$ ($3.8 \rightarrow 5.3 \times 10^{-5} \text{ M}$)	6.7	0.16
Gallamine	$3.0 \times 10^{-5} \text{ M}$ ($2.7 \rightarrow 3.5 \times 10^{-5} \text{ M}$)	$7.3 \times 10^{-4} \text{ M}$ ($6.4 \rightarrow 8.4 \times 10^{-4} \text{ M}$)	24.3	0.04
Pancuronium	$1.1 \times 10^{-6} \text{ M}$ ($0.96 \rightarrow 1.2 \times 10^{-6} \text{ M}$)	$2.2 \times 10^{-4} \text{ M}$ ($1.8 \rightarrow 2.6 \times 10^{-4} \text{ M}$)	200.0	1
Alcuronium	$1.4 \times 10^{-6} \text{ M}$ ($1.3 \rightarrow 1.5 \times 10^{-6} \text{ M}$)	$3.2 \times 10^{-5} \text{ M}$ ($2.7 \rightarrow 3.6 \times 10^{-5} \text{ M}$)	22.9	0.79
Fazadinium	$2.8 \times 10^{-5} \text{ M}$ ($2.5 \rightarrow 3.0 \times 10^{-5} \text{ M}$)	$6.4 \times 10^{-5} \text{ M}$ ($5.5 \rightarrow 7.5 \times 10^{-5} \text{ M}$)	2.3	0.04
Pentolinium		$4.5 \times 10^{-6} \text{ M}$ ($3.8 \rightarrow 5.3 \times 10^{-6} \text{ M}$)		
Trimetaphan		$1.0 \times 10^{-5} \text{ M}$ ($0.8 \rightarrow 1.3 \times 10^{-5} \text{ M}$)		
Hexamethonium		$2.5 \times 10^{-5} \text{ M}$ ($2.1 \rightarrow 3.1 \times 10^{-5} \text{ M}$)		

of the neuromuscular blocking drugs produced a blockade of ganglionic transmission.

Some comparisons are possible with measurements made by others on guinea-pig diaphragm, on diaphragm from different species and by different methods. Taylor, Prior & Bevan (1964) measured the potency of (+)-tubocurarine and gallamine on guinea-pig isolated diaphragm stimulated with single shocks through the phrenic nerve. After full paralysis, they successively reduced the bath concentration of drug to measure the degree of blockade at equilibrium (15 to 20 min). They obtained an EC_{50} for (+)-tubocurarine of $1.5 \mu\text{g/ml}$ ($1.9 \times 10^{-6} \text{ M}$) comparable with our mean value of $6.7 \times 10^{-6} \text{ M}$. Their ratio EC_{50} (+)-tubocurarine/ EC_{50} gallamine was 0.18 which is close to our value of 0.22.

On the other hand Lu (1970), also using the guinea-pig diaphragm, obtained EC_{50} s of $0.35 \times 10^{-6} \text{ M}$ and $3.09 \times 10^{-6} \text{ M}$ for (+)-tubocurarine and gallamine respectively. These are smaller than our values and those of Taylor *et al.* (1964) and the ratio was 0.11.

Chou (1947) reported an EC_{50} for (+)-tubocurarine based on 3 min equilibration on the rat isolated diaphragm of $1.8 \mu\text{g/ml}$ ($2.3 \times 10^{-6} \text{ M}$); we obtained $6.7 \times 10^{-6} \text{ M}$ on the guinea-pig. Chou (1947) pointed out the influence of the rate of stimulation on the value obtained, the drug appearing to be more potent at higher frequencies (20 per min) of stimulation. This observation probably accounts for the higher potencies for fazadinium and pancuronium reported by Brittain & Tyers (1973), when they used the rat isolated diaphragm stimulated at 45 Hz, compared with our values obtained on guinea-pig muscle at 0.2 Hz. Brittain & Tyers (1973) found EC_{50} s of $0.68 \mu\text{g/ml}$ ($1.58 \times 10^{-6} \text{ M}$) for fazadinium and $0.09 \mu\text{g/ml}$ ($0.15 \times 10^{-6} \text{ M}$) for pancuronium; these may be compared to our values of $28.0 \times 10^{-6} \text{ M}$ and $1.1 \times 10^{-6} \text{ M}$ respectively. For gallamine our EC_{50} of $30.0 \times 10^{-6} \text{ M}$ is closer to that of Brittain & Tyers (1973) who reported $16.5 \mu\text{g/ml}$ ($23.3 \times 10^{-6} \text{ M}$).

Potency measurements have been made also on intact animals and on man. Where it is possible to use published data to calculate potency ratios between drugs these may be compared with ratios calculated from our results. Brittain & Tyers (1973) obtained intravenous paralysing doses for mice and the ratio ED_{50} fazadinium/ ED_{50} pancuronium was 13.6; our ratio EC_{50} fazadinium/ EC_{50} pancuronium was 25.5. Gallamine is again different being 27.3 times less potent than pancuronium in our measurements but 119.4 times less potent when tested on mice by Brittain & Tyers (1973). Some comparisons are possible with measurements made on man. For fazadinium the ED_{50} of 0.098 mg/kg obtained by Brittain & Tyers (1973) for paralysis of mice was close to the ED_{50} of 0.11 mg/kg found by Hussain, Healy & Birmingham (1979) for reduction of thumb twitch in anaesthetized

patients. Lund & Stovner (1970) published intravenous ED_{50} s for reduction of grip strength in conscious subjects for pancuronium, alcuronium and (+)-tubocurarine. When calculated with respect to pancuronium the potency ratios were 0.33 for alcuronium and 0.26 for (+)-tubocurarine; comparable figures from our *in vitro* EC_{50} s were 0.79 and 0.16 respectively. It would seem therefore that comparisons between species and between methods of measurement should be approached with caution.

The propensity of skeletal muscle relaxants to produce some degree of autonomic ganglion blockade is well known. Paton (1959) referring to the ganglion-blocking activity of (+)-tubocurarine wrote "Its potency is not far short of that of hexamethonium". Our measurements confirm this. The EC_{50} of (+)-tubocurarine for blockade of the hypogastric ganglia was $4.5 \times 10^{-5} \text{ M}$ whereas that for hexamethonium was $2.5 \times 10^{-5} \text{ M}$. In clinical use an important factor will be the separation between the dose producing adequate muscle relaxation and that producing significant ganglion blockade. This separation may be expressed as the ratio between the doses producing the same degree of neuromuscular blockade and ganglion blockade. These equipotent ratios are shown in Table 1 for our *in vitro* measurements of sympathetic ganglion blockade. They range from 2.3 for fazadinium to 200.0 for pancuronium. The curves in Figure 1 show the five muscle relaxants to fall into two groups: Group 1, comprising (+)-tubocurarine, alcuronium and fazadinium, in which, as the concentration is increased, ganglion blockade follows neuromuscular blockade without an intervening augmentation of response to preganglionic stimulation; Group 2, comprising pancuronium and gallamine, in which the onset of ganglion blockade is preceded by an augmenting effect at lower concentrations.

Our ganglion-blocking/neuromuscular blocking potency ratio of 2.3 for fazadinium may be compared with that of 3.8 based on ED_{30} measurements of blockade of contractions of tibialis anterior and of nictitating membrane in the anaesthetized cat made by Marshall (1973). The influence of the rate of motor nerve stimulation on neuromuscular blocking potency is emphasised by the result of Tyers (personal communication) who stimulated the peroneal nerve in the cat at 1.0 Hz, compared with 0.1 Hz used by Marshall (1973). The neuromuscular blocking potency of fazadinium was greater at the higher frequency so the separation between neuromuscular blockade and ganglion blockade was wider with a potency ratio for fazadinium of 18.7.

For pancuronium, Buckett, Majoribanks, Marwick & Morton (1968) gave some indication of its ganglion blocking potency by stating it to be about 8 times less potent than hexamethonium against contractions of the cat nictitating membrane induced by pregangli-

onic nerve stimulation. From our figures, pancuronium was about nine times less potent than hexamethonium in blocking the response of the guinea-pig isolated vas deferens to preganglionic stimulation.

In clinical use as skeletal muscle relaxants both pancuronium (Loh, 1970; Komesaroff, 1970; Kelman & Kennedy, 1970; 1971) and gallamine (Marbury, Artusio, Wescoe & Riker, 1951; Smith & Whitcher, 1967; Kennedy & Farman, 1968) increase blood pressure and heart rate. These effects have been the subject of much investigation. For either drug the tachycardia has been ascribed to a selective blockade of cardiac vagal muscarinic receptors (Saxena & Bonta, 1970; Clark & Mitchelson, 1976). In addition, an indirect sympathomimetic action of gallamine has been reported by Brown & Crout (1970) and a sympathomimetic effect of pancuronium has been shown by Ivankovich, Miletich, Albrecht & Zahed (1975) to be associated with a blockade of noradrenaline neuronal uptake. These sympathomimetic mechanisms may explain the initial augmentation by pancuronium and

gallamine of the response of the guinea-pig vas to hypogastric nerve stimulation. It cannot be ascribed solely to an action at the ganglion because other work in this laboratory has shown the potentiation to apply also to post-ganglionic stimulation and to exogenously applied noradrenaline (Kapur & Tomlinson, personal communication).

We recognise that results obtained on isolated preparations of the diaphragm and a sympathetic ganglion are not necessarily predictive for man or animals of the relative effects on skeletal muscle and on heart rate and blood pressure. At muscle relaxing doses the effect on the cardiovascular system will be related to the resultant of the relative effects of blockade at sympathetic ganglia and parasympathetic (cardiac vagal) sites.

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