J. Pharm. Pharmac., 1972, **24**, 762–772 *Received March* 27, 1972

Neuromuscular blocking and ganglion blocking activities of some acetylcholine antagonists in the cat

W. C. BOWMAN AND SANDRA N. WEBB*

Department of Pharmacology, University of Strathclyde, Glasgow G1 1XW

The potencies of tubocurarine, gallamine, pancuronium, benzoquinonium, hexamethonium and mecamylamine in blocking neuromuscular transmission in the soleus muscle, and in blocking contractions of the nictitating membrane evoked by preganglionic sympathetic stimulation have been compared in cats under chloralose anaesthesia. On a molar basis, pancuronium was about 8 times and benzoquinonium about 2·5 times more potent than tubocurarine in blocking the soleus muscle; gallamine was less than half as potent, mecamylamine about 128 times and hexamethonium about 380 times less potent. In blocking the superior cervical ganglion, mecamylamine was about 17 times more, tubocurarine was about 5 times more and pancuronium about twice as potent as hexamethonium. Benzoquinonium was about half as potent as hexamethonium, and gallamine about 5 times less potent. The results emphasize that the shorter distance between charged centres, as in hexamethonium, reduces affinity for muscle receptors but does not necessarily enhance affinity for ganglion receptors, and from the point of view of deductions concerning the configuration of the ganglionic receptor, the ganglion blocking potencies of some neuromuscular blocking drugs should be taken into account.

As a preliminary to experiments in which the abilities of a range of acetylcholine-antagonists to block the effects of anticholinesterase drugs at the neuromuscular junction were studied (to be published), a comparison was made of the potencies of these drugs in blocking neuromuscular and ganglionic transmission. Despite an extensive literature on the subject, it was considered necessary to make these comparisons under identical experimental conditions. Accordingly, the abilities of tubocurarine, benzoquinonium, gallamine, pancuronium, hexamethonium and mecamylamine to block transmission through the superior cervical ganglion and to block neuromuscular transmission in the soleus muscle have been compared in cats under chloralose anaesthesia.

A study of the literature indicates that this is the first time that these drugs have been compared in this way, and our justification for reporting them is that they have apparently hitherto unrealized implications in relation to cholinoceptive receptors on ganglion cells.

METHODS

The experiments were made on 58 adult cats of either sex anaesthetized with chloralose (80 mg/kg) injected intraperitoneally as a 1% solution in 0·9% w/v NaCl solution.

*Present address: Department of Physiology, The Medical School, University of Bristol.

No adjuvants to the chloralose anaesthesia were used because most of these may influence junctional transmission to some extent.

Soleus muscle

The cat was laid prone on the operating table and a hind limb was rigidly clamped in a horizontal position by means of drills through the femur and the tibia and fibula. A skin incision was made from the level of the Achilles tendon to the popliteal space and the soleus muscle was separated from other muscles. The gastrocnemius-plantaris muscle was retracted, the sciatic nerve was cut in the popliteal space, and small shielded bipolar platinum electrodes were placed on the soleus branch of the nerve close to the muscle. The tendon of insertion of the soleus muscle was cut and attached to a Grass (model FT 10C) strain gauge and the skin flaps were raised to form a deep pool that was filled with warm mineral oil (heavy liquid paraffin B.P.). A small heating device was placed under the surface of the oil and muscle temperature was maintained at 36–38°. The pool temperature was recorded by means of a small thermocouple (Grant Instruments, Cambridge). The soleus nerve was stimulated at a frequency of 0·1 Hz with rectangular pulses of 100μs duration and of about twice the strength necessary to evoke a maximal twitch. Muscle tension was recorded on a Grass (Model 79) twin channel pen recorder. Drugs were injected intravenously through a cannula in the jugular vein, or intra-arterially through a fine polythene cannula tied retrogradely into the suralis artery (which passes along the medial aspect of the gastrocnemius muscle) so that its tip reached the junction with the popliteal artery.

Nictitating membrane

The cat was laid supine on the operating table and contractions of a nictitating membrane in response to pre-ganglionic stimulation of the cervical sympathetic trunk were recorded. The nerve was stimulated under warm mineral oil through bipolar platinum electrodes placed on the peripheral portion of the severed nerve. The stimuli were rectangular pulses of 0·5 ms duration and of a strength greater than that necessary to evoke a maximal contraction at the frequency of stimulation used. The output of the stimulator was fed through a system of Londex clocks so that the required stimulus pattern was delivered automatically. In most experiments, the pattern was 5 Hz for 10 s every 2 min, except in one series of experiments in which 50 Hz was used. The membrane was attached to a Grass (model FT 03C) strain gauge and contractions were recorded on the twin channel pen recorder. Resting tension on the membrane was adjusted to 5 g. Drugs were injected intravenously or intra-arterially. Intra-arterial injections were made in a volume not exceeding 0·2 ml into the carotid artery blood steam by means of a fine polythene cannula tied retrogradely into the lingual artery so that its tip reached the junction with the carotid artery.

In one series of experiments, nictitating membrane contractions and soleus muscle contractions were recorded simultaneously.

General arterial blood pressure was recorded in all experiments by means of a pressure transducer attached to a common carotid or femoral artery. Drugs used: tubocurarine chloride (Duncan Flockhart), benzoquinonium chloride (Sterling Winthrop), gallamine triethiodide (May & Baker), pancuronium bromide (Organon), hexamethonium bromide (May & Baker), mecamylamine hydrochloride (Merck,

Sharpe & Dohme) and atropine sulphate (British Drug Houses). Where doses are given by weight, they refer to these salts.

RESULTS

Neuromuscular block

Tubocurarine was used for comparison in all these experiments, and in each, one other drug was compared with it. The soleus muscle was stimulated indirectly at a frequency of 0·1 Hz and the drugs were injected intra-arterially. Although cumulative effects complicate the assessment of the results to some extent, the intra-arterial route of injection reduced cumulation to a minimum. Furthermore, in all cases the dose interval was chosen such that the twitches had become constant at the control amplitude for 30 min before the next injection. Thus, dose intervals of about 1 h were usual. In alternate experiments with the same pair of drugs, the starting order was reversed so as to cancel out the effects of cross cumulation as much as possible. In any one experiment, from 3 to 5 doses of each drug were injected.

Fig. 1 expresses graphically the results from individual experiments in which the neuromuscular blocking potencies of the drugs were compared with that of tubocurarine. In different cats there was wide variation in the doses of the individual drugs required to produce neuromuscular block. However, the relative potencies of the individual drugs, when compared with tubocurarine, showed little variation. Table 1 gives the effective doses, both by weight and on a molar basis, to produce

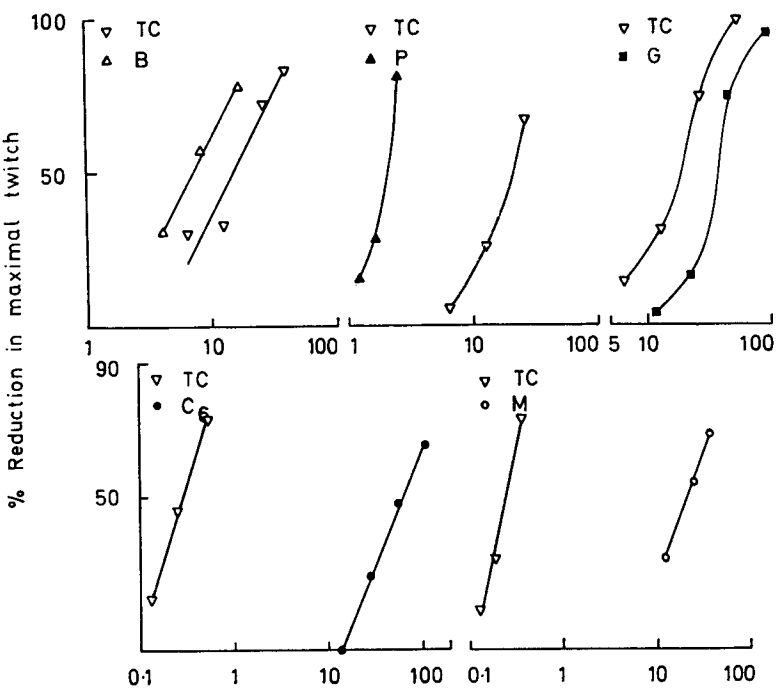

FIG. 1. Log dose-response curves constructed from experiments in which the potencies of the drugs were compared with that of tubocurarine in depressing the maximal twitches of the soleus muscle. TC, tubocurarine; B, benzoquinonium; P, pancuronium; G, gallamine; C6, hexamethonium; M, mecamylamine. All injections were intra-arterially. Abscissa: upper, dose $\times 10^{-8}$ mol; lower, dose $\times 10^{-6}$ mol.

Table 1. *Potency of compounds in depressing maximal twitch.*

Compound	Intra-arterial doses (± standard error of mean) producing 50% depression of maximal twitch	Relative molar potency (tubocurarine = 1)
Tubocurarine chloride	107·2 ± 39·6 μg	
	13·6 × 10^{-8} mol	1
Benzoquinonium chloride	41·3 ± 1·8 μg	
	6·7 × 10^{-8} mol	2·4 ± 0·45
Tubocurarine chloride	164 ± 32·1 μg	
	20·8 × 10^{-8} mol	1
Gallamine triethiodide	324 ± 65·6 μg	
	38·4 × 10^{-8} mol	0·44 ± 0·03
Tubocurarine chloride	103 ± 30·8 μg	
	13·1 × 10^{-8} mol	1
Pancuronium bromide	11·7 ± 1·9 μg	
	1·6 × 10^{-8} mol	8·15 ± 1·2
Tubocurarine chloride	127·5 ± 50·8 μg	
	16·2 × 10^{-8} mol	1
Hexamethonium bromide	17,500 ± 2,400 μg	
	48·2 × 10^{-6} mol	0·0029 ± 0·0009
Tubocurarine chloride	145 ± 36·6 μg	
	18·5 × 10^{-8} mol	1
Mecamylamine hydrochloride	5,500 ± 1,100 μg	
	27 × 10^{-6} mol	0·0078 ± 0·0022

The mean values quoted are from 3–5 experiments where an individual drug was compared with tubocurarine. The relative potencies quoted are the mean values (± standard error of the mean) from the individual experiments.

50% twitch block, and the potency ratios on a molar basis compared with tubocurarine.

Ganglion block

In these experiments, hexamethonium was used for comparison. With the exception of experiments with mecamylamine, the cervical sympathetic trunk was stimulated at 5 Hz for 10s every 2 min and the drugs were injected intra-arterially 30 s before a burst of stimulation. As in the experiments described in the previous section, the dose interval was chosen such that the contractions of the nictitating membrane had been constant in amplitude for 30 min before the next injection. In any one experiment 3 or 4 doses of each drug were injected. Fig. 2 illustrates parts of different experiments in which the potency of benzoquinonium, gallamine, pancuronium and tubocurarine were compared with that of hexamethonium. It was impossible to use this method for potency comparisons involving mecamylamine because of its long duration of action and its pronounced cumulative effects. Instead, the method of Kharkevich (1967) was used in which continuous stimulation (5 Hz) is applied, and the doses are added at short intervals as soon as the response is stabilized.

Fig. 3 expresses graphically the results from individual experiments in which the ganglion blocking potencies of the drugs were compared with that of hexamethonium. In different cats, there was wide variation in the doses of the individual drugs required to produce ganglion block, but the relative potencies of the individual drugs, when compared with hexamethonium, showed little variation.

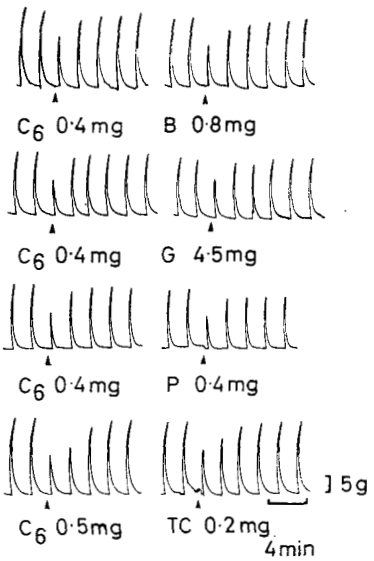

FIG. 2. Portions of records from 4 different experiments in which the potencies of the drugs were compared with that of hexamethonium in depressing the responses of the nictitating membrane to preganglionic stimulation (5 Hz for 10 s every 2 min). Responses to approximately equiactive doses are shown. All injections were intra-arterial.

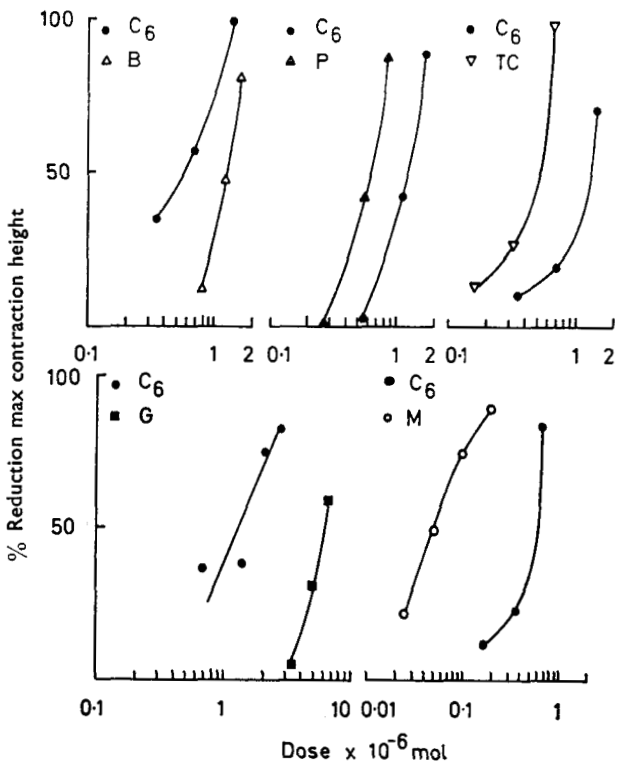

FIG. 3. Log dose-response curves constructed from experiments in which the potencies of the drugs were compared with that of hexamethonium in depressing the responses of the nictitating membrane to preganglionic stimulation (5 Hz for 10 s every 2 min). All injections were intra-arterial.

Table 2 gives the effective doses to produce 50% depression of the nictitating membrane responses, and the potency ratios compared with hexamethonium.

When the continuous stimulation technique was used, the effective dose of hexamethonium was about half of that required when shorter bursts of stimulation were applied. Paton & Zaimis (1951) made a similar observation. The difference is probably mainly due to transmitter output falling more rapidly to a lower level during continuous stimulation without rest. Another contributing factor may be that, when the interrupted pattern of stimulation is used and the drug is injected 30 s before stimulation, its effective concentration in the biophase at the time of stimulation is likely to have fallen from its peak value.

With the intra-arterial doses required to produce an appreciable degree of ganglion block, pancuronium and gallamine often caused tachycardia with an accompanying rise in blood pressure. The rises in blood pressure and tachycardia were much reduced in the atropinized cat (0·1 mg/kg, i.v.) or after bilateral vagotomy, and were probably mainly due to the known action of these drugs in blocking the cardiac vagus (Bovet, Depierre & others, 1949; Jacob & Depierre, 1950; Riker & Wescoe, 1951; Bonta, Goorissen & Derkx, 1968; Saxena & Bonta, 1970). Presumably sufficient of the drugs reached the general circulation to produce these effects. Gallamine has also been shown to release noradrenaline from the heart (Brown & Crout, 1970) but this action was apparently unimportant under the conditions of the present experiments. Rises in blood pressure produced by these drugs have also been described in the

Table 2. *Potency of compounds in depressing contractions of the nictitating membrane.*

Compound	Intra-arterial doses (± standard error of mean) producing 50% depression of nictitating membrane contractions.	Relative molar potency (Hexamethonium = 1)
Hexamethonium bromide	301·7 ± 67·2 μg 0·83 × 10^{-6} mol	1
Benzoquinonium chloride	843·3 ± 73·1 μg 1·36 × 10^{-6} mol	0·59 ± 0·08
Hexamethonium bromide	496·7 ± 20·3 μg 1·37 × 10^{-6} mol	1
Gallamine triethiodide	5,600 ± 450 μg 6·28 × 10^{-6} mol	0·22 ± 0·02
Hexamethonium bromide	250·0 ± 16 μg 0·69 × 10^{-6} mol	1
Mecamylamine hydrochloride	8·0 ± 0·4 μg 3·9 × 10^{-8} mol	17·8 ± 1·75
Hexamethonium bromide	535·0 ± 134·4 μg 1·47 × 10^{-6} mol	1
Pancuronium bromide	513·3 ± 46·6 μg 70·1 × 10^{-8} mol	2·29 ± 0·26
Hexamethonium bromide	491·0 ± 48·2 μg 1·35 × 10^{-6} mol	1
Tubocurarine chloride	246·0 ± 66·4 μg 31·2 × 10^{-8} mol	5·37 ± 1·66

The mean values quoted are from 3–6 experiments where an individual drug was compared with hexamethonium. The relative potencies quoted are the mean values (± standard error of the mean) from the individual experiments.

clinical situation (Smith & Whitcher, 1967; Baird, 1968; Kennedy & Farman, 1968; Loh, 1970; Smith, Proctor & Spence, 1970). In contrast, tubocurarine and benzoquinonium produced a fall in blood pressure, which can partly be attributed to their ganglion blocking activity exerted as the drugs reached the general circulation; histamine release by tubocurarine may have been added to its effect. The depressor effect of benzoquinonium was particularly pronounced, but was reduced, though not abolished, by atropine (0·1 mg/kg, i.v.). The depressor effect of benzoquinonium, which has also been described in man (Foldes, 1957), was therefore probably augmented by its pronounced anticholinesterase activity (Hoppe, 1950, 1951; Blaber & Bowman, 1962).

In another series of experiments the potency ratios were re-determined while stimulating at a higher frequency (50 Hz). Apart from the change in frequency, the design of the experiments was the same as that described above. The potency of hexamethonium was markedly increased at the higher frequency (Fig. 4). Those of benzoquinonium and tubocurarine (Fig. 4) were slightly increased, whereas those of

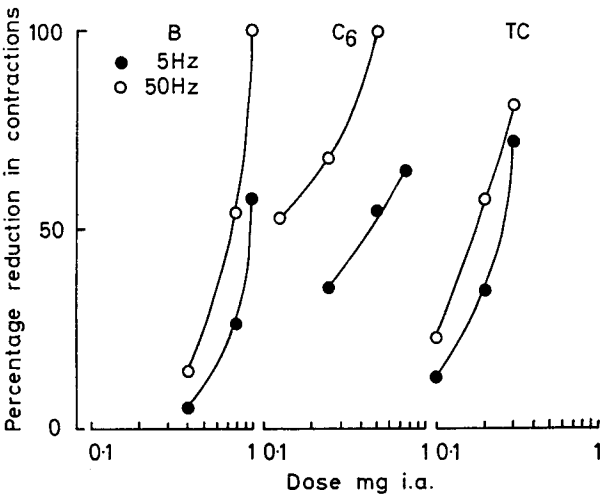

FIG. 4. Log dose-response curves constructed from 3 experiments in which the potencies of benzoquinonium (B), hexamethonium (C_6) and tubocurarine (TC) in depressing responses of the nictitating membrane were compared at different frequencies of stimulation of the preganglionic nerve.

gallamine, pancuronium and mecamylamine were not changed. Others have also noted a greater ganglionic blocking potency of hexamethonium at higher frequencies of stimulation (Paton & Zaimis, 1951; Riker & Komalahiranya, 1962; Elliott, 1965; Kharkevich, 1967).

Neuromuscular and ganglion block

In a further series of experiments, the drugs were injected intravenously and their effects on the soleus muscle and the nictitating membrane were studied simultaneously.

Tubocurarine (250–400 μg/kg) and benzoquinonium (180–400 μg/kg) usually depressed the contractions of the nictitating membrane in doses that produced more than 50% block of the soleus twitches (Fig. 5). In this respect, benzoquinonium was less effective than tubocurarine. The effect on the nictitating membrane matched

in its time course the fall in blood pressure produced by these drugs. Gallamine and pancuronium were without effect on the contractions of the nictitating membrane in doses big enough (gallamine, 1–2·5 mg/kg; pancuronium, 15–26 μg/kg) to produce complete block of soleus twitches (Fig. 5). These results with tubocurarine and gallamine confirm those of Hughes (1970). Hexamethonium (5–10 mg/kg) and mecamylamine (1–2 mg) produced complete block of the nictitating membrane in doses that did not affect the twitches of the soleus muscle (Fig. 5).

Benzoquinonium, gallamine, pancuronium and tubocurarine often, but not always, produced a fall in the background (resting) tension of the nictitating membrane in doses that had little or no effect on the evoked contractions of the membrane, but that did result in a significant degree of neuromuscular block. When evident, this effect matched, in its time course, the block of soleus muscle twitches. The fall in background tension produced by these drugs was probably due to neuromuscular block of skeletal muscles within the orbit which in some experiments impose a background tension on the membrane. Bowman, Callingham & Cuthbert (1964) demonstrated interference by skeletal muscle fibres with the nictitating membrane's response to single postganglionic shocks.

Hexamethonium and mecamylamine were without this effect on the background tension of the membrane, even in doses that produced complete ganglion block.

DISCUSSION

The results showed that, among the quaternary ammonium compounds used, tubocurarine was the most potent ganglion blocking drug on the cat superior cervical ganglion, being, on a molar basis, about five times more potent than hexamethonium at the level chosen for comparison. The ganglion blocking actions of curare and tubocurarine have long been known (Langley & Dickinson, 1889; Brown & Feldberg, 1936; Cannon & Rosenblueth, 1937) but it is not generally realized that tubocurarine may be more potent than hexamethonium under some conditions. Tubocurarine is

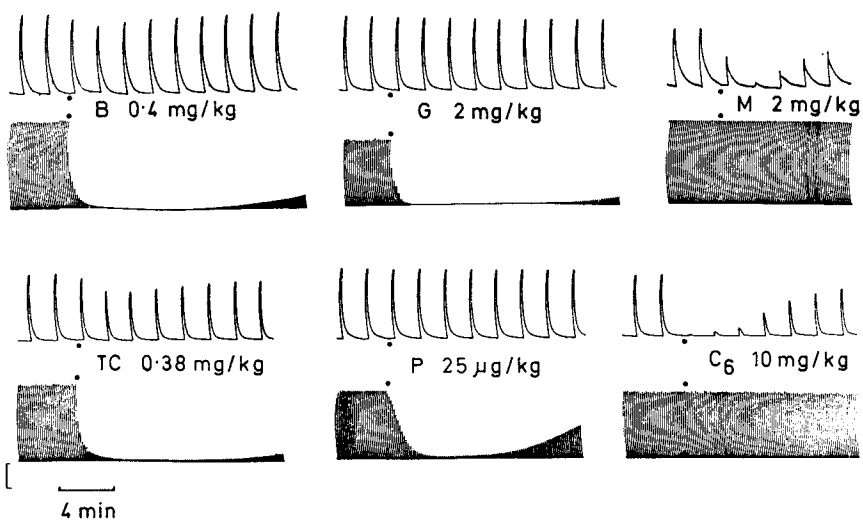

FIG. 5. Portions of 6 experiments in which contractions of the nictitating membrane (5 Hz for 10 s every 2 min) and of the soleus muscle (0·1 Hz) were recorded simultaneously. All injections were intravenous. Vertical calibration: 100 g for muscle and 5 g for nictitating membrane.

now considered to be a monoquaternary compound, the second nitrogen being tertiary (Everett, Lowe & Wilkinson, 1970), and the more pronounced ganglion blocking activity of tubocurarine compared with other neuromuscular blocking drugs, may be related to its monoquaternary nature.

Pancuronium was about twice as potent as hexamethonium on a molar basis (about equipotent by weight) in blocking transmission through the superior cervical ganglion when a frequency of stimulation of 5 Hz was used. In contrast, Buckett, Majoribanks & others (1968), who used a stimulation frequency of 50 Hz reported that pancuronium was eight times less potent on a weight basis than hexamethonium in blocking transmission through the same ganglion; we found that the ganglion blocking potency of pancuronium remained the same at this frequency. However, the potency of hexamethonium was increased so that the relative potency compared with that of pancuronium then more closely approached that determined by Buckett & others (1968).

Benzoquinonium, generally considered to be without ganglion blocking activity (Foldes, 1957), was found to be about half as potent as hexamethonium on a molar basis. Benzoquinonium may in fact be somewhat more potent as a ganglion blocking drug relative to hexamethonium than a simple comparison would indicate, since its powerful anticholinesterase activity might mask its receptor blocking action to some extent.

Benzoquinonium exhibited considerable ganglion blocking potency despite the fact that each quaternary nitrogen carries two ethyl groups and a benzyl group. Gallamine, on the other hand, with three ethyl groups on each quaternary nitrogen had only weak ganglion blocking activity, as noted also by Bülbring & Depierre (1949). Gallamine, however, has three side chains, each terminating in a quaternary nitrogen, and it is possible that one of these chains causes steric hindrance with the ganglionic receptors, although not with the muscle receptors, and that this accounts for its relative lack of ganglion blocking activity.

By intravenous injection, mecamylamine has been found to be about equipotent with hexamethonium on a weight basis in blocking autonomic ganglia (Stone, Torchiana & others, 1956). We found that hexamethonium and mecamylamine injected intravenously did not differ much in potency. However, when the drugs were injected intra-arterially, mecamylamine proved to be about 17 times more potent on a molar basis than hexamethonium (about 30 times more potent by weight), and this is the more relevant ratio in terms of structure-action relation. The relatively reduced activity of mecamylamine (which is a secondary amine) when injected intravenously, may be due to its greater lipid solubility causing it to be taken up and bound more avidly than hexamethonium by non specific sites all over the body. There is evidence that mecamylamine is taken up in this way and that the plasma concentration varies with the acid-base balance (Payne & Rowe, 1957).

In the clinical situation, the important factor is the selectivity for ganglia or muscle receptors that is reflected by the difference in the doses of the drugs required to affect each. Most of the drugs are relatively selective for one or the other, and probably only with tubocurarine are the ganglion blocking and neuromuscular blocking doses close enough for the former to be important. In fact, a number of autonomic reflexes arising in the course of surgical operations may be abolished by neuromuscular blocking doses of tubocurarine (Burstein, Jackson & Ravenstine, 1949; Burstein, Jackson & others, 1950).

Published ratios comparing neuromuscular and ganglion blocking potencies for different drugs vary over an extremely wide range. Factors that may affect such ratios include the species, the particular ganglion or muscle, the type of stimulation (chemical or through the nerve), the frequency of nerve stimulation, the method of application or route of administration of the drugs, and the anaesthetic used. Thus, such ratios can only be regarded as broad approximations.

It is often stated that ganglion blocking molecules should possess a range of interquaternary distances between the limits 6–7·8 Å (Gill, 1959; Triggle, 1965), whereas an interquaternary distance of 9–11 Å is optimal for neuromuscular blocking potency (see for example, Stenlake, 1963). Whereas the muscle receptors would appear to fit with this statement, the present results emphasise that the shorter distance between charged centres is not necessarily optimal for ganglion block. Tubocurarine, pancuronium and benzoquinonium, with the wider distances between charged centres, have pronounced ganglion blocking activity, tubocurarine and pancuronium being more potent than hexamethonium on a molar basis. The wider distance clearly imposes selective affinity for muscle so that neuromuscular block is produced by doses far below those needed to block ganglia. The shorter interquaternary distance, however, may not necessarily enhance affinity for ganglionic receptors. Rather, it greatly reduces affinity for muscle receptors so that selectivity is achieved in this way, despite the possibility of a slight fall off in ganglionic potency. It thus appears that the main difference in the two types of receptor is that the ganglionic receptor is less selective than the muscle receptor in that the former may combine with different compounds in which the distances between charged centres range from 6–11 Å. A reconsideration of published work on other compounds supports this idea. For example, in the methonium series of compounds (Paton & Zaimis, 1952) doses of decamethonium (interquaternary distance in solution, 9·5 Å—Elworthy, 1963) about 100 times greater than those needed to block muscle, are required to block ganglia, and doses of hexamethonium (interquaternary distance in solution, 6·3 Å—Elworthy, 1963) about 100 times greater than those that block ganglia are required to block muscle. In the present experiments the mean ratio of doses of hexamethonium for muscle and ganglia was about 50:1, but differences in ratios such as this are to be expected for the reasons already stated. Despite the obvious selectivity of these drugs in the doses used, a consideration of the effective doses supports the point being made. Decamethonium produces neuromuscular block in intravenous doses 30–40 μg/kg, and hexamethonium produces ganglion block in doses of 3–4 mg/kg. Taking the ratio of 100 mentioned above, then doses of decamethonium of 3–4 mg/kg would produce ganglion block, and on a molar basis this makes decamethonium a slightly more potent ganglion blocking drug than hexamethonium. In contrast, doses of hexamethonium of 300–400 mg/kg intravenously are far in excess of the neuromuscular blocking doses of decamethonium, once again emphasizing that reduction in interquaternary distance markedly attenuates affinity for muscle receptors, but does not enhance ganglion blocking potency.

Similar deductions might be drawn from recent work by Marshall & Martin-Smith (1972) who studied the ganglion blocking potency of some bisquaternary steroidal compounds with an interonium distance of about 6 Å. These compounds showed pronounced selectivity for ganglia compared with muscle, but on the basis of the present results, were actually less potent ganglion blocking drugs than pancuronium.

Clearly, from the point of view of deductions concerning the configuration of the

ganglionic receptor, the ganglion blocking potencies of neuromuscular blocking drugs should be taken into account more that has hitherto been so.

Acknowledgements

We are grateful to Organon Laboratories Ltd., for gifts of pancuronium. One of us (S.N.W.) is indebted to the University of Strathclyde for a studentship during the tenure of which this work was undertaken.

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