THE INFLUENCE OF CERTAIN GANGLIONIC BLOCKING AGENTS ON NEUROMUSCULAR TRANSMISSION

BY

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GANGLIONIC blockade was first used to produce controlled hypotension during surgery by Scurr (1951). This technique has since become generally accepted in anaesthetic practice.

Ganglion blocking drugs now available include the methonium compounds and the short acting agents trimetaphan and homatropinium (Tropheenium).

There is no doubt that these drugs act selectively on the sympathetic ganglia, which is, perhaps, surprising in view of the similar humoral transmission mechanism thought to operate at other synapses and also at the motor endplates. Bülbbring and Depierre (1949) suggested that the differences in the physiological mechanisms at sympathetic ganglia and the neuromuscular junction are quantitative rather than qualitative, and Paton (1954) considers the anatomical differences enough to account for dissimilarities in the actions of drugs at the two sites.

It seems likely that a drug which is active at sympathetic ganglia would, in sufficient concentration, be effective at the motor endplate (and vice versa).

The methonium compounds have been shown to have a neuromuscular blocking action in very large doses by Barlow and Ing (1948) and by Paton and Zaimis (1948). These workers showed that as the length of the chain between the quaternary nitrogen atoms decreases, so does the neuromuscular blocking effect diminish, being at its least in the hexane and pentane derivatives. However, large doses of hexamethonium will produce “head-drop” in the rabbit, and this effect is potentiated by curare.

With regard to trimetaphan, Acheson and Pereira (1946) stated that this drug had no curare-like effect. Randall et al. (1949) agreed with this observation and considered a slight muscular weakness noted in dogs to be due to the deficient blood supply caused by the hypotension. It is interesting to note that nearly all the animals which received a lethal dose of trimetaphan died of respiratory failure.

Tewfik (1957), noting a prolongation of suxamethonium apnoea in patients also receiving trimetaphan, suggested that trimetaphan has some slight muscle-paralyzing effect and may be destroyed by pseudocholinesterase. Payne (1957) has recently shown that trimetaphan has a weak neuromuscular blocking effect in cats previously given mecamylamine.

In the case of homatropinium, large doses are reported by Robertson et al. (1957) to produce respiratory paralysis in mice, rats, rabbits and cats. This may indicate the possibility of neuromuscular block occurring with this drug also.

Recent clinical experience has led us to believe that the effect of ganglion blocking drugs on neuromuscular transmission may be of practical importance. Accordingly, we decided to investigate and compare this effect in the case of hexamethonium, trimetaphan and homatropinium.

METHOD

The rat diaphragm preparation (Bülbring, 1946) was selected for this investigation. This provides a preparation of mammalian muscle which can easily be stimulated directly, or indirectly via the phrenic nerve. It may be studied under accurately controllable and reproducible conditions. Because of the large surface area and thin nature of the muscle, it is readily perfused and the effects of changes in the perfusion fluid are rapidly apparent.

Healthy, adult, albino rats were killed by a blow on the head and the diaphragm and phrenic nerves were removed. Each preparation consisted
of that part of the hemidiaphragm which is of
costal origin, together with its phrenic nerve.
This was perfused in 200 ml of Kreb's solution
at 37°C, through which was bubbled a mixture
of 95 per cent oxygen and 5 per cent carbon
dioxide. The muscle was secured by its costal
origin to an electrode. The insertion into the
central tendon was fastened to a fine steel wire
serving both as a second electrode and as attach-
ment to a recording lever writing on a smoked
drum. The phrenic nerve rested across another
pair of electrodes. Both direct muscle stimulation
via the first pair of electrodes and indirect (nerve)
stimulation via the second pair of electrodes were
effected by appropriate supramaximal, square-
wave pulses at a frequency of 5 per minute.
In accordance with the object of this investiga-
tion, preparations of the drugs involved were
those commonly used in anaesthesia.
Each ganglion blocking agent was investigated
by three different experiments, as follows.
(1) Effect of ganglion blocking agent alone.
Uniform contractions of the muscle in response
to both direct and to indirect stimulation were
recorded. Then, during indirect stimulation (i.e.
via the phrenic nerve), successive amounts of the
drug under investigation were added to the per-
fusion bath so as to produce a progressive increase
in concentration. Finally, direct muscle stimula-
tion was applied in order to determine whether
any effect produced by the drug was on the
indirect response alone. During this final period
of direct stimulation the drug concentration was
further increased.
(2) Effect of ganglion blocking agent plus curare.
A fresh preparation was used. Partial curariza-
tion was effected before the drug under investiga-
tion was added. This same preparation was then
thoroughly washed three times with fresh Kreb's
solution and allowed to recover fully. Experiment
1 was then performed upon it, in order to establish
that any difference in response had been due to
the presence of curare and not to any peculiarity
of the preparation.
(3) Effect of Neostigmine on recovery from gang-
li on blocking agent.
A preparation was exposed to a concentration
of ganglion blocking drug sufficient to produce
maximal response. It was then perfused in a
lower concentration so that relatively slow re-
covery occurred. During this recovery phase
indirect stimulation was applied and neostigmine
was then added.
RESULTS
In untreated preparations it was found that uni-
form contractions resulted from both direct and
indirect stimulation. Response to the former was
greater than the response to the latter. This is
usual with this preparation and the accepted
explanation is as follows. Direct stimulation
causes each muscle fibre to contract. The associ-
ated action potential traverses the fibre and excites
the nerve fibrils of the motor endplate as it passes.
A secondary response is produced and summation
results in an increased contraction. Neuromuscular
block will prevent this secondary effect from
influencing the muscle fibre, and the
observed twitch following direct stimulation is
then comparable to that caused by indirect stimu-
ation of an untreated (noncurarized) preparation.
All the drugs investigated modified the response
of the preparation. The effects produced were
as follows.
Hexamethonium bromide (fig. 1). 200 mg of
this drug produced no effect. A further 100 mg
produced a diminution of the twitch and a final
100 mg resulted in complete neuromuscular
block. Direct stimulation still produced active
contractions (reduced slightly to the level of the
original indirect response, as explained above)
and these were unaffected by two further 200
mg doses of hexamethonium.
Hexamethonium produced neither initial
potentiation of the contractions nor spontaneous
muscle twitches.
Hexamethonium plus curare (fig. 2). Two 0.1
mg doses of d-tubocurarine produced partial
neuromuscular block. Following this, only 250
mg of hexamethonium (in divided doses) pro-
duced total block. It is interesting to note the
initial antagonism to curare produced by the
first 100 mg dose of hexamethonium. After wash-
ing, this same preparation required a total of
375 mg of hexamethonium before total block
was produced (fig. 3).
Hexamethonium plus neostigmine (fig. 10a).
Neostigmine 1 mg assisted the recovery from
FIG. 1

Record of contractions of rat diaphragm preparation.
M = Direct muscle stimulation.  N = Indirect stimulation (via phrenic nerve).
All indicated doses in mg.
Neuromuscular block produced by the addition of successive doses of 200 mg, 100 mg and 100 mg of hexamethonium. Direct stimulation still produces an active response, unaffected by two further 200 mg doses of hexamethonium.

FIG. 2

Record of contractions of rat diaphragm preparation.
M = Direct muscle stimulation.  N = Indirect stimulation (via phrenic nerve).
All indicated doses in mg.
Partial neuromuscular block produced by two 0.1 mg doses of d-tubocurarine. Complete block produced by subsequent doses of 100 mg, 100 mg and 50 mg of hexamethonium.
neuromuscular block produced by hexamethonium.

Trimetaphan (fig. 4). Two 20 mg doses produced no effect, but a third similar dose produced total neuromuscular block. As before, the direct response was also slightly reduced, but further doses of 20 mg and 40 mg had no effect on it. No initial stimulation or muscle fasciculation was seen with trimetaphan.

Trimetaphan plus curare (fig. 5). Following partial curarization, only 20 mg of trimetaphan produced total block. After washing, this same preparation required 60 mg of trimetaphan (in divided doses) before complete block occurred (fig. 6).

Trimetaphan plus neostigmine (fig. 10b). Neostigmine 1 mg increased the degree of neuromuscular block in a preparation recovering from trimetaphan.

Homatropinium (fig. 7). 20 mg had no effect. A further 20 mg produced total neuromuscular block. Again the direct response was slightly depressed, but was unaffected by a further 20 mg and 40 mg of homatropinium. No initial stimulation or muscle fasciculation occurred.

Homatropinium plus curare (fig. 8). Following partial curarization, only 20 mg of homatropinium produced total block. After washing, this same preparation required 40 mg of homatropinium to effect total block (fig. 9).

Homatropinium plus neostigmine (fig. 10c). Neostigmine 1 mg accelerated the recovery from total homatropinium block.

The above results are summarized in table I.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose producing total neuromuscular block</th>
<th>Effect of neostigmine on block</th>
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<tbody>
<tr>
<td>Hexamethonium</td>
<td>400 mg (200 mg%)</td>
<td>Reversed</td>
</tr>
<tr>
<td>Trimetaphan</td>
<td>60 mg (30 mg%)</td>
<td>Potentiated</td>
</tr>
<tr>
<td>Homatropinium</td>
<td>40 mg (20 mg%)</td>
<td>Reversed</td>
</tr>
</tbody>
</table>
Fig. 4
Record of contractions of rat diaphragm preparation.
M = Direct muscle stimulation.  
N = Indirect stimulation (via phrenic nerve).  
All indicated doses in mg.
Neuromuscular block produced by three 20 mg doses of trimetaphan. Direct stimulation still produces an active response, unaffected by a further 20 mg and 40 mg of trimetaphan.

Fig. 5
Record of contractions of rat diaphragm preparation.
M = Direct muscle stimulation.  
N = Indirect stimulation (via phrenic nerve).  
All indicated doses in mg.
Partial neuromuscular block produced by two 0.1 mg doses of d-tubocurarine. Complete block produced by a subsequent dose of 20 mg of trimetaphan.
**Fig. 6**
Record of contractions of rat diaphragm preparation.

- **M** = Direct muscle stimulation.
- **N** = Indirect stimulation (via phrenic nerve).

All indicated doses in mg.

Same preparation as in figure 5 after washing and full recovery. Complete neuromuscular block after total of 60 mg of trimetaphan.

**Fig. 7**
Record of contractions of rat diaphragm preparation.

- **M** = Direct muscle stimulation.
- **N** = Indirect stimulation (via phrenic nerve).

All indicated doses in mg.

Neuromuscular block produced by two 20 mg doses of homatropinium. Direct stimulation still produces an active response, unaffected by a further 20 mg and 40 mg of homatropinium.
FIG. 8
Record of contractions of rat diaphragm preparation.
M = Direct muscle stimulation.
N = Indirect stimulation (via phrenic nerve).
All indicated doses in mg.
Partial neuromuscular block produced by two 0.1 mg doses of d-tubocurarine. Complete block produced by a subsequent dose of 20 mg of homatropinium.

FIG. 9
Record of contractions of rat diaphragm preparation.
M = Direct muscle stimulation.
N = Indirect stimulation (via phrenic nerve).
All indicated doses in mg.
Same preparation as in figure 8 after washing and full recovery. Complete neuromuscular block after total of 40 mg of homatropinium.
Record of contractions of rat diaphragm preparation.

M = Direct muscle stimulation. All indicated doses in mg.
N = Indirect stimulation (via phrenic nerve).

(a) Preparation recovering from complete neuromuscular block produced by hexamethonium. Improvement in contractions following neostigmine 1 mg.
(b) Preparation recovering from complete neuromuscular block produced by trimetaphan. Decrease in amplitude of contractions following neostigmine 1 mg.
(c) Preparation recovering from complete neuromuscular block produced by homatropinium. Improvement in contractions following neostigmine 1 mg.
(d) Improvement in contractions following the addition of neostigmine 1 mg to preparation unaffected by other drugs.

In order to establish the effect of neostigmine alone, 1 mg was added to a fresh preparation. This produced an increase in the amplitude of the contractions, as shown in figure 10d.

DISCUSSION

All three ganglion blocking drugs examined were found capable of neuromuscular blockade. This has not previously been reported in the case of trimetaphan or homatropinium.

In no case was any initial muscle stimulation or fasciculation seen. This probably indicates that the neuromuscular blocking mechanisms are not of the depolarizing type. This is supported by the improvement in contractions that followed the addition of neostigmine to preparations recovering from total hexamethonium and homatropinium block. The neuromuscular blocking effect of hexamethonium, reported by Paton and Zaimis (1952), is recognized to be of nondepolarizing type. In the case of trimetaphan, however, the recovery from total block was halted, and, in fact, the block made more profound by the addition of neostigmine. Tewfik (1957) has shown experimentally that, in vitro, trimetaphan suppresses cholinesterase. It may be that this is the mechanism whereby trimetaphan upsets neuromuscular transmission, and this would explain the potentiation produced by neostigmine, which, of course, also has powerful anticholinesterase activity.

To assess their clinical significance, these results must be considered quantitatively.

In the case of hexamethonium, the huge total of 400 mg was required to produce neuromuscular block, in a perfusion bath of 200 ml capacity.
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Even after partial curarization, 250 mg was required. It is unusual for more than 300 mg of hexamethonium bromide to be used in anaesthetic practice, and we consider, therefore, that, normally, the curare-like effect of this drug can be ignored. However, Payne (1957) has recommended caution in the administration of hexamethonium to patients receiving mecamylamine, as he considers that this combination might produce neuromuscular block.

Trimetaphan produced paralysis of the preparation after a total of 60 mg (30 mg per cent) had been given, but only 20 mg (10 mg per cent) was required after partial curarization. The clinical requirements of trimetaphan vary considerably. Large amounts may be needed in resistant patients, when tachyphylaxis occurs, or if coarctation of the aorta exists. Vermeulen-Cranch (1956) records the use of 2,400 mg and doses of this order are not uncommon. In such cases we believe neuromuscular transmission may be depressed.

The fate of trimetaphan in the body is not known, but the transient hypotensive effect of a single dose suggests a rapid breakdown. Gertner et al. (1955) recovered, unchanged, from the urine only one third of the amount administered. If the remainder is, as Tewfik (1957) suggests, destroyed in vivo by pseudocholinesterase, then patients having a low pseudocholinesterase level would be more likely to show neuromuscular effects, particularly if relaxants or neostigmine are also given.

Homatropinium produced complete block in lower dosage than trimetaphan. After partial curarization only 20 mg (10 mg per cent) was required. In clinical use, Robertson (1957) reports the administration of 2,280 mg to one patient. It appears, therefore, that the neuromuscular blocking action of homatropinium may be of practical significance. A point in favour of this drug, as compared with trimetaphan, is that this curare-like effect is antagonized by neostigmine.

SUMMARY

Experiments to investigate the actions of hexamethonium, trimetaphan and homatropinium on neuromuscular transmission are described. All three drugs are shown to produce neuromuscular block. Preliminary curarization reduces the dose required. Neostigmine antagonizes this action of hexamethonium and homatropinium, but potentiation occurs in the case of trimetaphan. These results and their possible clinical implications are discussed.

ACKNOWLEDGMENTS

Our thanks are due to Dr. A. H. Galley for the provision of apparatus and facilities, to Mr. P. E. B. Holmes for suggestions relating to experimental technique, and to Dr. G. Patterson for his most valuable advice. We are also indebted to Miss. M. Sandiford for her untiring assistance in the supply of the animal material.

REFERENCES

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