THE CLASSIFICATION OF THE MYONEURAL BLOCKING AGENTS

BY

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The classification of myoneural blocking agents at present accepted at least in Great Britain, divides these drugs into two groups, viz. those which compete with acetylcholine and prevent its access to the muscle end plate, i.e. the competitive blockers, and those which themselves depolarize the end plate with the result that the normal depolarizer, acetylcholine, is no longer able to exert its physiological function. It is, however, admitted already on all sides that substances exist which are capable of blocking transmission across the myoneural junction, yet cannot be assigned to either of these groups. For the want of a better description drugs of this type are referred to as possessing a 'mixed' action (Paton, 1953). The issue has become further complicated. For in order to explain some of the actions of decamethonium, the prototype of the depolarizing myoneural blockers, it has become necessary to postulate that this agent, while initially exerting its typical action, later exerts its paralysing activity by competing with acetylcholine (Zaimis, 1953). It therefore seems as if the classification of agents of this type into the accepted hard and fast groups is not satisfactory.

CLINICAL CONSIDERATIONS

This difficulty becomes even more apparent when the phenomena associated with the clinical administration of myoneural blocking agents in anaesthesia is considered. In the last few years the author has tested two synthetic 'curarizing' drugs (benzoquinonium and laudexium) which were found on laboratory testing to be 'competitive blockers' like d-tubocurarine. In clinical use, however, neither of these agents produced relaxation with exactly the same characteristics as those of the prototype com-

| Table I |
| The clinical properties of relaxant drugs |

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Decamethonium</th>
<th>Benzoquinonium</th>
<th>Laudexium</th>
<th>d-Tubocurarine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Useful partial paralysis</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Neostigmine reversibility</td>
<td>-</td>
<td>±</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tendency to cumulation</td>
<td>++</td>
<td>±</td>
<td>±</td>
<td>-</td>
</tr>
<tr>
<td>Type of recovery</td>
<td>Abrupt</td>
<td>Gradual</td>
<td>Gradual</td>
<td>Gradual</td>
</tr>
</tbody>
</table>
petitive blockers (Hunter, 1952, 1954). Two other agents, gallamine triethiodide and dimethyl-tubocurarine, also classified in the laboratory as competitive blockers, on the other hand did seem in clinical use to possess actions at the myoneural junction qualitatively comparable to d-tubocurarine.

A possible way out of this difficulty is suggested by a comparison of the clinical effects of the myoneural blocking agents already referred to (table I). It will be seen that there is no sharp differentiation of the drugs into two distinct groups but a gradual transition in type of action from that of decamethonium with its abrupt recovery of muscle power, its marked sparing of the diaphragm, its tendency to produce cumulative effects and the virtual absence of neostigmine reversibility to the action of the typical competitive blocker like d-tubocurarine. In this group the characteristic features are a gradual disappearance of the paralysis produced by a single dose, negligible diaphragmatic sparing, virtually no tendency to cumulation in ordinary clinical doses and complete reversibility by neostigmine. Benzoquinonium and laudexium occupy intermediate places in this table and have properties to correspond. Clinical experience, therefore, suggests that it is more profitable to regard relaxant drugs not as members of one of two sharply defined groups but as a series of agents all possessing the same basic properties, though in varying degrees.

EXPERIMENTAL EVIDENCE

If the actions of relaxant drugs observed in the laboratory are reviewed it will be found that there is a comparable gradation of effect. This is particularly marked in relation to spontaneous acetylcholine sensitizing power.

Acetylcholine Potentiation.

The various evidences of acetylcholine potentiation produced by some typical myoneural blocking agents will be seen in table II. In their first study of decamethonium, Paton and Zaimis (1949) observed that if this drug was given to a cat whose gastrocnemius was being stimulated by way of the motor nerve, the first effect was an increase in the force of the twitch, which was in fact converted into a short tetanus. Riker and his colleagues (1949) observed the same phenomenon when drugs like Tensilon were beginning to take effect. Winter and Lehmann (1950) who investigated the action of dipropam.
mine did not find any such changes in the cat but did observe that the drug increased the contraction of a frog’s rectus muscle produced by acetylcholine.

There is a close parallelism between these effects of myoneural blocking agents and their powers of producing contraction of a muscle when injected into the artery going directly to it. Decamethonium produces this response (Paton and Zaimis, 1949); so also do drugs like Tensilon (Riker et al., 1949) apparently in greater degree. Dipropamine does not possess this property (Hunter, 1953a) but like the drugs at the other end of the scale, benzoquinonium, laudexium, d-tubocurarine and gallamine triethiodide, it produces paralysis without preliminary stimulation. It is, however, possible with special techniques to obtain evidence that even the last of these agents produces a little stimulation before it paralyses skeletal muscle (Bulbring and Depierre, 1949; Riker and Wescoe, 1951).

The author has observed a similar gradation of effect when these drugs are given to mice. When a large dose of Tensilon is given there can be seen obvious fibrillation, fasciculation and vigorous tonic contractions of the limb muscles. Sometimes, indeed, these are forcible enough to jerk the animal into the air. They are not true convulsions but it is convenient to refer to them by this title. They are also obvious after the administration of decamethonium and like drugs and when dipropamine has been injected in large doses (Hunter, 1953a). They are produced by laudexium and benzoquinonium though in less marked degree, while after d-tubocurarine and gallamine triethiodide, the syndrome of exitus usually consists of head drop and respiratory paralysis with virtually no spontaneous muscular activity.

Another piece of evidence concerning the acetylcholine potentiating action of these agents is found in their power of reversing the paralysis produced by d-tubocurarine and gallamine triethiodide. Tensilon possesses this action in very marked degree. Neither decamethonium nor its di-thia analogue (Ro 3-0386) (Hunter, 1953b) is as potent in this respect but reversal can quite readily be demonstrated, though its action is evanescent. Dipropamine also reverses paralysis produced by d-tubocurarine (Winter and Lehman, 1950), while benzoquinonium and laudexium lack this action completely. Indeed their action after d-tubocurarine is to intensify the myoneural block.

Though gradation in the properties of myoneural blocking agents is most marked in relation to their power of potentiating

<table>
<thead>
<tr>
<th></th>
<th>Tensilon</th>
<th>Decamethonium</th>
<th>Mytolon</th>
<th>Laudolissin</th>
<th>Gallamine triethiodide</th>
<th>d-Tubocurarine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine release</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sympathetic ganglion block</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Parasympathetic ganglion block</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Muscarinic action</td>
<td></td>
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</tbody>
</table>
acetylcholine it can also be seen in other aspects of their action at the muscle end-plate. The author and most other workers in this field have observed that when d-tubocurarine or gallamine triethiodide is given to a cat there is a very marked weakening of the response of a muscle to rapidly repeated stimuli, i.e. to a tetanus. This is by no means so obvious when laudexium and benzoquinonium have been injected and is then apparent only during the deepest phases of the action of decamethonium and like drugs.

**Neostigmine Reversibility.**

There is a similar gradation in the response of the paralysed animal to neostigmine. The action of d-tubocurarine and gallamine triethiodide are promptly and completely reversed by this drug. In the case of laudexium the antagonism is not so satisfactory in the cat (Hunter, 1955) while the reversal of benzoquinonium by neostigmine has been reported only in the dog and that from comparatively slight degrees of myoneural block (Hoppe, 1950). This varied response to neostigmine is even more marked when the antagonist is used to try to protect mice against lethal doses of the relaxant. With gallamine triethiodide, it affords nearly complete protection against an L.D.95. With laudexium the protection is less marked while neostigmine increases the toxicity of benzoquinonium (Hunter, 1952), though this may be due to the summation of the anticholinesterase activity of these two drugs.

**Effects on Autonomic Nervous System.**

Gradation of activity can also be seen in the effects of the myoneural blocking agents on the synapses of the autonomic nervous system. Tensilon has a very mild muscarinic action which is probably exerted at the nerve endings of the parasympathetic but it does not block ganglion conduction. Decamethonium and dipropamine have little action on any part of the autonomic nervous system. The effects of benzoquinonium on the parasympathetic are masked by its powerful anticholinesterase action, but it has no action on the transmission through the sympathetic ganglia. Laudexium produces block at this latter site but its activity is only one quarter of that of d-tubocurarine. Gallamine triethiodide is less active than d-tubocurarine as a blocker of sympathetic ganglia in the cat (Randall, 1951) but in man its most obvious action is the interruption of the parasympathetic which it produces.

**Gradation of Chemical Structure.**

Finally the gradation is not confined to pharmacological activity. It can be seen in the chemical structure at least of the relaxants which the author has tested. In these there can be seen a gradual transition from the simple phenyl-alkyl-ammonium structure of Tensilon to the double ended compounds of high activity like decamethonium, dipropamine and benzoquinonium. A further development is shown in the last of these compounds which is combined with benzyl chloride instead being a simple salt of an inorganic acid. In laudexium the terminal trimethylammonium group is replaced by the complex nitrogen containing ring of isoquinoline. Finally in d-tubocurarine the decamethylene chain is replaced by a series of benzene ring linkages. Gallamine
triethiodide does not fit very clearly into this scheme of things but it is quite atypical in that it contains three quaternary groups which are triethyl ammonium and not the trimethylammonium structures usually associated with myoneural blocking activity.

DISCUSSION

There is nothing in the conception of gradation of activity which conflicts with current pharmacological teaching. It is well recognized that many drugs have an initial stimulatory and a subsequent paralysing effect and this is particularly common in those exerting effects on the cholinergic synapses of the autonomic nervous system. In fact it has long been known that some drugs, e.g. hexamethonium, paralyse the sympathetic without preliminary stimulation, while others like nicotine produce marked initial activity before interrupting the function of these ganglia. It is therefore not surprising that agents acting at the motor end-plate should also have a variable amount of stimulatory activity before they produce acetylcholine block at the site of their action. With this in view, it is suggested that the myoneural blocking agents be regarded not as two distinct groups of substances but as drugs occupying places on a ladder, those at the bottom possessing very marked initial stimulatory effects while those at the other end are almost pure depressors with virtually no initial stimulatory effect.

The substitution of the classification here suggested offers two advantages over that at present in use. From the clinical point of view it will put an end to the misleading description of new myoneural blocking agents. It will no longer be found that agents which have been described in the laboratory as ‘competitive blockers’ in fact prove to possess only some of the properties of d-tubocurarine and in consequence are less useful clinically. Secondly, by placing the emphasis on the amount of acetylcholine potentiation exerted by drugs of this type, rather than on their physiological effect at the end-plate it may be possible to obtain a reconciliation of many of the contradictory results obtained by workers studying myoneural blocking agents in the laboratory.

SUMMARY

The existing classification of myoneural blocking agents is misleading especially when applied to their clinical use. It is suggested that instead of describing drugs of this type as belonging to two hard and fast groups they should be regarded as substances possessing essentially the same properties but those in varying degree. They differ mainly in the amount of overactivity which they produce at the myoneural junction before paralysis develops. If they are graded on this basis it would appear that many of their other properties, such as neostigmine reversibility, their action on the effect on a tetanus and perhaps even their ganglion blocking activity will show a more or less comparable variation.

REFERENCES

—— (1953a). Anaesthesia, 8, 90.
BOOK REVIEW


Of recent years great interest has been taken in the distribution of fluid and electrolytes in the human body, and seeing the body is made up of no less than 70 per cent of H₂O it is obvious that a knowledge of its distribution and functions is a matter of the utmost importance. Until we know the normal we are not in a position to appreciate modification thereof, such for example as takes place when the body is subjected to surgical interference.

These changes are described. They consist of water and salt retention in the first 24 to 48 hours following operation, and are attributed in the main to the secretion of the posterior pituitary antidiuretic hormone. Many patients have lost their lives following surgical interference, not because of any lack of surgical dexterity but simply on account of being inadequately prepared for operation. The author points out that post-operative morbidity and mortality are significantly higher in patients in whom the distribution of H₂O and electrolytes is abnormal; also he stresses that the abnormality is less easily corrected after operation than before. A pre-operative assessment in all doubtful cases is therefore essential and consists of a careful clinical appraisement of the patient's condition. This should take note of the following points:

1. Mental condition.
2. Blood pressure.
3. Condition of skin, subcutaneous tissue, mouth and muscle tone.
4. Urine—quantity, specific gravity and chloride concentration.
5. Blood urea.

If there is any deficiency of salt or H₂O this must be remedied by the mouth if possible, as this is a safer route than by the veins. This sounds simple, but in point of fact the interpretation of the results of examination, and the various tests applied, requires both skill and experience, and the cases illustrated in Appendix B provide a most useful guide.

Alike to the student, the practising surgeon and the anaesthetist, to whom this is a matter of great importance, this book will prove an up-to-date account of a subject of great interest.*

E. Falkner Hill

*The author points out there is a mistake in the figures on p. 87. For the two solutions described read:

1. KCl 3.0 gm./L (K 40 m.equiv./L: Cl 40 m.equiv./L)
2. KCl 3.0 gm./L: NaCl 2.25 gm./L (K 40 m.equiv./L: Na 40 m.equiv./L: Cl 80 m.equiv./L)