THE "COMPETITIVE" MUSCLE RELAXANTS*

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Pharmacological Review

The pharmacology of nerve impulse transmission at the neuromuscular junction and the effect of the various relaxant drugs should be understood by all who use these drugs. Curare is one of the few drugs which, in therapeutic doses, acts at one site only with a reversible pharmacological action. It is said to be "the most purely elective drug" known.

The muscle relaxants—d-tubocurare (d-tubocurarine), Flaxedil (gallamine triethoidide), Metubine (di-methyltubocurarine), Laudolissin—are grouped together because of their mechanism of action in producing striated muscle relaxation. It is postulated that there are specific acetylcholine (ACh) receptors, located in the motor-end plate region of muscle cells. These relaxants, mentioned above, also fit the configuration of these receptors, and thus occupy these receptors, preventing fixation of ACh and hence inhibiting the action of ACh. This is called substrate competition. The ACh which is present and "unfixed" because of the substrate competition by a relaxant drug is then hydrolysed by cholinesterase.

In the following discussion, I wish to bring out three points which are directly related to the clinical use of these drugs.

1. The degree of muscular relaxation depends not only upon the particular relaxant used, and the amount of the drug, but also upon the amount of ACh released as a response to nerve impulses received at the motor-end plate. Thus in the lighter planes of anaesthesia, which are commonly used today—i.e. 1st plane, 2nd stage (Guedel), or stage of anaesthetic sleep (Harris)—effector nerve impulses (rhythmic impulses from higher centres, which maintain normal muscle tone) are still present. Thus the amount of ACh present is greater than in the deeper planes of anaesthesia, and more relaxant is required to compete with the ACh to produce a given state of muscular relaxation. *Therefore* lighter planes of general anaesthesia require more relaxant.

2. The loss of muscle tone in skeletal muscles can be maintained for as long as the accumulation of an effective concentration of ACh at the neuromuscular junction is prevented. Thus if a patient be kept continuously anaesthetized to the level of complete sensory loss (between the second and third planes) a given degree of relaxation with one dose of d-tubocurarine can be maintained for up to five hours. Under these conditions the release of ACh is effectively prevented by the maintenance of anaesthesia to the level of complete sensory loss throughout. *Therefore* the depth of anaesthesia affects the duration of action of relaxants.

3. It is suggested that different muscle groups have different quantities of ACh formation at their respective neuromuscular junctions. Thus the small

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muscles of the eyes, mouth, etc., have less than the medium muscles (limbs), and they less than the flat muscles in the following order: abdominals, back, intercostals, and intercostal portion of the diaphragm, and finally the crural fibres of the diaphragm. The large limb and trunk muscles receive more effector impluses to maintain posture, and the crural fibres of the diaphragm receive the most as they are under continual bombardment from the respiratory centre. Thus one can see that various muscle groups will be paralysed to a different degree by a given dose of relaxant and as the depth of anaesthesia affects the amount of ACh present, *therefore*—the depth of anaesthesia affects the site of relaxation.

It is said that some relaxants, particularly Flaxedil and di-methyltubocurarine, spare the intercostals, yet at the same time give adequate abdominal relaxation. This is only a clinical impression, fostered particularly by the makers of the said drugs. It has never been proven, and I personally do not believe it.

Blood-borne anaesthetics do not depress the excitability or the conductivity of nerve fibres in concentrations used in clinical practice but they do reduce impulse formation in the upper motor neurons by brain depression. Impulse formation is not stopped completely but may be sufficient to be a major factor in complete loss of muscle tone, except in the crural fibres of the diaphragm. At the same time, the concentration of blood-borne anaesthetics at the neuromuscular junction may be sufficient to inhibit the small quantity of ACh released. This action enhances the action of relaxants and is particularly so of ether. There is some suggestion that hyperglycaemia inhibits ACh release, and this may be a factor with ether.

Natural Alkaloids versus Synthetic Relaxants

There has been a tendency in recent years to discredit the natural alkaloids, d-tubocurarine and its dimethylester, in favour of synthetic agents, Flaxedil, Mytolon and more recently Laudolissin. It must be remembered that most of the synthetic relaxants were developed in Great Britain and France because of the dollar problem since the United States controlled d-tubocurarine. Although we are all familiar with Flaxedil and have used it for about four years, it has only been used in the United States for the past year. As a rule the synthetic substances are cheaper than the natural alkaloids.

The argument against d-tubocurarine has been based on the so-called side reactions, the liberation of histamine causing bronchospasm, and, with large doses, hypotension, irreversible shock and C.N.S. depression. This was probably true in the early days of curare when the agent was not pure d-tubocurarine, but a mixture of alkaloids, curarines and curines. The present-day purified drug does not cause bronchospasm and in therapeutic doses, even such large ones as 50 to 60 mg., has no central effects except in the presence of anoxia and causes no cardiac depression, no change in cardiac output or in peripheral resistance. However, very massive doses will block autonomic ganglia (and perhaps all other relaxant drugs do likewise) and depress the vagus nerve. D-tubocurarine has no effect on liver, uterine or rental function and does not pass through the placenta.

Choice of Relaxant

Personally, I can see little difference in relaxing properties of these various drugs. Each drug enjoys enthusiastic support by certain groups and is in disfavour with others. From the conflicting reports of the superiority of one drug over another, one can only conclude that all the drugs are efficient and any differences noted are not due to the drug but to the manner in which it is used and the dosage.

Of all the drugs in this group, Mytolon has been the only one to fall by the wayside, because of its possible irritating and haemolytic properties. Some groups of anaesthetists use one drug exclusively for all purposes, but I believe it is better to use them all, and fit the drug to the specific purpose in mind, as they do have differences in time of onset of relaxation, duration of action, and miscibility with sodium thiopentone.

The details of dosage will not be mentioned. The duration of action varies somewhat, but, as pointed out above, this is greatly affected by the depth of anaesthesia, so that duration figures actually mean little. The onset of action does vary from ½ to 1½ minutes for Flaxedil, 2–4 minutes for di-methyl and d-tubocurarine, to 5 minutes for Laudolissin. Flaxedil does have a vagolytic action resulting in a varying degree of tachycardia, which is unimportant except perhaps in patients with cardiac disease. Because of this vagolytic action, Flaxedil has a tendency to depress the cough reflex and intubation with this relaxant may be smoother than with the others of the series.

All of the four drugs can be antagonized by prostigmine. This is a safe procedure if enough atropine (1/50 gr. for adults) is used 3–5 minutes before an adequate dose of prostigmine (2.5–5.0 mg.). All of these drugs except Laudolissin are miscible with thioperitone.

Laudolissin (Compound 20) is the newest of the drugs, not yet available on the market. It is a heterocylic decamethylene compound, and its structure is suggestive of a combination of d-tubocurarine and decamethonium. It was first described by Taylor and Collier in England in 1952. It is a true curarizing agent with a potency in man just one-half that of d-tubocurarine (whereas dimethylcurare is twice as potent). It has a somewhat longer action than d-tubocurarine and is antagonized by prostigmine. A dose of 30 mg. is roughly equivalent to 15 mg. of d-tubocurarine. Its onset of action is slower (5 minutes) and it has no "sparing" action on the intercostal muscles. It does not produce good vocal cord relaxation, unlike Flaxedil, and thus some other agent is better used for intubation purposes (succinyl choline is an excellent adjunct). It is said that "Syncurine" and Succinylcholine will reverse the effects of Laudolissin but this has not been my experience. There are no side effects with Laudolissin and it is not miscible with thiopentone.

Contra-Indications to the Use of Relaxant Drugs

1. Absolute—myasthenia gravis, and perhaps cases of motor neuron disease.
2. Relative

(*a*) *Age*: particularly in the elderly, poor risk patients, with decreased

metabolic rates; with children use reduced dosage, e.g. d-tubocurarine 1 mg./6 pd.; Flaxedil 1 mg./pd.

(*b*) Pulmonary emphysema and pulmonary fibrosis, where ventilation is dependent upon the action of the secondary respiratory muscles (scalenii, trapezii, etc.).

(*c*) Cardia disease. Flaxedil causes tachycardia and profound relaxation may reduce venous return and cardiac output in an already embarrassed cardiovascular system.

(*d*) Dehydration and vomiting, where potassium deficiency is suspected; it has been postulated that K^+ deficiency will prolong the action of relaxants.

Summary

The mode of action of the "Competitive" or "Blocking" relaxant drugs has been briefly reviewed. The degree of muscular relaxation obtained, the duration of relaxation and the site of relaxation are all affected by the depth of anaesthesia. Absolute and relative contra-indications to the use of relaxing drugs are briefly discussed.

Résumé

Les relâcheurs musculaires d-tubo-curarine, Flaxedil, Métubine et Laudolissine sont groupés parce que le mécanisme par lequel ils produisent un relâchement du muscle strié est identique. L'on postule qu'il y a des récepteurs spécifiques d'acétylcholine (ACh) situés dans la région de la plaque motrice des cellules musculaires. Ce groupe de relâcheurs s'adapte aussi à la configuration de ces récepteurs et en les "occupant" bloque l'action de l'ACh.

Le degré de relâchement musculaire, la durée du relâchement et l'endroit du relâchement maximum se rapportent inversement à la quantité d'ACh libérée dans la région des récepteurs de la plaque motrice, en réponse à l'excitation arrivant par les voies nerveuses. Etant donné que l'excitation est réduite par des plans plus profonds d'anesthésie, tout ceci est directement influencé par la profondeur de l'anesthésie. Une plus grande quantité du relâcheur est nécessaire pour une anesthésie plus légère, une quantité moindre pour une anesthésie profonde. La durée de l'action varie directement avec la profondeur de l'anesthésie.

Myaesthenia gravis est une contre-indication absolue à l'emploi de ces drogues. Des contre-indications relatives sont des extrêmes d'âge, un métabolisme diminué, l'emphysème pulmonaire ou fibrose, les maladies cardiaques, la déshydration et le vomissement.