DIALLYL NOR-TOXIFERINE—A NEW RELAXANT

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Ever since 1914, when George Crile Senior, put forward his theory of anoci-association, anaesthesia began to develope along certain lines. Instead of just producing an unconscious patient who felt no pain, the anaesthetist began to divide the anaesthetic state into its components parts of sleep, analgesia and muscular relaxation. The neuromuscular blocking agents were used with increasing frequency, and, from 1948 onwards, when Gray and Halton published their paper on curare, these agents became an essential part of the armamentarium of the present day anaesthetist.

However, the neuromuscular blocking agents in common use, in particular the shorter acting ones, have certain disadvantages which preclude their use in operative procedures lasting half to one hour.

Suxamethonium. This depolarizing agent, given in intermittent doses, should be the ideal relaxant for operative procedures like appendicectomies and herniorraphies, but for the fact that it produces a rather high incidence of post-operative muscle pains, which may be particullarly distressing to the highly sensitive type of patient. The reason for these pains has not been fully established, but amongst the contributory factors may be:— (a) liberation of potassium ions, (b) the initial muscle fasciculations causing mechanical lesions, and (c) the liberation of lactic acid. In addition, suxamethonium may exhibit a marked parasympathomimetic effect, more so in the unatropinised patient, in whom it may precipitate cardiac arrest.

Decamethonium. Also a depolarizing agent, decamethonium has a duration of action lasting about 30 minutes; it is a useful agent, but it also produces post-operative muscle pains which may last a few hours. Again, there is the danger of a dual block developing if used in doses of more than 10 mgms.

Gallamine Triethiodide. This non-depolarizing agent also has disadvantages—it produces a marked vagal blocking effect, leading to tachycardia, and it crosses the placenta, limiting its use in obstetric procedures like Caesarian sections.

Newer relaxants. Recently, 2 other neuromuscular blocking agents were developed, but their use has been discarded in the majority of centres after clinical trials were carried out. One was diohexadecanium bromide (Prestonal) which was found to act for 6 to 8 minutes; claimed at first to be a non-depolarizing agent, it was found (Jolly, 1957) that anti-cholinesterases actually potentiated the block instead of reversing it. In addition, it produces a marked tachycardia and peripheral vasodilatation, and despite the fact that it produces apnoea, the jaw muscles remain stiff, rendering intubation difficult.

The other compound, hexamethylene bis-carbominoylcholine bromide (Imbretil) is still being used in certain centres; like suxamethonium it produces fasciculations and cramp-like pains; believed at first to have both depolarizing and non-depolarizing properties, it has subsequently been shown that it is a depolarizing agent, which in large doses will give rise to a dual block. In addition, it crosses the placental barrier.

DIALLYL NOR-TOXIFERINE

Diallyl nor-toxiferine is a synthetic derivative of the Calabash alkaloid, C-toxiferine I, and like the latter, contains 2 quaternary ammonium atoms separated by about 15 Angstrom units; it may be recalled that these 2 properties are essential to make up the key, so that the door of muscle-excitation can be locked or opened at will.

Diallyl nor-toxiferine is colourless, odourless and crystalline. It is unstable in the presence of air and light; the ready-packed solutions appeared to deteriorate in strength, even when kept in a cool, dark place. This was evident during the clinical trials when more than the calculated dose had to be used if the ready-packed solutions were used. The preparation of powder and solvent, mixed just before using, appeared to keep better in Singapore, and deterioration in potency was not so pronounced. Diallyl nor-toxiferine is incompatible with barbiturates.

Like C-toxiferine I, diallyl nor-toxiferine is a non-depolarizing relaxant; it does not produce the preliminary muscle fasciculations seen with the depolarizing agents, and does not give rise to post-operative muscle pains. Being a non-depolarizing agent one would expect it to be reversed by neostigmine. In actual fact, smaller

doses of neostigmine were needed for reversal when using diallyl nor-toxiferine.

Originally, C-toxiferine I was claimed to be the natural successor to d-tubocurarine chloride, but it has fallen into disuse for the following reasons:— (a) it has the longest duration of action of all the known non-depolarizing agents, including laudexium methylsulphate, making it useful only in long operations and in the treatment of tetanus. (b) there is also the danger of recurarization, even after apparently adequate reversal by neostigmine.

The duration of action of diallyl nor-toxiferine corresponds approximately to that of gallamine triethiodide, that is, 20 to 25 minutes, but this, of course, depends on the dosage used, higher initial doses tending to cause a longer period of block. Diallyl nor-toxiferine produces a more profound relaxation of the abdominal musculature compared with equipotent doses of gallamine triethiodide. It is said to have no ganglion blocking effect and does not cause histamine-release, as does curare and gallamine.

Clinical Applications:— Diallyl nor-toxiferine has been used in 302 cases, distributed as follows:—

General surgery	207
Orthopaedic cases	42
Gynaecological cases	35
Obstetric cases	13
Radiological investigations	2
Oral surgery	2
Otorhinolaryngology	1

The 207 cases listed under general surgery were comprised of 26 operations in the head and neck region, 23 operations in the thorax, and 158 abdominal operations. Most of the 42 orthopaedic cases were major procedures, such as laminectomies and pin and plating of fractured femurs.

The 35 gynaecological cases were all major operations and the 13 obstetric procedures were all lower segment Caesarian sections.

DOSAGE AND METHOD OF ADMINISTRATION

Initially, the dose used was based on the recommendation of Hugin and Kissling (1961), and modified to mgms. per stone body weight. The dose first used for intubation and relaxation was 1 mgm. per stone body weight, but it was found that at such dosage, endotracheal intubation was difficult even after waiting for 5 minutes; relaxation with this dosage, however, was sufficient for lower abdominal procedures like appendicectomies and herniorraphies, provided intubation was not attempted. Increasing the dose to 1.5 mgms. per stone body weight made intubation easier, but at 2.0 mgms. per stone body weight, intubation was as easy as with suxamethonium, though abdominal relaxation persisted for as long as 40 minutes, compared with the 10 to 15 minutes after doses of 1 mgm. per stone body weight. In the majority of cases, 1.5 to 2.00 mgms. per stone body weight were used, smaller doses being used for the very ill patient and the geriatric case. At this dosage level, diallyl nor-toxiferine is about one and a half times to twice the strength of d-tubocurarine chloride which is used in doses of 3 mgms. per stone body weight.

Diallyl nor-toxiferine was administered intravenously, via a Mitchell's needle, before or after a sleep dose of either methohexitone or thiopentone, and in most cases, a test dose of 2 mgms. was given. The test dose was given routinely to all patients undergoing subtotal thyroidectomy for thyrotoxicosis, in view of the possible relationship between thyrotoxicosis and myasthenia gravis. The patient has to be ventilated with nitrous oxide and oxygen for at least 2 minutes before direct vision intubation can be performed. In certain instances, where difficulty is anticipated with intubation because of anatomical peculiarities, suxamethonium in 25 to 50 mgm. doses was given; diallyl nor-toxiferine was given after the resumption of breathing. On some occasions, d-tubocurarine chloride in 3 mgm. doses, was used to supplement diallyl nor-toxiferine. This was very satisfactory, and there were no cases of prolonged block as a result of combining the 2 non-depolarizing agents together. The other cases were supplemented with intermittent doses of diallyl nor-toxiferine. In all cases, anaesthesia was maintained with nitrous oxide, oxygen and hyperventilation (Geddes and Gray, 1959).

Ether and halothane, which are said to potentiate the action of non-depolarizing agents, have not been used in conjunction with diallyl nor-toxiferine, because it was felt that the intravenous barbiturate, relaxant, nitrous oxide, oxygen sequence was adequate for most types of major and minor surgery, without having recourse to other potent agents which only tend to complicate the picture should any eventuality occur.

There was no noticeable effect on the blood pressure or pulse rate, and no evidence of histamine release as occasionally seen in the form of wheals after the administration of d-tubocurarine chloride. Reversal was adequately achie-

ved in most cases with only half the amount of neostigmine usually used for d-tubocurarine chloride, i.e. 2.5 mgms. instead of 5.0 mgms.; in all cases the neostigmine was preceded by atropine in 1.3 mgm. doses.

Diallyl nor-toxiferine is eminently suited for plastic operations on the head and neck, block dissections of the neck and thyroidectomies, where the surgeon desires to infiltrate the skin and tissues with adrenaline. The danger of cardiac arrhythmias is averted, and the patient is lightly anaesthetised, thereby ensuring rapid return to consciousness at the end of the operation. Whereas relaxation could be adequately provided by curare, it is felt that there is less tendency to prolonged apnoea when using diallyl nor-toxiferine, because it is more easily reversed by neostigmine.

In abdominal surgery, however, there is always the danger of overdosage in operations lasting more than an hour. This can be avoided by using small maintenance doses of curare; for an extensive procedure such as Allison's operation for carcinoma of the cardia of the stomach, only 25 mgms. of diallyl nor-toxiferine and 6 mgms. of curare were used. For operations of lesser magnitude, diallyl nor-toxiferine was used per se, and proved very suitable.

Much the same conditions were observed, as in abdominal surgery, when using diallyl nor-toxiferine in gynaecological operations. In the lower segment Caesarian sections, the babies were in no way affected, and it was deduced that the drug either did not cross the placenta, or if it did, the quantities going across were insufficient to affect the foetus.

SUMMARY

Diallyl nor-toxiferine is a non-depolarizing agent about one and a half times to twice the potency of d-tubocurarine chloride, but of shorter duration of action than the older drug. It is easily reversed by neostigmine and has been found suitable for a variety of operative procedures, including most operations on the head and neck, thorax, abdomen and pelvis. If a more stable form could be developed, it should prove popular with anaesthetists who use the intravenous barbiturate, relaxant, nitrous oxide, oxygen sequence.

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REFERENCES

Crile, G.W., and Lower, W.E. (1914) Anoci-association. Philadelphia, Saunders.

Gray, T.C., and Halton, J. (1948) Brit. Med. Jour. 1. 784.

Jolly, C. (1957) Anaesthesia., 12, 3.

Geddes, I.C. and Gray, T.C. (1959) Lancet, 2. 4.

Hugin, Von. W. and Kissling, P. (1961) Schweizerische. Medizinische Wochenschrift, 91, 15, 455-457.