Clinical potentialities of certain bisquaternary salts causing neuromuscular and ganglionic block / [W.D.M. Paton, E.J. Zaimis].

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Clinical Potentialities of Certain Bisquaternary Salts Causing Neuromuscular and Ganglionic Block

Two members of the polymethylene αω-bistrimethylammonium series[1] ($[N^+(CH_3)_3.(CH_2)_n.N^+(CH_3)_3]$ $2I^-$) appear to possess activities which may be suitable for clinical use—the C 10 derivative ($n = 10$) to produce neuromuscular block, the C 6 derivative ($n = 6$) to produce ganglionic block. We wish to describe briefly the main characteristics of these compounds, in view of the great attention being paid to possible substitutes for *d*-tubocurarine chloride[2,3] and to the use of tetraethylammonium iodide for ganglionic block[4].

The accompanying table gives the doses of C 10 and *d*-tubocurarine chloride which are approximately equipotent in causing neuromuscular block when injected intravenously into unanæsthetized monkeys (*Macaca mulatta*), cats and rabbits.

	Monkey	Cat	Rabbit
d-Tubocurarine chloride (mgm./kgm.)	0·1	0·15	0·17
C 10 compound mgm./kgm.)	0·3	0·03	0·10

These results show variation of potency of the C 10 derivative of the bistrimethylammonium salt with species (as we previously reported); preliminary trials indicate that man is close to the cat in sensitivity. The onset of the paralysis is smooth and uneventful in the monkey and the cat; in the rabbit, transient fine fasciculations (of the type reported in the cat under chloralose[1]) are just detectable. In general, the order in which the various muscles are paralysed and recover from paralysis is much the same as with *d*-tubocurarine chloride.

The main difference between the C 10 compound and *d*-tubocurarine chloride lies in the relative sparing of the respiration by the former in the monkey and the cat. In the monkey, even a small dose of *d*-tubocurarine chloride (0·075 mgm./kgm.), sufficient to produce weakness for about ten minutes, is accompanied by exaggerated movements of the nostrils and trunk indicative of respiratory difficulty. Similar respiratory signs can only be produced by the C 10 compound under test with a dose of 0·5 mgm./kgm., which causes complete paralysis of

the animal for ten minutes, and weakness for an hour. Similar observations have been made in unanæsthetized and anæsthetized cats, and (to a less extent) in the rabbit. The ratio of the dose which just suspends respiration in half the animals to that which produces definite weakness for at least 10 min. has been estimated, as an index of the relative activity on respiratory and other muscles. In the monkey, the ratio is 2·6 for the C 10 compound, and 1·5 for *d*-tubocurarine; in the cat, the ratios are respectively 2·2 and 1·25. In the rabbit we have not been able to demonstrate any significant difference by this method, the ratio in both cases being close to unity. It is also noteworthy that the duration in the monkey of a paralysis due to the C 10 compound is usually two to three times longer than that of one of equal initial intensity due to *d*-tubocurarine chloride.

Eserine and prostigmine do not antagonize the C 10 compound; but a lower member of the series, C 5, has proved to be a useful antagonist. In all three species, an injection of 0·5–5 mgm./kgm. of C 5 cuts short a moderate or shallow paralysis, accelerates recovery from a deep curarization, and restores to normal a respiration that is becoming inadequate, where these conditions are due to the C 10 compound.

The C 10 compound must be compared with *d*-tubocurarine chloride in two other respects: (*a*) the latter is active in paralysing autonomic ganglia, and may thereby cause a small fall in blood pressure; the former exhibits some activity of this kind, but requires a dose five to ten times as great to produce the same effect; (*b*) the latter is known to liberate histamine[5], and such liberation might cause undesirable side-effects; the former can also be shown to produce an effect on the blood pressure characteristic of histamine liberation[6]; but it requires a dose at least four times larger. We have confirmed Barlow and Ing's[7] finding that this series of compounds possesses a weak anti-esterase activity; but this activity does not appear to produce any side actions, except possibly the fine fasciculations in the rabbit mentioned above. Chronic toxicity tests have shown that rabbits and cats can receive curarizing doses of the C 10 compound daily for six weeks without change in type or degree of the paralysis, or deterioration in the health of the animal.

As a possible substitute for *d*-tubocurarine chloride, therefore, this C 10 compound merits consideration, since it is both potent and can be antagonized; it also has the following advantages: (1) it spares the respiration; (2) it has less ganglionic action; (3) it has less power of liberating histamine; (4) it is a simple compound easily synthesized.

The C 6 derivative possesses great potency in paralysing autonomic ganglia, although it is inactive in other respects except in very large doses. Its effects, when injected in a dose of 0·1–1 mgm./kgm., are closely similar to those of tetraethylammonium iodide (paralysis of contraction of cat's nictitating membrane excited by preganglionic stimulation; fall of blood pressure, no longer obtainable after a paralysing dose of nicotine; paralysis of peristaltic reflex of rabbit intestine; paralysis of parasympathetic ganglia of the heart), and have been shown to be restricted to the autonomic ganglia. C 6 differs from tetraethylammonium iodide in its greater potency (ten to twenty times, according to test object), and in its slower onset and three to four times greater duration of action.

The C 6 derivative, therefore, offers possibilities of clinical usefulness in such fields as hypertension and vascular disease, whenever tetraethylammonium iodide has too brief or slight an action.

Details of the pharmacological investigations will be published in full elsewhere.

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[1] Paton, W. D. M., and Zaimis, E. J., *Nature*, **161**, 718 (1948).
[2] Bovet, D., Depierre, F., and de Lestrange, Y., *C.R. Acad. Sci., Paris*, **225**, 74 (1947).
[3] Collier, H. O. J., Paris, S. K., and Woolf, L. I., *Nature*, **161**, 817 (1948).
[4] Lyons, R. H., *et al.*, *Amer. J. Med. Sci.*, **213**, 315 (1947).
[5] Gregory, R. A., and Schild, H. O., XVII *Inter. Physiol. Cong. Proc.*, 288 (1947).
[6] MacIntosh, F. C., and Paton, W. D. M., XVII *Inter. Physiol. Cong. Proc.*, 240 (1947).
[7] Barlow, R. B., and Ing, H. R., *Nature*, **161**, 718 (1948).

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