NEUROMUSCULAR BLOCKING ACTIVITY IN SOME *NS*-BIS-ONIUM COMPOUNDS

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STUDIES by Edwards and his colleagues[1–4] on linear *NNN*, *NSN* and *NNNN*-onium salts have shown that these possess decamethonium (C 10), tubocurarine (TC)-like and transitional properties. *NS*-Compounds with muscle relaxant properties have been investigated by Bovet and his co-workers[5] and Walker[6]. Walker, using the rabbit head drop method, has reported that decamethylene-1,10-bisdimethylsulphonium di-iodide and decamethylene-1-dimethylsulphonium-10-trimethylammonium di-iodide have powerful C 10-like activity but are less potent than C 10 itself.

To gain a more complete picture of the properties of linear *NS*-compounds for comparison with the *NNN*, *NSN* and *NNNN*-derivatives of Edwards and others, we have investigated the properties of octamethylene-1-ethylmethylsulphonium-8-dimethylethylammonium di-iodide (I), decamethylene-1-dimethylsulphonium-10-trimethylammonium di-iodide (II) and octamethylene-1-dimethylsulphonium-8-trimethylammonium di-iodide (III).

The techniques and materials used have been described elsewhere[1–4].

Using 2 to 4 kg. cats anaesthetised by intraperitoneal sodium pentobarbitone the contractions of the gastrocnemius muscle in response to indirect stimulation *via* the scientic nerve were recorded. I (0·1 to 0·5 mg./kg.), II (0·05 to 0·1 mg./kg.) and III (0·1 to 0·5 mg./kg.) reduced twitch amplitude. II (0·025 mg./kg.) caused an initial increase of twitch height without subsequent reduction in its amplitude. When I was used muscular twitching and fasciculation were sometimes observed. I, II and III all resembled C 10 rather than TC; the similarity was closest with II, while III had transitional properties and was additive with both C 10 and TC (Fig. 1). C 10 was approximately 2·5 times more potent than II, ten times more potent than I and eight times more potent than III. After I, II or III the response of the partially blocked muscle to indirect tetanisation was well maintained. Neostigmine (0·05 to 0·1 mg./kg.) and edrophonium (0·5 mg./kg.) either potentiated or had little effect on the intensity of block due to I, II or III. Adrenaline (0·05 mg./kg.) and potassium chloride (15 to 20 mg./kg.) temporarily antagonised the block. Eserine (0·5 to 1·0 mg./kg.) or ether anaesthesia had little effect. The neuromuscular blocking effects of I, II and III were additive with each other and those of C 10 and with the exception of III antagonised the actions of TC.

When tested on the isolated frog rectus abdominis muscle I, II and III (1·0; 0·2; 1·0 mg./ml. respectively) caused a direct contraction and

augmented the stimulant effects of acetylcholine (0·1 μg./ml.). II was the most potent compound of the group. The order of potency was C 10 > II > III > I. When injected intraperitoneally into day-old chicks (10 mg./kg. every 30 seconds until death ensued) II produced a typical

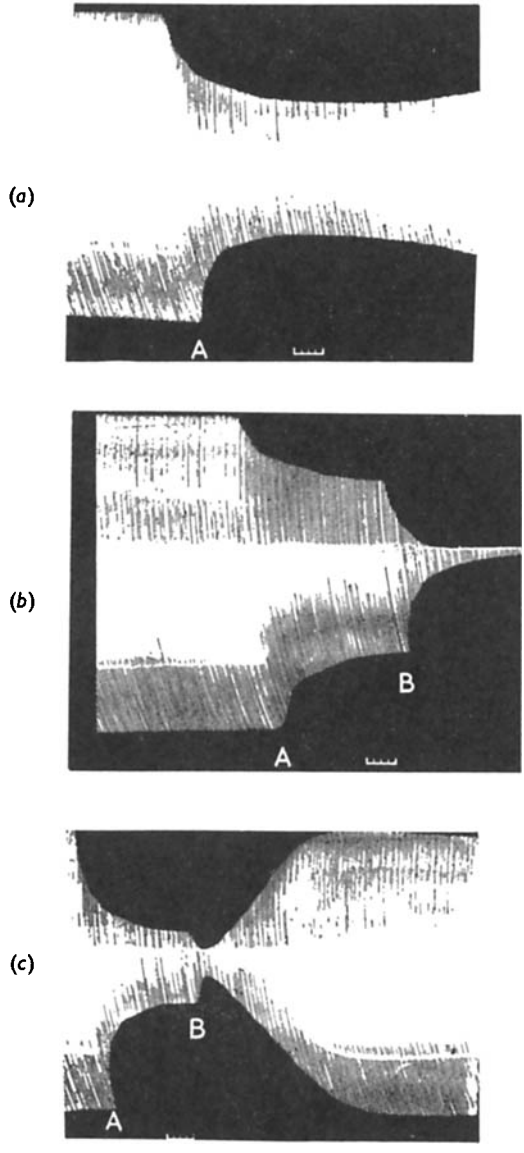

FIG. 1. Cat gastrocnemius-sciatic preparation. Pentobarbitone anaesthesia. Indirect stimulation via sciatic nerve; contraction downwards. Drugs administered intravenously. (*a*) At A, III 0·15 mg./kg., (*b*) at A, III 0·15 mg./kg., at B, C 10, 0·02 mg./kg., (*c*) at A, III 0·15 mg./kg., and at B, TC 0·2 mg./kg.

C 10-like spastic paralysis. I and III, less potent than II, produced an initial spastic paralysis which became flaccid prior to death. The order of potency was C 10 > II > I > III.

I, II and III were injected intraperitoneally into groups of ten mice and all three compounds showed paralysing activity followed by convulsions and death. The effects produced qualitatively resembled those produced by C 10. I had an approximate PD50 of 4·07 mg./kg. and an approximate LD50 of 11·09 mg./kg. The figures for II were 4·1 and 9·33, for III, 3·05 and 24·27, for C 10, 1·78 and 3·81; and TC, 0·13 and 0·26.

In doses sufficient to produce partial neuromuscular block (0·05 to 0·5 mg./kg.) I, II and II had no effect upon the blood pressure level of sodium pentobarbitone-anaesthetised cats, but 250 to 500 μg./kg. of II caused a prolonged rise. The average doses required to paralyse respiration were obtained by infusing the drug solution (I, 1 mg./ml.; II, II and C 10, 0·1 mg./ml.) intravenously at a rate of 0·75 ml./min. into the femoral vein of anaesthetised cats using a Palmer's constant rate infusion apparatus. The values obtained were as follows: I, 1·4 mg./kg.; II, 0·36 mg./kg.; III, 0·43 mg./kg.; C 10, 0·11 mg./kg.

In doses of from 1 to 6 times the muscle relaxant dose I, II or III did not reduce the response of the nictitating membrane of the cat to electrical preganglionic stimulation of the cervical sympathetic but after II (0·3 mg./kg.) there was an increase in amplitude indicating a possible ganglion stimulant action.

Discussion

I, II and III resemble C 10 rather than TC and so differ from dioctasulphonium and dioctazonium which have predominantly TC-like properties and resemble didecasulphonium which is C 10-like[2]. It seems, therefore, that increasing the number of onium centres increases the tendency to TC-like activity. Barlow[7] and Thesleff and Unna[8] have shown that stepwise preplacement of methyl by ethyl in C 10 alters activity from C 10-like to TC-like. Replacement of one quaternary N by tertiary S in C 10 does not alter the type of activity but reduces potency. In compounds I and III activity is mainly C 10-like but potency is very much reduced; both compounds cause a mixed spastic to flaccid paralysis in chicks but unlike I, III is not antagonised being potentiated by TC and C 10. Of these compounds III is the more potent, thus, introduction of an ethyl group lowers potency. Paton and Zaimis[9] have shown that octamethylene-α-ω-bistrimethyl: ammonium chloride has weak C 10-like properties on the cat tibialis preparation. III, in which one quaternary nitrogen has been replaced by tertiary sulphur, also has C 10-like activity. Both I and III have mainly methyl substituents on the onium atoms so that C 10-like activity is not unexpected.

Mr. D. M. Brown tells us that in the straight chain NS bis-ethonium series compounds with polymethylene chains containing 4, 5 or 6 members are potent ganglion blocking agents with little or no neuromuscular blocking activity.

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After Mr. Muir presented the communication there was a DISCUSSION.