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EVALUATION OF TWO SYNTHETIC CURARIZING AGENTS IN CONSCIOUS VOLUNTEERS

BY

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This paper is concerned with evaluating in conscious volunteers two synthetic muscle-relaxants described by Taylor and Collier (1950, 1951). They are decamethylene bis-(1: 2: 3: 4-tetrahydro-6: 7: 8-trimethoxy-2-methyl*iso*quinolinium) diiodide [Compound 15] and decamethylene bis-[1: 2: 3: 4-tetrahydro-6: 7-dimethoxy-1-(3′: 4′-dimethoxybenzyl)-2-methyl*iso*quinolinium] dimethosulphate [Compound 20, which has been named " Laudolissin "]. The chemistry of these drugs is described by Taylor (1951, 1952), and their pharmacology by Collier and Macauley (1952) in another paper in this journal.

Previous attempts to assay muscle-relaxants in man were made when Organe, Paton, and Zaimis (1949) introduced decamethonium iodide and when Mushin, Wien, Mason, and Langston (1949) described gallamine triethiodide. Since then an exhaustive study of these two drugs, of *d*-tubocurarine, and of its dimethyl ether has been made in volunteers by Unna, Pelikan, Macfarlane, Cazort, Sadove, Nelson, and Drucker (1950) and by Unna, Pelikan, Macfarlane, and Sadove (1950).

The experiments described here differ from those done by Organe *et al.* and Mushin *et al.* with decamethonium iodide and gallamine triethiodide, in that an attempt was made to reproduce in man the quantitative experiments already carried out in animals. *d*-Tubocurarine has been investigated in the same way to afford a comparison.

It is clearly desirable to study a new muscle-relaxant in conscious volunteers before injecting it into the anaesthetized patient. The findings provided by the pharmacologist relate to animals and he cannot foretell what species differences may occur in man. On the other hand, although the clinical anaesthetist can detect the quality of such variations, he can only arrive at an impression of the drug's properties after considerable experience in its use. Collier (1951) discusses the properties required by a muscle-relaxant for clinical use, and Doughty (1951) has listed the information an anaesthetist needs before using such a drug.

The properties of a muscle-relaxant fall into two groups. First are the characteristics relating to its relaxing properties, i.e., potency, duration of action, relative effect on respiratory muscles, and antagonism by a suitable drug. Second are the side-effects, such as the release of histamine and the blocking of sympathetic or parasympathetic ganglia.

METHODS

The methods used were designed first to compare the power of Compound 15 and 20 and of tubocurarine to paralyse the flexor muscles of the hand, and secondly to measure

their effect on the respiratory muscles, special attention being paid to any disparity in the effect of the drugs on these two groups of muscles, which might be called "sparing of respiration."

Effect on hand-grip.—The volunteers were healthy young men, lying at rest on a couch. The strength of the right hand-grip was measured by compressing a rubber bulb of convenient size (5 cm. diameter) connected to a mercury manometer, 150 cm. high. In the experiments on Compound 15 the system used was precisely the same as that of the clinical sphygmomanometer; after a number of squeezes with the right hand, a height was reached which represented the maximum pressure that the volunteer could apply to the bulb. It was thought, however, that this method might cause unnecessary fatigue, so the system was modified for the tests on Compound 20 and tubocurarine. For these experiments, a plain bulb with no valve was connected to the manometer and the bulb and rubber tubing filled with water; the relative incompressibility of the water allowed the mercury to be raised to the maximum height by a single pressure of the hand. The mercury tended to oscillate when the grip was first tightened, so that it rose to a peak and then fell 5 or 10 cm. to a steady level; the latter point was taken as the reading. Attempts to damp the oscillation of the mercury resulted in alterations in the response at high dosages, because this introduced a time factor and the hand, when weakened by a curarizing agent, was unable to maintain its pressure long enough to raise the mercury to the undamped level. With experience on the part of the volunteer and observer, reasonably consistent readings, not deviating more than 5 per cent from their average, were obtainable in the preliminary trials before the injection of the relaxant. The results tabled below fall within a limit of 15 per cent from the regression lines for each series, which is satisfactory in a biological experiment of this sort.

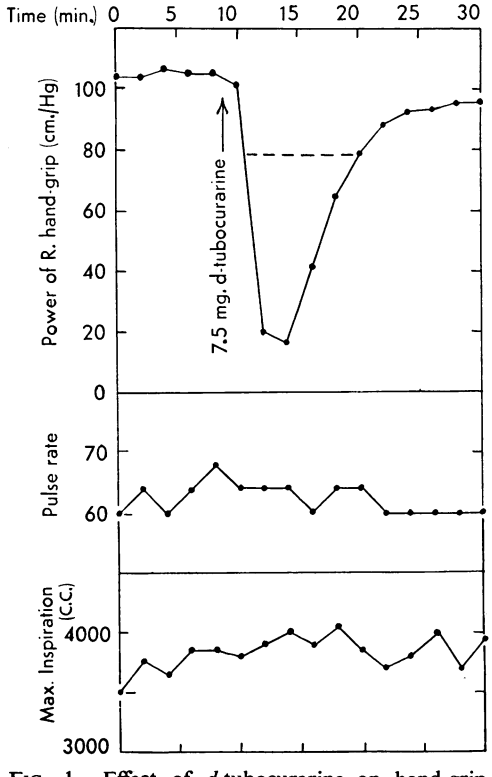


FIG. 1.—Effect of *d*-tubocurarine on hand-grip, pulse rate, and maximum inspiration.

Readings were taken strictly at two minute intervals; this timing was found necessary in order to eliminate the effects of fatigue. Five preliminary readings were taken and the drug was injected intravenously in a single dose, in less than three seconds, between the fifth and sixth reading.

The average of the five preliminary readings was taken as the volunteer's normal strength. The depression in grip strength to the single lowest reading after injection of the drug was expressed as a percentage of the normal. Thus, if the average of the preliminary readings was 105 cm. Hg, and the weakest effort after the injection was 17 cm. Hg, this was represented as 84 per cent depression of the hand-grip: a dose-response curve was thus constructed for the drug concerned.

By plotting strength of hand-grip against time, during the loss and return of power (see Fig. 1), it was possible to

estimate the duration of action of the drug. This was measured as the time taken between losing and regaining 75 per cent of the normal power of the hand (equivalent to the t_{75} of Unna *et al.*), in those experiments where more than 40 per cent paralysis occurred.

In some experiments neostigmine was injected intravenously immediately before the first preliminary trial, so that a period of ten minutes elapsed between the injections of neostigmine and the relaxant. It was thought more satisfactory to give the neostigmine beforehand, for two reasons: First, it makes certain that the neostigmine is acting effectively when the maximal paralysis occurs, i.e., within 3–5 minutes of injecting the relaxant. Secondly, it allows larger doses of relaxant to be given without causing undue apprehension to the volunteer, who need not worry that he might become apnoeic before the neostigmine takes effect.

Effect on respiration.—The function of the respiratory muscles was measured on a recording spirometer; after each test of the hand-grip a mask was placed over the face, and after three normal quiet respirations the volunteer took a maximum inspiration. This measurement varied very little, rarely more than ±5 per cent in the preliminary readings.

Other effects.—The volunteers were encouraged to describe their sensations during the experiments, and great attention was paid to their subjective feelings, so that warning of possible side-effects might be obtained. The volunteers were able to talk throughout all these experiments (Bodman, 1951b).

Observations of pulse rate and blood pressure were made in some instances, and electrocardiograms were recorded in some of the experiments on Compounds 15 and 20.

Histamine-release.—A special effort was made to estimate the release of histamine, a side-effect which appears to be common to all true curarizing agents. Comroe and Dripps (1946) observed that "Intocostrin" when injected intradermally produced a weal, and Grob, Lilienthal, and Harvey (1947) measured such weals and flares in a number of subjects. Bain, Hellier, and Warin (1948) showed that the areas of the weals and flares produced by histamine itself given intradermally were proportional to the log of the dose injected, over a wide range. Consequently, when it was suspected that the side-effects produced in volunteers by Compound 15 (see below) were due to histamine-release, I decided to try the effect of injecting these drugs intradermally. Equipotent doses of tubocurarine, Compound 15, Compound 20, and a saline control were injected intradermally on the palmar surface of the forearm just below the fold of the skin at the elbow, two drugs in each arm. When the weals reached their maxima, and before they lost their discrete contours—between 10 and 15 minutes after injection—they were ringed with a ball pen. These rings were transferred to millimetre squared paper by wiping this with surgical spirit and gently pressing it down over the weals. The squares within the contours were counted and the results are given in Table I.

TABLE I

WEAL AREAS AFTER INTRADERMAL INJECTIONS OF TUBOCURARINE (TC), COMPOUND 15, AND COMPOUND 20 IN 0.05 ML. SALINE AND SALINE CONTROL

Subject	Drug and dose			
	TC 0.1 mg.	"15" 0.33 mg.	"20" 0.2 mg.	Saline
H.M.	56	78.5	59	28.5
J.W.	60	144.5	76	29
S.S.	58.5	109.5	67.5	19
R.B.	94.5	165.0	87	41
P.B.	104	144.5	110.5	25
J.L.	74	103.5	78	0

RESULTS

Compound 15 (*decamethylene bis*-(1: 2: 3: 4-*tetrahydro*-6: 7: 8-*trimethoxy*-2-*methyl*isoquinoline) *di-iodide*)

Compound 15 was the first drug to be investigated in this series. Doses from 1 to 20 mg. were given to volunteers in nine experiments (Bodman, 1951a). The larger doses gave rise to symptoms such as " pins and needles," flushing, palpitations, and headache; but no depression of hand-grip was produced until a dose of 260 μg./kg. body weight caused a depression of 57 per cent, but with this dose symptoms were intolerable. By comparing this single result with those for tubocurarine (Fig. 3) it will be seen that a dose of 80 μg./kg. of *d*-tubocurarine would be likely to produce the same depression of hand-grip. The ratio of the potency of Compound 15 to tubocurarine is therefore roughly 0.3–1.0.

A tachycardia of more than 160 per min. was recorded with Compound 15, although no changes were detected in the electrocardiogram. It was decided to abandon the use of this drug on account of the severe side-effects, which were thought to be due to the release of histamine. The difference in weal areas produced by Compound 15 and those produced by Compound 20 and tubocurarine (Table I) is highly significant ($P<0.01$). The weals produced pseudopodia and caused itching, which confirms the opinion that they were due to histamine-release. There is little doubt that Compound 15 in equipotent doses releases more histamine than either tubocurarine or Compound 20.

Compound 20 (*decamethylene bis*-[1: 2: 3: 4-*tetrahydro*-6: 7-*dimethoxy*-1-(3′: 4′-*dimethoxybenzyl*)-2-*methyl*iso*quinolinium*] *dimethosulphate*)

Compound 20 and tubocurarine were compared as regards potency, antagonism by neostigmine, duration of action, effect on respiratory muscles, release of histamine, and other side-effects.

Table II presents the results of 11 experiments with Compound 20; doses less than 10 mg. produced no depression of hand-grip. In four experiments the effect of 1.0 mg. neostigmine is shown. In Table III the results of 13 experiments with

TABLE II

EFFECT OF COMPOUND 20 ON HAND-GRIP AND MAXIMUM INSPIRATION

Exp. No.	Subject	Compound 20 (mg.)	Dose/wt. (μg./kg.)	Maximum depression of hand-grip %	Duration of 25% depression (min.)	% reduction of maximum inspiration
15	T.R.S.	11	120	25	..	0
16	W.E.A.	11	139	43	7.5	0
17	R.I.B.	12	156	48	11.5	0
18	W.E.A.	12.5	158	60	9.5	0
19	R.I.B.	12.5	162	84	19	..
20	W.E.A.	14	178	88	17	0
21	R.I.B.	15	195	100	27	34
22	T.R.S.	12.5	138	0*	..	0
23	R.I.B.	14	182	16*	..	0
24	R.I.B.	15	195	47.5*	8	..
25	R.I.B.	17	220	67*	18	13

* 1 mg. neostigmine 10 min. before Compound 20.

TABLE III

EFFECT OF TUBOCURARINE ON HAND-GRIP AND MAXIMUM INSPIRATION

Exp. No.	Subject	*d*-Tubocurarine (mg.)	Dose/wt. (μg./kg.)	Maximum depression of hand-grip %	Duration of 25% depression	% reduction of maximum inspiration
26	R.I.B.	4.5	59	15	..	..
27	W.E.A.	5	64	34	..	..
28	R.I.B.	5.5	72.5	49.5	5.5	..
29	R.I.B.	6	79	60	7	0
30	W.E.A.	6.5	85	59	6	..
31	R.I.B.	7	92	74	10.5	0
32	W.E.A.	7.5	100	84	9.5	0
33	W.E.A.	8	106	100	12.5	0
34	R.I.B.	7	92	0*	..	..
35	R.I.B.	8	105	17*	..	..
36	R.I.B.	9	118	26*	..	0
37	R.I.B.	9.5	125	32.5*	..	0
38	R.I.B.	10	132	64*	6.5	0

* 1 mg neostigmine 10 min. before tubocurarine.

tubocurarine are given in the same way. These results are expressed graphically in Figs. 2 and 3. In Fig. 4 the percentage depression of hand-grip has been plotted against the duration of 25 per cent depression for three doses each of tubocurarine and Compound 20, in two volunteers.

Potency.—It will be seen from Figs. 2 and 3 that the dose of Compound 20 which causes 50 per cent depression of the hand-grip is 146 μg./kg., and that of tubocurarine is 76 μg./kg., from which it may be concluded that the ratio of the potency of Compound 20 to tubocurarine is 0.52 to 1.

Antagonism by neostigmine.—In both Figs. 2 and 3 the injection of neostigmine before the relaxant has resulted in a shift of the curve to the right, which demon-

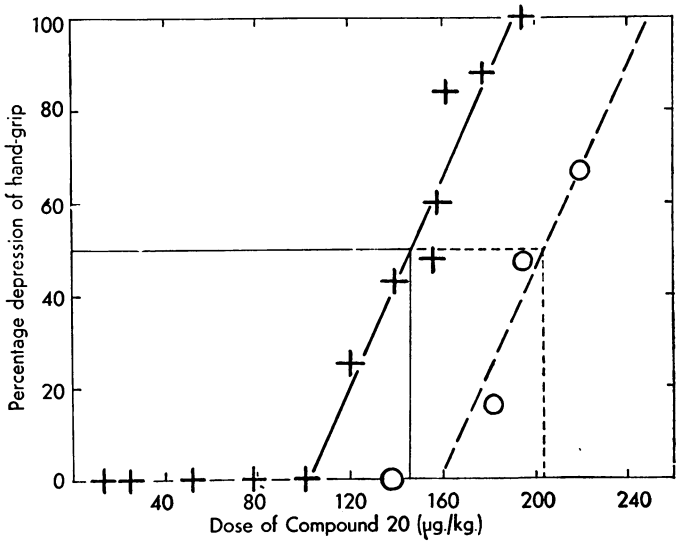


FIG. 2. — Dose-response curve for Compound 20. + = Compound 20 given alone. O = Compound 20 given after neostigmine.

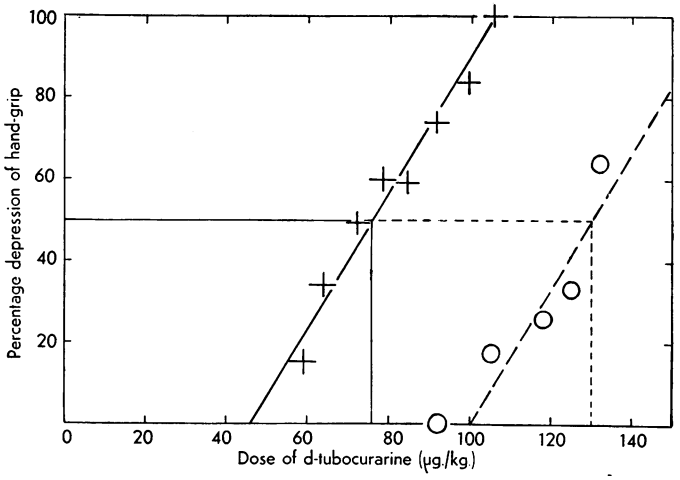
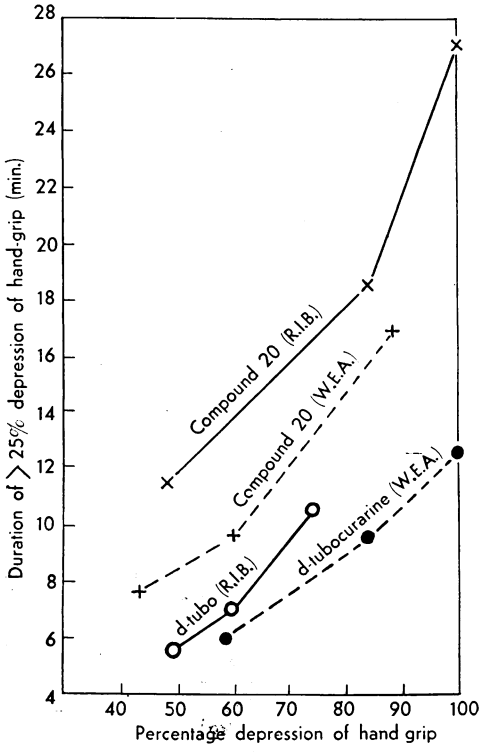


FIG. 3. — Dose-response curve for *d*-tubocurarine. + = *d*-tubocurarine given alone. O = *d*-tubocurarine given after neostigmine.

FIG. 4.—Duration plotted against percentage depression of hand-grip, in two individuals. ——— = R.I.B. - - - - = W.E.A. Circles = *d*-tubocurarine. Crosses = Compound 20.



strates that both these drugs are antagonized by neostigmine. Although the results were not subjected to an analysis of co-variance, it appears from the graphs that the potency of tubocurarine is lowered by neostigmine by a factor of 1.7; that of Compound 20 by a factor of 1.4 (both at the 50 per cent depression of hand-grip level).

Duration of action.—On the basis of an analysis of co-variance, which was carried out on these data, it appears that the duration of depression, corrected for differences in dose, does not differ significantly, if we take as a standard the conventional level of probability. But the difference is sufficiently great to be significant at approximately the 10 per cent level. The two volunteers involved showed different sensitivities to tubocurarine and Compound 20 as regards the duration of action (Fig. 4), and this may account for the difference in the average response being too small at the 5 per cent level of significance.

Effect on respiratory muscles.—No reduction in the maximum inspiratory effort occurred in any experiment which caused less than 100 per cent depression

of the hand-grip when neostigmine was not used. In one experiment (No. 25) a dose of Compound 20 (17 mg.), sufficient to produce 100 per cent depression of the hand-grip when given alone, was given after 1 mg. neostigmine, and caused a reduction of 13 per cent in the maximum inspiratory effort.

Release of histamine.—The results in Table I show no significant difference in the amount of histamine released by equipotent doses of Compound 20 and *d*-tubocurarine.

Other side-effects.—Subjectively, neither Compound 20 nor *d*-tubocurarine produced any of the symptoms seen with Compound 15, i.e., flushing, " pins and needles," palpitations, and headache (Bodman, 1951a); nor was any change in the pulse rate or blood pressure seen after the injection.

An account of a new relaxant would not be complete without some reference to its effect on the autonomic nervous system. Gallamine triethiodide causes a tachycardia by blocking the vagus (Marbury *et al.*, 1951). Win 2747, on the other hand, is reported by Arrowood (1951) to cause salivation, and this may be a parasympathomimetic effect. In this series of experiments none of the above effects has been detected after either Compound 20 or tubocurarine. On the other hand, the parasympathomimetic effects of neostigmine—bradycardia, salivation, and abdominal cramps—were well marked, even with the small doses used in these experiments.

The volunteers could detect no difference between tubocurarine and Compound 20, except perhaps in the larger doses, when the longer duration of action of Compound 20 became apparent

Discussion

It has been demonstrated that the undesirable side-effects of Compound 15 are most probably due to the release of histamine. These effects are severe enough to make the drug clinically useless.

Compound 20 has properties very similar to those of *d*-tubocurarine. It paralyses voluntary muscle without initial stimulation and it is antagonized by neostigmine. There seems little doubt that its action is a true curarizing one. In doses of equal potency the effect of Compound 20 lasts a little longer than that of tubocurarine, and there is hardly any difference in the amount of histamine released by the two drugs. Finally, Compound 20 and tubocurarine are practically indistinguishable subjectively.

I do not wish to discuss the merits of the hand-grip method of evaluating relaxant drugs. I agree with Paton and Zaimis (1950) that anomalous results may be expected when this method is used with drugs which have different types of action, such as decamethonium and tubocurarine. In this series of experiments, however, it was assumed from the start that the new compounds acted in the same way as tubocurarine. This assumption has not been challenged by subsequent experience and the experimental work consisted in assaying three drugs, one known and two unknown, by the same method and noting the differences which occurred.

The principle of assaying new muscle-relaxants in volunteers may be justified by considering the following points: (1) it avoids injecting an unknown drug into an unconscious human being undergoing an operation; (2) it can provide essential information about the properties of the drug in man with the minimum number

of experiments; and (3) it provides an opportunity for detecting any serious species variation between experimental animals and man. It may be noted that in exhaustive animal experiments both Compound 15 and Compound 20 appeared to be equally suitable for use as muscle-relaxants in man. Compound 15, however, has had to be discarded, whereas Compound 20 shows promise of proving a useful synthetic substitute for *d*-tubocurarine and is now being subjected to clinical investigation.

SUMMARY

1. The results of assaying two synthetic muscle-relaxants in conscious volunteers are described. They are decamethylene bis-(1: 2: 3: 4-tetrahydro-6: 7: 8-trimethoxy-2-methyl*iso*quinolinium) di-iodide (Compound 15) and decamethylene bis-(1: 2: 3: 4-tetrahydro-1-(3′: 4′-dimethoxybenzyl) -2- methyl*iso*quinolinium) dimethosulphate (Compound 20 or " Laudolissin ").

2. Compound 15 was found to be unsuitable for clinical use, as it released an excessive amount of histamine.

3. Compound 20 was found to be very similar in its actions and lack of side-effects to *d*-tubocurarine. The ratio of the potency of Compound 20 to tubocurarine is approximately as 0.5 to 1, when measured by the reduction of hand-grip. The duration of action of Compound 20, measured in the same way, is longer than that of tubocurarine. It is antagonized by neostigmine.

4. The amount of histamine released by Compound 20 on intradermal injection was no more than that released by an equipotent dose of tubocurarine. No other side-effects were detected.

5. In view of the satisfactory results of these experiments with Compound 20, a clinical trial of the drug is now being undertaken.

I must thank the members of the Departments of Anaesthetics at St. Thomas's Hospital and the Bristol Royal Hospital for volunteering for the experiments. I am grateful to Dr. G. Herdan of Bristol University for help with the statistics.

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