Brit. J. Pharmacol. (1952), 7, 398.

THE PHARMACOLOGICAL PROPERTIES OF "LAUDOLISSIN"*—A LONG-ACTING CURARIZING AGENT

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(Received February 28, 1952)

The development of a new group of synthetic muscle-relaxant drugs (Collier and Taylor, 1949; Taylor and Collier, 1950, 1951) led to the preparation of a number of compounds showing very high paralysing activities, which in the rabbit were of the same order as that of dimethyltubocurarine. These highly active compounds, and especially No. 20 (laudolissin), also resembled dimethyltubocurarine in chemical structure; and two of them, Compounds 15 and 20, appeared from these preliminary studies to merit further pharmacological investigation, with a view to their possible use as muscle-relaxants in surgical operations. At the outset of such an investigation, the question arises as to what pharmacological properties are of particular interest to the anaesthetist. Collier (1951) has discussed these properties and the pharmacological methods involved in assessing them; and Doughty (1951) has outlined the following pharmacological data that an anaesthetist requires before administering a new muscle-relaxant drug.

"(1) The type of drug—i.e., whether like *d*-tubocurarine or decamethonium in action. (2) The efficacy of the antidotes if any. (3) Its autonomic blocking activity both sympathetic and parasympathetic. (4) Its capacity in releasing histamine. (5) Duration of its effect—i.e., short- or long-acting. (6) Its respiration-sparing effect. (7) Its potentiation by anaesthetic agents. (8) Any special peculiarity of the drug."

These aspects of the new drugs, and their relation to *d*-tubocurarine, are presented below.

Both laudolissin and Compound 15 have been administered by Bodman (1951a and b, 1952) to human volunteers. He found that laudolissin could be administered to man in effective doses without obvious side-effects, but Compound 15 released so much histamine as to render it unsuitable for clinical use as a muscle-relaxant. The relations between his findings and our work are also considered in this paper.

The experiments described below, except those on the antagonism between laudolissin and succinylcholine, have been carried out with both laudolissin and Compound 15. Unless the latter is specifically mentioned, it can be taken that its properties closely resemble those of laudolissin. In addition to their activities, which will be discussed below, both laudolissin and Compound 15 possess considerable antibacterial activity, which will be described in detail later (Collier, Potter, and Taylor, 1952).

* "Laudolissin" is the registered name for decamethylenebis [1:2:3:4-tetrahydro-6:7-dimethoxy-1-(3′:4′-dimethoxybenzyl)-2-methyl*iso*quinolinium salts] (Compound 20).

Materials and Methods

Materials

The iodide, bromide, and methosulphate of laudolissin and the iodide of Compound 15 were used (Taylor, 1951, 1952). Since the methosulphate of laudolissin and the iodide of Compound 15 were administered to volunteers by Bodman, values are given below in terms of these salts. For comparison with these drugs, *d*-tubocurarine chloride was used. Drugs were administered in solution in 0.9 per cent saline intravenously to the species of experimental animal used; namely, mouse, rat (Wistar), rabbit (Himalayan and Ermine Rex), cat, and chick (Rhode Island Red × Light Sussex).

Measurement of potency and toxicity

Curarizing potency was determined by three methods. (1) In the intact rat and rabbit by the presence or absence of the righting response following treatment (see Collier, Fieller, and Hall, 1949). (2) In the mouse with the rotating drum described by Collier, Hall, and Fieller (1949). (3) In the cat with the tibialis anticus preparation described by Paton and Zaimis (1949), using a neon-lamp stimulator adjusted to deliver four shocks per minute. The curarizing potency of these drugs in the rat, rabbit, and mouse was expressed as the dose paralysing 50 per cent of animals (ED50).

The toxicity of single doses was estimated from the proportions of animals killed at several dose levels. Since death, which was due to failure of respiratory muscles, was almost immediate, and no delayed deaths were seen, results were assessed on the kill within 16 hours of treatment. Toxicity was expressed as the dose killing 50 per cent of animals (LD50).

Blocking of autonomic ganglia

In order to estimate block in autonomic ganglia two methods were used. (1) Depression of the contraction of the nictitating membrane in the cat, described by Paton and Zaimis (1949), in which block in a sympathetic ganglion is measured. (2) The inhibition of the response of the isolated guinea-pig ileum to nicotine, as described by Feldberg (1951). Here the blocking action is on ganglia of the myenteric plexus, which are generally assumed to be parasympathetic relay stations. The freshly isolated ileum preparation was suspended in modified Tyrode's solution in an oxygenated bath at 35° C. Responses to nicotine alone were compared with those obtained in the presence of a curarizing drug. Doses of histamine were interpolated regularly to check the condition of the preparation. For control purposes the effects of the drug on the responses of the ileum to histamine and to acetylcholine were also examined.

Release of histamine

The potency of the curarizing drugs in releasing histamine was investigated by four methods. First, by the delayed depressor action in the cat described by Macintosh and Paton (1949). For this purpose the cat was prepared for recording arterial blood pressure. Autonomic ganglia were blocked initially by one or more intravenous doses of 0.5 or 1.0 mg. hexamethonium iodide per kg., followed by further doses at half-hourly or hourly intervals. Doses of curarizing drugs were given intravenously at intervals of 20–30 minutes. Mepyramine maleate ("Neonantergan") was used to antagonize histamine in some experiments. Secondly, the release of histamine from the rat diaphragm *in vitro* was investigated by the method of Rocha e Silva and Schild (1949). One or more diaphragms, removed from freshly killed rats, were cut in half, weighed, and soaked in oxygenated Tyrode's solution at 37° C. for 30 minutes. One half of each diaphragm was then transferred to a 1 in 2,000 solution of *d*-tubocurarine chloride. The other halves were placed in solutions of either 1 in 2,000 laudolissin or Compound 15 or 1 in 1,000 *d*-tubocurarine or in Tyrode's solution. The histamine released was estimated by means of the guinea-pig ileum preparation.

In a third method of investigating release of histamine, we utilized the bronchoconstriction that this substance causes in the guinea-pig. A guinea-pig, anaesthetized with

pentobarbital sodium ("Nembutal"), was pithed and maintained by artificial respiration from a Palmer's " Ideal " pump. By means of a hook and thread the sternum was connected with a lever so as to record its excursions on smoked paper. In response to graded doses of histamine of the order of 1–20 μg. per kg. graded depressions of the excursions of the chest wall were obtained, attributable to broncho-constriction. A similar response was obtained to intravenous injection of a known histamine-liberator (Compound 48/80; see Paton, 1951).

Fourthly, liberation of histamine was assessed by weal formation in human skin. Intradermal doses of 0.04 ml. of drugs dissolved in saline and adjusted to *p*H 6.8–7.2 were administered to two normal subjects. Two to three injections of the test compound and of *d*-tubocurarine were given at two to three dose levels on the volar surface of the forearm of each volunteer, as illustrated in the preceding paper (Collier, 1952). Maximal weal areas were outlined in ink and measured on squared paper either by counting squares, as described by Bain, Broadbent, and Warin (1949), or by cutting out and weighing the paper. Since MacIntosh and Paton have reported that, after intradermal injection of a histamine liberator, the skin remains refractory for at least 24 hours, experiments of this type were conducted at intervals of four or more days. Promethazine hydrochloride ("Phenergan") was taken by mouth to antagonize histamine in two experiments.

RESULTS

The curarizing activity of laudolissin

Mode of action and relation to other drugs.—After a fully effective dose of laudolissin in the cat, the tibialis fails to respond to stimulation of its motor nerve. The muscle remains excitable and contractile, however, since a direct stimulus produces a normal twitch. This suggests that the paralysis by laudolissin is due to neuromuscular block. The following facts indicate that laudolissin is a true curarizing agent. First, administration to the chick produces, as does *d*-tubocurarine, a flaccid paralysis, distinct from the spastic paralysis produced by decamethonium (Buttle and Zaimis, 1949). Secondly neostigmine, and thirdly succinylcholine, antagonize the paralysing action of laudolissin, as they do that of *d*-tubocurarine. Fourthly, ether, which antagonizes paralysis caused by decamethonium, potentiates those caused by laudolissin and *d*-tubocurarine.

The fact that neostigmine antagonizes laudolissin is shown by the following experiment. The ED50 of laudolissin was determined in a group of 20 rabbits. On the following day the ED50 of the same drug was determined in the same animals immediately after giving a dose of 50 μg. neostigmine methosulphate per kg. On the third day the ED50 of the group was again determined without neostigmine. By this method we found that 50 μg. of neostigmine raised the ED50 of laudolissin in the rabbit by a factor of 1.54, and of tubocurarine by 1.57. In both experiments the ED50 on the third day was the same as that on the first day; and therefore the possibility of cumulative effects influencing the results can be excluded. Neostigmine also antagonizes laudolissin in man (Bodman, 1952) and the cat.

Succinylcholine chloride (" Scoline "), which acts like decamethonium by depolarization at the motor end plate, itself produces a very brief neuromuscular block. We have observed its antagonism to laudolissin in experiments on the cat tibialis preparation, one of which is illustrated in Fig. 1, which shows the effect of succinylcholine on the course of recovery of the tibialis twitch of the cat from a fully effective

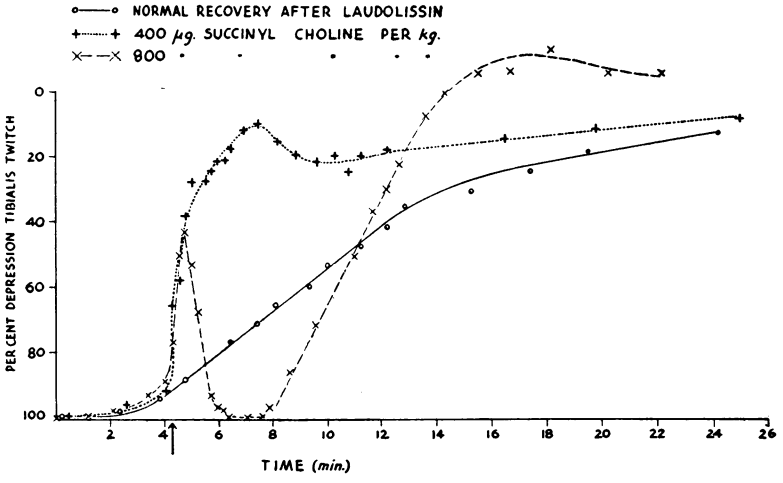

FIG. 1.—Cat, chloralose. Effect of succinylcholine on recovery of tibialis from 100% depression caused by 300 μg. laudolissin per kg. At ↑ succinylcholine given.

dose of laudolissin. It will be seen that a moderate dose of succinylcholine immediately increased the twitch and hastened recovery. A larger dose of succinylcholine first increased the twitch, then produced deeper paralysis, followed by a more rapid recovery. We have also observed a similar antagonism between succinylcholine and *d*-tubocurarine.

Experiments performed in mice on the effect of ether and of thiopentone sodium on the toxicity of laudolissin are summarized in Table I. It will be seen from the Table that when mice were exposed to an effective dose of ether vapour, immediately after injection of laudolissin, the toxicity of the latter compound was almost doubled. It can also be seen from this Table that administration of an effective dose of thiopentone immediately before laudolissin had no effect on the toxicity of the curarizing compound.

TABLE I

EFFECT OF ETHER AND OF THIOPENTONE ON THE TOXICITY OF LAUDOLISSIN TO MICE

No. mice	Dose of laudolissin (μg. per kg.)	Exposure to ether (sec.)	Dose of thiopentone (mg. per kg.)	No. mice killed
10	400	—	—	2
10	450	—	—	6
15	—	30	—	0*
20	200	30	—	6
20	300	30	—	17
20	400	—	—	4
20	550	—	—	15
20	—	—	20	0*
20	400	—	20	3
20	550	—	20	14

* All mice narcotized.

Curarizing potency in various species.—Experiments showed that successive doses of laudolissin at intervals of 20 or 30 minutes exerted a cumulative effect on the depression of the cat tibialis muscle. On the other hand, doses administered at hourly intervals did not generally exert a cumulative effect. Accordingly, the potency of laudolissin and other drugs in depressing the tibialis twitch was estimated by giving doses at hourly intervals. This precaution was not adopted in previous preliminary

TABLE II

PARALYSING ACTIVITIES AND TOXICITIES OF LAUDOLISSIN, *d*-TUBOCURARINE, AND COMPOUND 15 INTRAVENOUSLY IN VARIOUS SPECIES. IN BRACKETS NUMBER OF ANIMALS USED. VALUES IN μG. PER KG. ± STANDARD ERROR

Drug	Mouse	Rat		Rabbit	
	ED50	ED50	LD50	ED50	LD50
Laudolissin methosulphate	276±8.54 (540)	1,329±31 (30)	2,269±58 (40)	28.5±1.56 (155)	48±5.20 (56)
d-Tubocurarine chloride	81±4.02 (150)	52±2.23 (52)	105±7.27 (30)	94.0±7.25 (47)	168±9.27 (22)
Compound 15 iodide ..	288±11.3 (160)	1,059±44 (22)	1,534±35 (20)	19.0±1.01 (123)	42±4.93 (55)

TABLE III

DURATION AND POTENCY OF LAUDOLISSIN, *d*-TUBOCURARINE, AND COMPOUND 15 IN CAT TIBIALIS PREPARATION. DATA FOR ALL DOSES CAUSING >74 AND <100% DEPRESSION OF NORMAL TWITCH TENSION

Cat No.	Drug	Dose (μg./kg.)	Depression tibialis (%)	Duration 25% depression (min.)	Mean dose (μg./kg.) ± std. error	Mean depression (%)	Mean duration (min.) ± std. error
5	Laudolissin	100	76	20.75			
6		100	94	36.5			
7		100	83	35.5			
8		200	99.9	22.75	142	89.4	30.78
9		200	93	18.0	±26.35		±3.59
10		300	98.5	32.5			
11		75	97	53.75			
11		50	81	27·5			
12		150	82	29.75			
1	*d*-Tubocurarine	300	75	14.5			
1		300	86	21.0			
4		150	75	12.5			
5		150	99	15.25	236	87.5	20.17
8		225	97	16.25	±23.24		±2.72
8		200	77	11.25			
10		350	98	29.0			
11		250	85.5	33.75			
12		200	95	28.0			
2	Compound 15	150	87	5.25			
3		100	86	12.5			
3		90	87	19.0			
4		150	99	3.5	148	90.2	9.54
9		100	85	6.25	±31.19		±2.35
10		300	97	10.75			

estimates, which are probably somewhat too high (Collier, 1951). In another series of experiments, doses of laudolissin and other curarizing drugs were given daily to rabbits. No cumulative effect was seen.

Estimates of the potencies and toxicities in various animal species of the curarizing drugs under consideration are given in Table II. It will be seen that both synthetic compounds are more active than tubocurarine in the rabbit and less active in the mouse and rat. The figures for cat tibialis given in Table III show that laudolissin is significantly more active than *d*-tubocurarine ($P<0.02$).

The value $\frac{LD50}{ED50}$ gives some indication of the relative effect of a curarizing agent on respiration and on co-ordination of the limb muscles. This ratio for laudolissin in the rat and rabbit is about 1.7, which does not differ appreciably from those for *d*-tubocurarine.

Duration of paralysis.—Our results in the cat indicate that the paralysis produced by laudolissin lasts longer than that produced by doses of *d*-tubocurarine that depress the tibialis tension to the same degree. We compared the mean durations of all doses of laudolissin, *d*-tubocurarine, and Compound 15 that depressed the normal muscle-tension by 75 to 99.9 per cent. The durations of responses falling within the above limits are given in Table III. It will be seen that laudolissin is significantly longer ($P<0.05$) and Compound 15 shorter ($P<0.02$) in action than *d*-tubocurarine.

Block of autonomic ganglia

In three experiments, the abilities of laudolissin, *d*-tubocurarine, and Compound 15 to block sympathetic ganglia were compared in the cat's nictitating membrane preparation. In these, laudolissin exhibited between one-quarter and one-sixth of the blocking activity of *d*-tubocurarine, and Compound 15 was more active than laudolissin and less active than *d*-tubocurarine, as may be seen in Fig. 2.

In experiments with the guinea-pig ileum *in vitro*, *d*-tubocurarine and laudolissin both depressed the response to nicotine at concentrations that were too low to depress the response to acetylcholine (see Fig. 3). In five comparisons of their ganglionic blocking activity made with this preparation, laudolissin exhibited about one-quarter

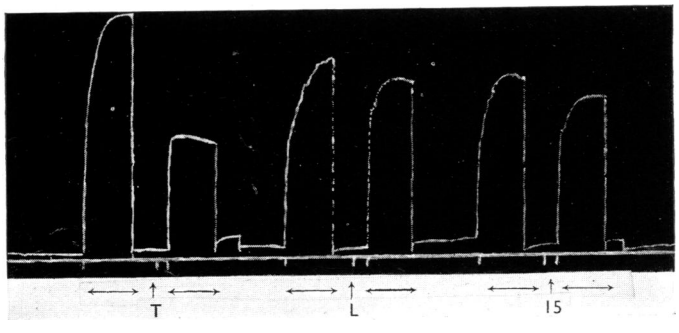

FIG. 2.—Cat, chloralose. Contractions of nictitating membranes in response to electrical stimulation of ipsilateral cervical sympathetic. Drug injected 1 min. after end of previous, and ½ min. before subsequent stimulation. ⟷ = stimulation 2½ min.; T = 0.75 mg. *d*-tubocurarine per kg. L = 3 mg. laudolissin per kg.; 15 = 1.5 mg. Compound 15 per kg.

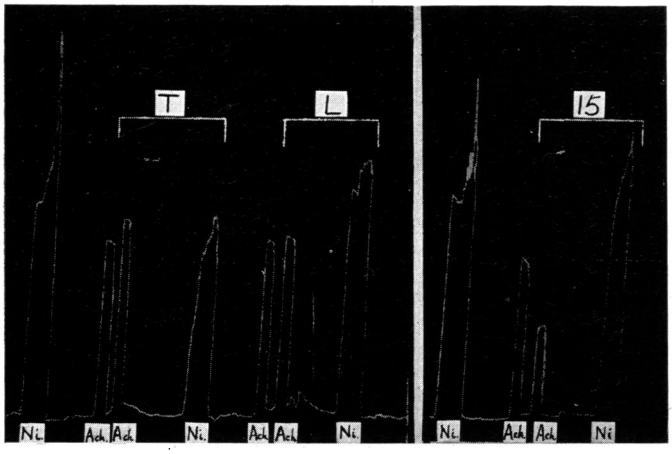

FIG. 3.—Guinea-pig ileum preparation in 15 ml. bath. Effect of 20 μg. *d*-tubocurarine (T), 40 μg. laudolissin (L), and 30 μg. Compound 15 (15) on responses to 0.5 μg. acetylcholine (Ach) and to 10 μg. nicotine (Ni). 4 min. intervals between additions of drugs.

to one-third of the activity of *d*-tubocurarine. In contrast with laudolissin, concentrations of Compound 15 that depressed the nicotine response also depressed the acetylcholine response. But, as will be seen from Fig. 3, Compound 15 depressed the nicotine responses of the ileum less than did *d*-tubocurarine, which indicates that its ganglionic blocking activity in this preparation is lower than that of *d*-tubocurarine.

Release of histamine

When the ability to release histamine was investigated in the cat, in the rat diaphragm, in the guinea-pig, and in human skin, it was found that the relative activities of laudolissin, *d*-tubocurarine, and Compound 15 varied according to the method used. In the cat prepared for recording arterial blood pressure, with the autonomic ganglia blocked by hexamethonium, we found that *d*-tubocurarine at doses of 0.5 mg. per kg. caused a typical delayed depressor response, as described

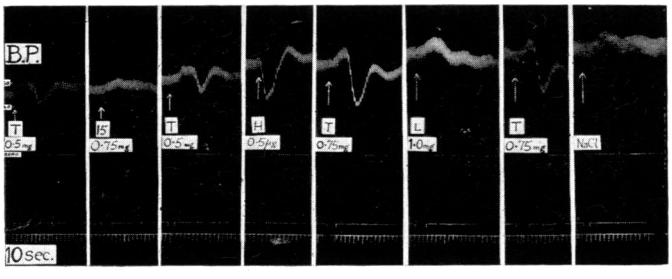

FIG. 4.—Cat, chloralose: blood pressure. Effects of intravenous *d*-tubocurarine, laudolissin, and Compound 15 after blocking autonomic ganglia with hexamethonium. T = *d*-tubocurarine; L = laudolissin; 15 = Compound 15; H = histamine; NaCl = 0.9% saline. Doses per kg. Curarizing drugs given at half-hourly intervals. 0.5 or 1 mg. hexamethonium per kg. given before beginning experiment and at hourly intervals.

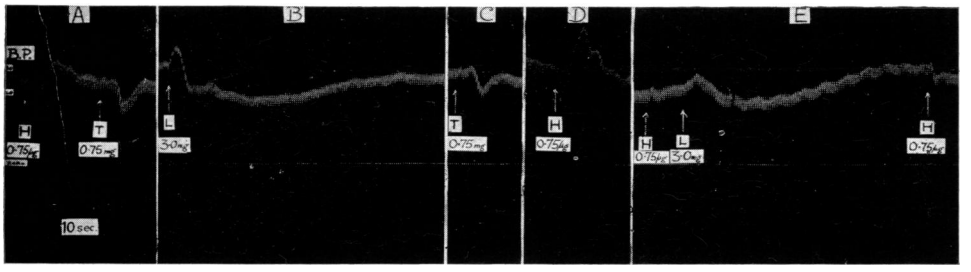

FIG. 5.—Cat, chloralose: blood pressure. Effect of intravenous *d*-tubocurarine, laudolissin, and histamine after blocking autonomic ganglia with hexamethonium; effect of mepyramine. Lettering and time intervals between doses of curarizing drugs as Fig. 4. 1 mg. hexamethonium per kg. given 2 min. before each dose of curarizing drug. Two doses of 0.25 mg. mepyramine per kg. given between D and E.

by MacIntosh and Paton (1949). Laudolissin at double and Compound 15 at one-and-a-half times this dose caused no fall in blood pressure (see Fig. 4). Still larger doses of both compounds (3 mg. laudolissin; 2 mg. Compound 15 per kg.) produced a slight delayed depression that lasted several minutes, as illustrated in Fig. 5. The depressor activity of these two compounds was removed by mepyramine maleate to approximately the same extent as those of histamine and *d*-tubocurarine. We conclude from these experiments that, in the cat, Compound 15 releases less histamine than *d*-tubocurarine, while laudolissin releases less than Compound 15.

While we were able to confirm the observation of Rocha e Silva and Schild (1949) that *d*-tubocurarine enhances the response of the guinea-pig ileum to histamine, we found that, on the contrary, laudolissin depressed this response. For this reason we were unable to investigate the release of histamine by solutions of the synthetic drug more concentrated than 1 in 2,000. In a series of comparisons of the amount of histamine liberated by tubocurarine with that liberated by laudolissin, we found that laudolissin can liberate as much histamine as does *d*-tubocurarine from the isolated diaphragm of the rat, but that no quantitative comparison can be made; even in Tyrode's solution there is a " spontaneous " small release of histamine.

When doses of *d*-tubocurarine were given to the pithed guinea-pig prepared for recording respiratory excursions of the chest-wall, we found that the largest dose used (30 mg. per kg.) failed to produce signs of broncho-constriction. This result agrees with that of de Schaepdryver (1950), who used somewhat smaller doses but a comparable method. Large doses of laudolissin and of Compound 15 (30 mg. per kg.), however, produced broncho-constriction in the guinea-pig, although this effect was not obtained with smaller doses. After a dose of laudolissin or Compound 15, the guinea-pig preparation was much less sensitive to histamine.

In the human skin, the weals and flares produced by intradermal injection of small quantities of laudolissin, *d*-tubocurarine, and Compound 15 resembled those produced by histamine. The areas of weals caused by these compounds and by *d*-tubocurarine were markedly reduced after oral doses of the antihistamine drug promethazine (" Phenergan "), as illustrated in Table IV. These observations indicate that laudolissin, *d*-tubocurarine, and Compound 15 release histamine in

TABLE IV

EFFECT OF PROMETHAZINE ON SKIN RESPONSES TO CURARIZING DRUGS

Subject	Drug	Intradermal dose (mg.)	Weal areas (sq. mm.)	
			Before promethazine	3–3½ hr. after oral promethazine
H.O.J.C.	Histamine	0.001 0.004	150 271	58 85
	d-Tubocurarine	0.054 0.216	119 180	70 84
	Laudolissin	0.108 0.432	115 143	39 87
	Compound 15	0.0135 0.054	115 151	100 93
B.M.	Histamine	0.001 0.004	71 186	64 100
	d-Tubocurarine	0.108 0.432	117 171	75 78
	Laudolissin	0.108 0.432	123 125	56 78
	Compound 15	0.027 0.108	103 191	71 84

man, and confirm the findings that *d*-tubocurarine (Grob, Lilienthal, and Harvey, 1947; Prescott, 1948), and Compound 15 (Bodman, 1951a) release histamine in man.

A series of different doses of laudolissin, *d*-tubocurarine, and Compound 15 was administered intradermally to two subjects. Fig. 6 is constructed from 59 weal areas in one subject and 51 in another obtained during a period of five months. It will be evident from this Figure that weal areas produced by laudolissin and *d*-tubocurarine are related to the dose. In one subject (B.M.) laudolissin proved to exert about one-half and in the other (H.O.J.C.) about one-quarter of the histamine-releasing activity of *d*-tubocurarine. In human skin, in contrast to the cat, Compound 15 released considerably more histamine than *d*-tubocurarine.

Discussion

Our experiments in laboratory animals showed that Compound 15 differs substantially from laudolissin only in the shorter duration of its curarizing action; while, in ability to block autonomic ganglia and to release histamine in the cat, Compound 15 is little more active than laudolissin. But in man Compound 15 differs from laudolissin by causing a much more pronounced release of histamine. Bodman found that Compound 15, given intravenously, produced general symptoms of histamine intoxication. When intradermal injections of Compound 15 and laudolissin were compared, it was found that in the human skin Compound 15 was a much more

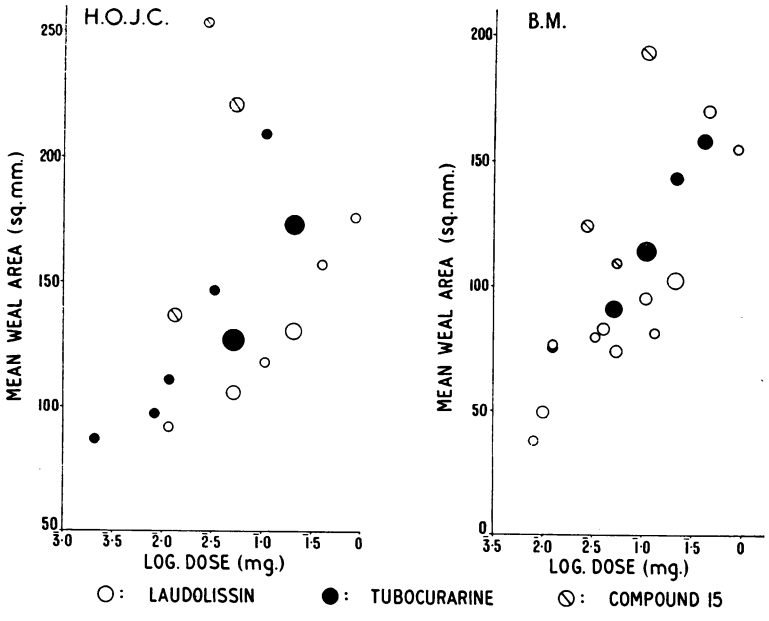

FIG. 6.—Skin reactions of two human subjects to intradermal injections of curarizing drugs. Summaries of 59 (B.M.) and 51 (H.O.J.C.) observations. Diameters circles proportional to numbers of observations.

potent histamine-liberator. This greater activity of Compound 15 made it unsuitable for clinical trials; no such objection applies to laudolissin.

From estimating the capacities of these curarizing drugs to release histamine in different species, we were struck by the extent to which their histamine-releasing potencies varied from species to species, just as their curarizing potencies did. It follows that, before clinical trial, it is as necessary to assess the capacity of a new compound to release histamine as it is to assess its curarizing activity in volunteers.

The antagonism of laudolissin by succinylcholine raises interesting clinical possibilities. After a dose of laudolissin has been given to a patient, the situation may arise in the recovery phase when a brief intensification of relaxation is needed. In these circumstances succinylcholine would seem to be the drug of choice, since a large dose of this compound may be expected to produce a deeper relaxation, soon followed by a recovery from laudolissin that is sharper than normal. The possibility also exists of using succinylcholine in smaller doses as an antagonist of laudolissin and *d*-tubocurarine. There would seem to be no objection to giving succinylcholine as a relaxant (e.g. for intubation) a few minutes before a dose of laudolissin, though a slightly higher dose of the latter compound might be required.

Both laudolissin and Compound 15 possess more curarizing activity than *d*-tubocurarine in the rabbit and cat, and less in man (see Bodman, 1952). Taking into account Bodman's findings, the order of sensitivity of different species to laudolissin may be stated as follows:

Rabbit > Cat > Man > Mouse > Rat

SUMMARY

1. Laudolissin and Compound 15 are synthetic curarizing agents. They are more potent than *d*-tubocurarine in the rabbit and cat, and less potent in the mouse and rat.

2. In equipotent doses laudolissin is longer-acting and Compound 15 shorter-acting than *d*-tubocurarine when tested on the tibialis anticus of the cat.

3. Paralysis caused by laudolissin or by Compound 15 is antagonized by neostigmine. After laudolissin or *d*-tubocurarine, small doses of succinylcholine hasten recovery, while larger doses cause paralysis followed by more rapid recovery. Both laudolissin and Compound 15 act synergistically with ether, while their toxicities are unaffected by thiopentone.

4. Laudolissin blocks autonomic ganglia less readily than Compound 15, which in turn blocks ganglia less readily than *d*-tubocurarine.

5. In man laudolissin releases less and Compound 15 considerably more histamine than *d*-tubocurarine. In the cat laudolissin releases less histamine than Compound 15, which in turn releases less than *d*-tubocurarine. In the rat diaphragm *in vitro*, both drugs release histamine, and in the guinea-pig both appear to be slightly more potent histamine-liberators than *d*-tubocurarine.

We should like to thank Miss M. P. Hatton for technical assistance. We are indebted for much valuable advice at various stages of this work to Drs. B. D. Burns, W. Feldberg, F.R.S., J. A. B. Gray, H. O. Schild, and E. J. Zaimis. We have to thank the directors of Messrs. Allen and Hanburys Ltd. for permission to publish this work. The samples of laudolissin and Compound 15 were prepared by Dr. E. P. Taylor. A sample of gallamine triethiodide was kindly supplied by Messrs. May and Baker Ltd., and of Compound 48/80 by the Wellcome Research Laboratories.

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