THE ACTION OF LAUDEXIUM IN MAN AND EXPERIMENTAL ANIMALS

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THE drug laudexium methylsulphate (Laudolissin) was developed as a result of the researches of Taylor and Collier (1950 and 1951) into the relationship of chemical structure and pharmacological activity among myoneural blocking agents. It has received several clinical trials (Bodman, Morton and Wylie, 1952; Binning, 1953; Sara, Marshall and Balthasar, 1954) and has been reported to be a completely satisfactory substitute for d-tubocurarine in anaesthesia. Just lately, however, after an investigation of a large series of cases, Dundee, Gray and Riding (1954) have had occasion to question this conclusion. Early in 1953 the author carried out a clinical study of the action of laudexium. Some of the results of that work indicated that the action of this drug might differ in some respects from that of d-tubocurarine, with the result that a re-investigation of its properties in experimental animals was undertaken. This paper is an account of the clinical study and of the experimental work to which it led.

CLINICAL STUDIES

Methods

Patients were premedicated with omnopon gr. 1/3 (20 mg.) and scopolamine gr. 1/300 (0.2 mg.) if they were between the ages of 16 and 60, and with morphine gr. 1/6 (10 mg.) and atropine gr. 1/100 (0.6 mg.) if they were older. Anaesthesia was induced with thiopentone or thialbarbitone (Kemithal) and an endotracheal tube passed. Nitrous oxide and oxygen were then administered in the proportions of 6 : 2 l. per minute in a semi-closed system; pethidine and, if necessary, additional barbiturate were used as supplements. In all, 86 cases were studied.

The types of operation performed are shown in table I, and their approximate duration in table II. The methods of intubation used are given in table III. An initial dose of 10 mg. of laudexium was given in each case, and thereafter the drug was injected in 10-mg. increments until the abdomen relaxed or, where this was necessary because the chest was to be opened, until artificial respiration was readily performed. In the vast majority of patients, relaxation for the entire operation, including abdominal closure, was produced by laudexium.

TABLE I

The type of operation performed

Operation on	No. of cases
Stomach	14
Gall bladder and bile ducts	17
Appendix and colon	13
Other viscera	12
Prostate gland	4
	—
Total abdominal operations ...	60
Major thoracotomy	14
Thoracoplasty	12
	—
	86

TABLE II
The duration of the operations

ABDOMINAL OPERATIONS

Duration of operation (minutes)	No. of cases
0– 30	5
31– 60	23
61– 90	15
91–120	9
121–150	3
150 + ...	4
	—
	59

1 case not completed under laudexium

CHEST OPERATIONS

	Average duration (minutes)	No. of cases
First stage thoracoplasty ...	100	8
Second stage thoracoplasty ...	60	4
Major thoracotomy	240	14
		—
		26

TABLE III
The technique of intubation

Method of intubation	No. of cases
Local anaesthetic spray	2
With suxamethonium	40
With gallamine triethiodide	44
	—
	86

Results

Dosage.

As in previous studies of "curarizing" agents the potency of laudexium was estimated by determining the dose which would produce enough relaxation for the opening of the abdomen during a laparotomy. In those who had received suxamethonium, or had been intubated with a local anaesthetic spray, this was 28.9 ±

8.7 mg. The comparable amount of d-tubocurarine had already been found to be 17.2 ± 7.7 mg. (Hunter, 1952). Where gallamine triethiodide was used for intubation, 18.3 ± 11.3 mg. of laudexium was required to relax the abdomen. This small amount was no doubt due to the fact that the action of the gallamine had not completely worn off by the time at which the laudexium was given, viz. 15 to 25 minutes after intubation. There was thus a marked summation of the effects of these two agents (cf. Dundee *et al.*, 1954).

There was some variation in the duration of a single dose, but the mean amount required for periods of relaxation lasting half an hour or less was virtually the same as that needed to induce abdominal relaxation (table IV). In cases where the relaxation was maintained for 31 to 45 minutes, the total amount of the drug given exceeded this amount by 13 to 14 mg. showing that additional doses were required if the period of relaxation was to be extended.

The numbers in the groups where yet longer periods of relaxation were required are too small for detailed analysis. Over all, however, in 15 patients undergoing major upper abdominal operations and intubated while under the influence of

TABLE IV
The dose of laudexium
(The numbers in brackets indicate the range of doses)

Purpose	Method of intubation	
	Suxamethonium or spray (mg.)	Gallamine Triethiodide (mg.)
To relax abdomen	28.9 ± 8.7	18.3 ± 11.3
For relaxation lasting up to 30 minutes	26 (range 20–30)	15 (range 10–20)
For relaxation lasting 31–45 minutes	40 (range 25–50)	28 (range 20–30)
For major upper abdominal operations (mean duration of relaxation 73.5 minutes)	—	42.3
For major chest operations (mean duration of relaxation 193 minutes)	—	50.3

gallamine triethiodide, 42.3 mg. of laudexium were required for an average of 73.5 minutes of relaxation. By contrast, in 14 major thoracotomies where laudexium was used to facilitate artificial respiration, a mean amount of 50.3 mg. was used over 193 minutes. This low rate of dosage during chest operations does not indicate any special virtue on the part of laudexium. It has also been noted when d-tubocurarine has been used in such cases.

Action on Respiration.

Like all " curarizing " drugs, laudexium produced paralysis of the respiratory muscles. As Dundee and his colleagues (1954) remarked, so in this series too, it was found to be very easy to take over the patient's breathing, even when respiratory movements were still present. There was, however, one important difference between the action of laudexium on the breathing, and that of other neuromuscular blocking agents. With other drugs it was possible in an appreciable number of cases to obtain abdominal relaxation without depressing respiration to the point at which manifest anoxia or hypercarbia developed. With laudexium it was rarely possible to do this. Indeed, in some cases, in the presence of an apparently adequate though reduced respiratory excursion, the signs of obvious respiratory insufficiency appeared. There was never any evidence of bronchospasm in these cases to account for the failure of ventilation, but in two instances there was a considerable increase in the amount of bronchial secretion. It is possible that this interfered with air entry into the lungs in the cases where oxygenation failed in the presence of apparently adequate respiratory displacement. In

this connection it is interesting that Collier and Macauley (1954) have shown that laudexium increases secretion from the related salivary glands in cats.

Circulatory Effects.

Some quite marked changes in the blood pressure occurred when laudexium was given. These are shown in table V. Most of the rises were asphyxial, and traceable to the marked interference with respiratory function produced by the drug. The falls in the blood pressure, however, seemed to be a specific effect of the agent. They appeared in poor risk cases, and only after the first dose of the drug. No special treatment for this hypotension was necessary, and it rarely persisted for more than 10 minutes.

Antagonism by Neostigmine.

As the patients were anaesthetized by a method which allowed nearly complete recovery of consciousness within a few minutes of withdrawing the anaesthetic, it was possible to assess fairly accurately the effectiveness of neostigmine as an antidote. If, after its administration normal breathing was fully restored, the patient was able to cough effectively on his tube, and he could, when asked to do so, open his eyes and keep them open, decurarization was regarded as complete. If his eyelids tended to droop, if the coughing produced by moving the endotracheal tube was ineffective, or if intercostal paralysis or chin tugging persisted, it was considered that decurarization had failed.

Neostigmine was given to 68 patients in doses of 1.25 mg. or 2.5 mg. with the amounts of atropine recommended by Hunter (1953) to prevent muscarinic effects. It early became apparent that,

TABLE V
The blood pressure changes after the administration of laudexium

Blood pressure rise	−10 mm.	−20 mm.	−30 mm.	−40 mm.		
Number of cases	2	1	3	2		
Blood pressure fall	−10 mm.	−20 mm.	−30 mm.	−40 mm.	−50 mm.	−60 mm.
Number of cases	13	11	2 ·	3	1	1

Blood pressure unchanged	31 cases
No record	15 cases

though the smaller of these doses would quickly abolish mild respiratory depression due to d-tubocurarine or gallamine triethiodide, it was often ineffective against that due to laudexium. There were, however, cases in which 2.5 mg. of neostigmine was incompletely effective, and in one instance even a total of 3.75 mg. of this drug failed to produce the desired response (table VI). There are no comparable figures for d-tubocurarine, but only once in the course of several hundred administrations of this relaxant drug have I failed to obtain a complete reversal of paralysis with neostigmine.

These clinical results raised some interesting problems which were further investigated in the experimental laboratory.

EXPERIMENTAL STUDIES

Methods

The effects of laudexium on the breathing were studied on 5 cats anaesthetized with pentobarbitone given by intraperitoneal injection in a dose of 40 mg./kg.; adequate maintenance doses of this drug were subsequently given by the intravenous route. Respiration was recorded by tambours placed on the chest and abdomen. The mean blood pressure was taken with the aid of a mercury manometer connected by a column of citrate to one carotid artery. Restoration of normal breathing after its paralysis by laudexium was the criterion of successful antagonism.

Antagonism in mice was studied on a simple survival basis. Drugs were given either by intraperitoneal or intravenous injection to mice weighing 18–40 g. By neither route did the volume given exceed 0.21 ml.

Results

Cats. Laudexium was given in the dosage necessary to produce profound respiratory depression or apnoea (usually 100 γ/kg.) on seven occasions 0.1 mg./kg. of neostigmine given immediately thereafter either failed to produce any response or gave rise only to a partial restoration of breathing. Even with 0.2 mg./kg. of neostigmine, complete reversal of the paralysis was obtained in only one animal, though this amount had always proved effective in reversing paralysis produced by d-tubocurarine and gallamine triethiodide.

Physostigmine in a dose of 0.12 mg./kg. with an equal amount of atropine was also tested as an antidote. Though this dose of the drug produced fasciculation and fibrillation of voluntary muscle when administered to the normal animal, it did not produce any apparent reversal of respiratory depression due to laudexium. Physostigmine, however, may have been too slowly acting an antidote to be effective on such a test, though in a control study with gallamine triethiodide some evidence of recovery was observed.

In one animal the sciatic nerve was stimulated while laudexium was acting, and there was observed a phenomenon which had a parallel in the human sub-

TABLE VI
The effect of neostigmine on laudexium paralysis

Degree of decurarization	Complete	Doubtful	Failed	None given
Number of cases	46	8	14	14
		Incomplete records 4		

ject. During the administration of this drug in clinical anaesthesia it had been noted that breathing often became inefficient before abdominal relaxation occurred. It was found in the cat that apnoea appeared while the response of the unloaded foreleg muscles both to a single twitch and to a tetanus had scarcely been impaired.

Mice. An attempt was made to obtain additional information on these matters by studies in mice. It was shown that 0.3 mg./kg. of neostigmine with an equal amount of atropine given by intraperitoneal injection produced an appreciable reduction in the toxicity of gallamine triethiodide given intravenously in doses of 5.0 mg./kg. This dose of neostigmine was apparently ineffective in reducing toxicity of 0.25 mg./kg. of laudexium (table VII). It was, however, possible to demonstrate protection against laudexium in a larger dose (0.4 mg./kg.) by 0.2 mg./kg. neostigmine with 0.2 mg./kg. of atropine given intravenously in the same syringe.

The degree of protection obtained was not, however, so great as that which could be conferred against a comparable amount of gallamine triethiodide (table VIII). It was intended to study the corresponding antagonism with physostigmine, but the control tests with gallamine were so unpromising that the experiment with laudexium was not performed (table IX).

One other study was made. At the time when this work was done, the author

TABLE VII

Drugs	Dose given mg./kg.	Route of injection	Mice used	Mice survived
Laudexium	0.25	i.v	14	6*
Neostigmine	0.3	i.p.	6	6
Atropine	0.3			
Neostigmine	0.3	i.p.	6	3*
Atropine	0.3			
Laudexium	0.25	i.v.		
		5 minutes later		
Neostigmine	0.3	i.p.	8	7†
Atropine	0.3			
Gallamine triethiodide	5.0	i.v.		
		5 minutes later		
Gallamine triethiodide	5.0	i.v.	8	1†

* $X^2=0.025$ $P<0.9>0.8$
† $X^2=6.25$ $P<0.02>0.01$

TABLE VIII

Drugs	Dose given mg./kg.	Route of injection	Mice used	Mice survived
Laudexium	0.3	i.v.	5	2
Laudexium	0.4	i.v.	15	0*
Laudexium	0.4	i.v.	17	8*
Neostigmine	0.2			
Atropine	0.2			
Neostigmine	0.2	i.v.	6	6
Atropine	0.2			
Gallamine triethiodide	3.0	i.v.	7	4
Gallamine triethiodide	5.0	i.v.	8	0†
Gallamine triethiodide	5.0	i.v.	8	8†
Neostigmine	0.2			
Atropine	0.2			

* $X^2=7.07$ $P<0.01$ † $X^2=12.25$ $P<0.01$

TABLE IX

Drugs	Dose given mg./kg.	Route of injection	Mice used	Mice survived
Physostigmine	0.2	i.v.	9	9
Atropine	0.4			
Physostigmine	0.2	i.v.	5	1
Atropine	0.4			
Gallamine triethiodide	5.0			
Physostigmine	0.5	i.v.	6	6*
Atropine	0.5			
Physostigmine	0.5	i.v.	8	4*
Atropine	0.5			
Gallamine triethiodide	5.0			

* $X^2=3.00$ $P<0.10>0.05$

believed that if antagonism could be demonstrated between a curarizing drug and a depolarizing blocking agent, the former could be regarded as a competition blocker. Mice which had survived the administration of 0.25 mg./kg. of laudexium were given 1.8 mg./kg. Ro 3-0386, which is approximately the L.D. 95. An appreciable number survived (table X).

TABLE X

Drugs	Dose given mg./kg.	Route of injection	Mice used	Mice survived
Ro 3-0386	1.8	i.v.	7	0
Laudexium	0.2	i.v.	5	4
Ro 3-0386	1.8	10 minutes later		

* $X^2 = 5.2$ $P < 0.05$ $P > 0.02$

DISCUSSION

The results of the clinical study here reported confirm the conclusions reached by Dundee and his co-workers (1954) indicating, as they do, that laudexium cannot be used on all occasions in place of d-tubocurarine, chiefly because the paralysis produced by it is not completely reversed by neostigmine. In this study also, two minor defects of laudexium have come to light, namely, its peculiarly marked tendency to interfere with the breathing and its hypotensive action. These would not, however, be insuperable drawbacks to the use of the drug in clinical anaesthesia. Respiratory depression is readily rectified by artificial ventilation of the lungs and the fall in blood pressure noted was rarely serious and always evanescent.

The differences in the conclusions reached here and confirmed by Dundee and his colleagues (1954) from those of other workers are probably traceable to two factors. First, the depth of the anaesthesia obtained from nitrous oxide and oxygen given with a non-volatile supplement is

never more than Plane 1 of Stage III of the Guedel classification. In consequence the whole of the relaxation for abdominal operations must be provided by a myoneural blocking agent. Not only so, in such cases deep " curarization " must be maintained until the abdomen has been closed. If volatile supplements to nitrous oxide and oxygen are employed, or if cyclopropane is used for anaesthesia, a relatively lighter plane of curarization will provide equally good relaxation, and very often it will be possible to close the abdomen without an additional dose of relaxant, especially if the anaesthesia is deepened at this time. In such cases antidote drugs are not often necessary. When they are given they are used to reverse a less profound myoneural block than exists in those who have received only Plane 1 nitrous oxide and oxygen anaesthesia. The apparent failure of the author and of the Liverpool team to obtain effective reversal of laudexium by neostigmine is therefore not an insuperable obstacle to the use of the drug. It is merely an indication that this agent, like decamethonium, requires for its successful administration a little more profound general anaesthesia than is necessary when d-tubocurarine or gallamine triethiodide is being given. Alternatively, it is an indication that, as in Binning's cases (1953), suxamethonium should be used to provide relaxation for abdominal closure.

Many of the differences between the author's experimental results and those of Collier and Macauley (1952) are also related to differences in the anaesthesia employed. It had been found in a previous study of decamethonium (Hunter, 1950) that the findings of the animal work

carried out under pentobarbitone were more applicable to the clinical administration of that relaxant by the technique outlined above than were those of Paton and Zaimis (1949) who used chloralose. Similarly in the present study, the results obtained from investigations on animals under pentobarbitone anaesthesia have given results approximating more closely to those obtained under clinical conditions than do those of Collier and Macauley (1952) who also used chloralose.

Other differences in the experimental results from those of Collier and Macauley (1952) are traceable to diversity of method. These workers demonstrated the antagonism between laudexium and neostigmine by a reversal of the dose which caused loss of the righting reflex in rabbits, that is, in animals only very lightly curarized. Collier and Macauley also found an antagonism in cats presumably from experiments with an isometric myograph. In this instrument also, truly complete paralysis is rarely induced, especially if the muscle is loaded. By contrast, the dose of a myoneural blocking agent which produces apnoea in a cat or mouse represents an amount which will inhibit more or less completely all conduction at myoneural junctions. It is, therefore, not surprising that neostigmine proved ineffective then, though it was apparently a satisfactory antidote at the lighter levels of curarization.

Finally it must be emphasized that though the experimental results here reported are in accord with the conclusions reached in the clinical investigation, the technique of anaesthesia used for this differed from those employed in the earlier studies of laudexium. It therefore seems that, when the usefulness of any curarizing drug is being assessed in the laboratory, it is desirable not merely to carry out experiments to show what are its general properties, but also to investigate the drug to find out whether it is likely to give the best results when combined with very light nitrous oxide and oxygen anaesthesia, or whether it will probably be more satisfactorily given at the slightly deeper plane of narcosis obtained with cyclopropane or other similar methods.

SUMMARY

(1) Laudexium was used to produce relaxation in 86 patients anaesthetized by nitrous oxide and oxygen with a non-volatile supplement.

(2) It provided satisfactory relaxation during the operation, but the paralysis could not always be reversed by neostigmine.

(3) It had a profound effect on respiration and sometimes lowered the blood pressure, though only for a short period.

(4) In a subsequent laboratory investigation neostigmine was not completely effective as an antagonist to laudexium in the cat and mouse.

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