CLINICAL STUDY OF PRESTONAL AS A MUSCLE RELAXANT IN ANAESTHESIA: A PRELIMINARY REPORT*

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IT IS now over fourteen years since a relaxant drug was first employed in clinical anaesthesia (1). During this period of years, many different drugs have been introduced into anaesthesia because of their ability to relax skeletal muscles. Before considering the study of another such preparation, let us contemplate a few of the basic principles involved in an evaluation of new drugs in anaesthesia, as suggested by Melville (2).

I. *Effectiveness*

Is the drug really effective for the specific purpose for which it is being studied? Is it superior or inferior to the known agents used for the same purpose? In answering these questions, individual differences in susceptibility to drugs must always be kept in mind. A critical investigation of 10 or 20 cases, involving a more or less individualized and detailed study in each case, might be a more fruitful approach to the problem than a superficial and less critical study of 100 or 200 cases.

II. *Safety*

Is the drug free from injurious effects in the body?

III. *Dosage*

In making an evaluation, it is wise to start with minimal doses and gradually increase as the effects are observed. The intravenous method of administration is most easily controlled.

IV. *Influence of Other Drugs used in Anaesthesia*

"Combination" does not necessarily mean "potentiation"

During the last two years, Rudolf Frey (5) of Heidelberg, Germany, has studied various new drugs proposed as relaxants in anaesthesia:

(1) DESOXYDAURIZIN—*rejected* because of too weak action and too heavy histaminic side effects.
(2) PRAPARAT 9909—*rejected* because of depressive action on the respiratory centre.
(3) BELLADONNINBROMAETHYLAT—*rejected* because of central respiratory disturbances.

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(4) Various other test preparations—*rejected* because of considerable increase in pulse rate.

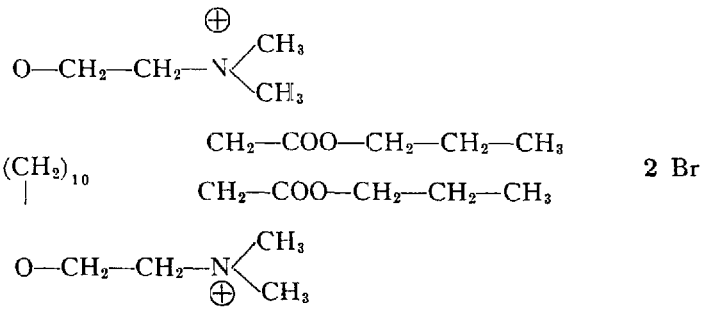
(5) Dioxahexadekaniumbromid, PRESTONAL (Geigy)—*recommended.*

Frey has now used Prestonal in clinical anaesthesia in over 1000 cases, although less than a third of these cases have been studied in detail.

CHEMICAL PROPERTIES

The chemical formula for Prestonal has been outlined as follows:

N, N, N′, N′-Tetramethyl-N, N′-bis-(carbopropoxymethyl)-3, 14-dioxahexadecane-1, 16-diammonium bromide



Prestonal differs from the other such compounds in having a much longer chain between the two quaternary ammonium groups (molecular weight = 678.6). The substance is a colourless crystalline powder, easily soluble in water, with a melting point of 146°C. An aqueous solution is practically neutral, but at a pH of 7.4 and 37°C., Prestonal is spontaneously decomposed by hydrolysis to an extent of 50 per cent in 40 minutes. At a higher pH the half-life becomes shorter, at a lower pH, longer. Consequently, the J. R. Geigy Company of Basle, Switzerland, have prepared the product *Prestonal Geigy* (G 25, 178) in a 1 per cent solution, with 100 mg. in each 10 ml. ampoule (i.e., 10 mg. per ml.). This solution has been adjusted to a pH 3 2 approximately and has proven to be stable, even when stored for a considerable period.

When 50 mg. of this solution of Prestonal are mixed in a syringe with 375 or 500 mg. of 2 or 3 per cent thiopental respectively, a milky solution results. However, if this solution is left quietly on the table for a few minutes, it readily becomes very clear and is satisfactory for use.

HISTAMINE RESPONSES

Since some muscle relaxants are thought to release histamine in various degrees (3), simple observations were made on four of ourselves, using the method of small intracutaneous wheals. The amount and the speed of appearance of redness and induration were observed, using the following solutions:

1. Prestonal (10 mg. per ml.)
2. d-tubocurarine (3 mg. per ml.)
3. Succinylcholine (20 mg. per ml.)
4. Decamethonium (1 mg. per ml.)
5. N-saline

The results of these skin tests (see Table I) indicate that Prestonal and

TABLE I

SKIN SENSITIVITY TESTS (HUMANS)

	Subject A		Subject B		Subject C		Subject D		Average grade
	Wheal	Redness	Wheal	Redness	Wheal	Redness	Wheal	Redness	
I. Prestonal	4	6	5	5	4	6	5	5	5
II d-Tubocurarine	4	3	3	4	4	4	3	4	4
III Succinylcholine	2	2	1	3	2	2	2	3	2
IV. Decamethonium	1	2	1	1	0	1	1	2	1
V Normal saline	0	0	0	0	0	0	0	0	0

Reactions were graded from 0 to 6, considering both the immediate and delayed responses, following small intracutaneous injections

d-tubocurarine produce skin reactions of the highest order with Prestonal even exceeding d.T.c in this respect. Succinylcholine produced a reaction less than half that of the former two drugs, whereas decamethonium produced a positive result of the lowest order The normal saline solution produced a negative response in all cases.

When decamethonium was first introduced into anaesthesia, this very low histamine response was hailed as one of its advantages over d T c. (4).

It was observed sharply by all our volunteers that intracutaneous Prestonal produced an immediate and somewhat prolonged "stinging" sensation and that succinylcholine produced a very mild and short "sting" Comparatively speaking, the other injections were painless The acidity or the vehicle may be the cause of the "stinging" response.

CLINICAL STUDY OF PRESTONAL

Our clinical observations and impressions will, of necessity, be limited. We have used Prestonal as a muscle relaxant during anaesthesia for surgical procedures on only twenty-six patients.

In Table II the details of the cases are presented. It will be noted that the ages ranged from 14 to 78 years (see Tables II and III).

Of the 26 cases, 17 patients had abdominal surgery and thus required relaxation for major procedures both in the upper and in the lower abdomen.

Eight patients were postured in the Trendelenburg position for gynaecology.

As all of the patients (except one, who was undergoing bronchoscopy) were orally intubated by direct vision using a Macintosh laryngoscope, conditions for this procedure could be evaluated.

The anaesthetic agents and methods were quite uniform. Two per cent thiopental solution, in doses ranging from 100 to 500 mg., was used for induction in all cases and cyclopropane or nitrous oxide for maintenance.

Prestonal was given intravenously in various concentrations varying from 0.05 to 1 per cent solutions and of course in variable dosage, ranging from 40 to 265 mg. (see Table IV).

TABLE II

DETAILS OF PATIENTS RECEIVING PRESTONAL

Case No	Patient	Sex	Age	Operation	Duration	Prestonal	Anaesthetics			Tensilon	Prestonal action		OT Intubation	Remarks
							Thiopental	C_3H_6	N_2O		Peak after first dose	Duration after last dose		
					Mins	Mg	Mg			Mg	Mins.	Mins.		
1	F T	F	27	Pelvic laparotomy	100	60+ 20= 80	200	Yes	—	—	3	50	Yes	
2	C E.	M	20	Laparotomy	90	50+ 10= 60	375	Yes	—	—	2 5	40	Yes	Bowel contracted
3	N S.	F	68	Cholecystectomy	120	50+105=155	320	Yes	—	—	3	40	Yes	Bowel contracted
4.	J V.	F	30	Cholecystectomy	65	60+ 60=120	300	Yes	—	—	2	20	Yes	Bowel contracted
5	W M.	M	33	Excision of tumor in neck	120	60+ 40=100	300	Yes	—	—	3	—	Yes	Secretions moderate
6	L.C	M	22	Trauma— repair of face	120	80	500	Yes	—	—	3 5	—	Yes	
7.	J.T.	F	47	Hysterectomy	100	75+100=175	300	Yes	—	—	4	15	Yes	Cough 6′ after 1st dose
8	A.C.	F	56	Hysterectomy (radical)	180	75+190=265	300	Yes	—	—	3	20	Yes	Note large dose
9.	J K	F	44	Hysterectomy	100	40+ 85=125	220	Yes	—	—	2	25	Yes	Bowel contracted
10.	D.S	F	38	Mastectomy	60	40	300	Yes	—	—	3	25	Yes	

TABLE II

DETAILS OF PATIENTS RECEIVING PRESTONAL (*continued*)

Case No.	Patient	Sex	Age	Operation	Duration	Prestonal	Anaesthetics			Tensilon	Prestonal action		O T Intubation	Remarks
							Thiopental	C_3H_8	N_2O		Peak after first dose	Duration after last dose		
					Mins	Mg	Mg			Mg	Mins	Mins		
11.	W.H.	F	43	Hysterectomy	120	30+10+80=120	200	Yes	—	10	3	17	Yes	Difficult intubation
12.	S T.	F	58	Appendectomy	60	40+20= 60	180	Yes	—	10+5	2	20	Yes	Tensilon—no effect
13.	F S	F	40	Diagnostic D & C	30	10+10+ 18+30= 68	100	—	Yes	10+10	2	12	Yes	Pulse from 124–80 (with Tensilon) very light anaesthesia
14.	M S.	F	43	Hysterectomy	120	40+14+10+10 +10+40+20+20	240	—	Yes	10	3	30	Yes	Prestonal extravenously
15	J S.	F	48	Mastectomy	220	50	240	Yes	—	—	2	—	Yes	
16	M.T.	M	74	Bowel anastomosis (CA)	90	20+20+20 +30=90	100	Yes	—	10+10	2 5	20	Yes	Anectine 40 mg for intubation
17	F C.	M	30	Revision of leg amputation	30	50+50=100	320	Yes	—	—	3	10	Yes	Initial dose inadequate
18.	R O	M	14	Appendectomy	70	20+20+20=60	240	Yes	—	—	—	—	Yes	Anectine 50 mg. for intubation Prestonal ineffectual More Anectine.
19.	S.M.	F	61	Mastectomy	65	50	260	Yes	—	—	2 5	25	Yes	Reacted on tube

TABLE II

DETAILS OF PATIENTS RECEIVING PRESTONAL (*continued*)

Case No	Patient	Sex	Age	Operation	Duration	Prestonal	Anaesthetics			Tensilon	Prestonal action		O T Intubation	Remarks
							Thiopental	C_3H_6	N_2O		Peak after first dose	Duration after last dose		
					Mins	Mg	Mg			Mg	Mins	Mins		
20	T V.	F	26	Appendectomy	75	20+30+20 +30=100	260	Yes	Yes	—	—	60	Yes	Inadequate with small doses but later good
21	M G.	F	55	Cholecystectomy	80	50+30=80	990	Yes	Yes	—	3	30	Yes	
22	A W	F	64	Mastectomy	80	60+20=80	160	Yes and Ethylene		—	3	4	Yes	Apnoea with cords still
23.	J.V	F	38	Hysterectomy	120	60+60+40+ 60=220	240	Yes	—	—	3 5	30	Yes	Duration 2nd and 3rd dose 20 min each
24	J O	M	64	Bronchoscopy	20	50+20=70	200	—	Yes	10	4	20	No	Spontaneous breathing Skin flush
25	J M	F	33	Hysterectomy	110	50+20+10+ 15+30+30=155	240	Yes	—	—	4	20	Yes	Small doses inadequate
26	J.W	M	78	Resection of oesophagus	240	60	120	Yes	—	—	3	8	Yes	Bad risk (thoracotomy)

TABLE III

AGE DISTRIBUTION

Age	Number of cases
10—19 years	1
20—29 "	4
30—39 "	6
40—49 "	6
50—59 "	3
60—69 "	4
70—79 "	2
Total	26

TABLE IV

PRESTONAL RANGE OF DOSAGE AND CONCENTRATION

Case No.	Intubation dose		Maintenance dose		Total dose Mg	Duration of operation minutes	Remarks
	Mg	Conc'n.	Mg	Conc'n.			
1	60	1%	20	1%	80	100	
2	50	1	10	1	60	90	
3	50	1	105	0 05	155	120	
4	60	1	60	0 05	120	65	
5	60+40	1	None		100	—	
6	80	1	None		80	—	
7	75	1	100	0 05	175	100	
8	75	1	190	0 05	265	180	
9	40	1	85	0 10	125	100	
10	40	1	None		40	—	
11	30+10	1	80	0 10	120	60	
12	40	1	20	1	60	60	
13	30	1	48	1	68	—	Special case
14	40	1	124	1	164	120	
15	50	1	None		50	—	
16	None		90	1	90	90	Intubated with Succinylcholine
17	50+50	1	None		100	—	
18	None		60	1		70	Succinylcholine before & after Prestonal
19	50	1	None		50	—	
20	20+30 +20+30	1	None		100	75	Initial doses inadequate
21	50	1	30	1	80	80	
22	60	1	20	1	80	—	2nd dose to cover light anaesthesia
23	60	1	160	1	220	120	
24	50+20	1				20	Bronchoscopy
25	50	1	105	1	155	110	
26	60	1	None		60	—	
AVERAGE	60		80		140	100	

Discussion of Results

1. *Conditions for Intubation*

It was consistently easy to obtain good conditions for intubation if an adequate dose was given. With doses of 30 or 40 mg. the jaw muscles and those of the pharynx might be adequately relaxed to expose the glottis but the vocal cords would be actively moving as spontaneous breathing was well maintained. If the upper respiratory passages were allowed to become obstructed, this spontaneous diaphragmatic breathing might cease and the patient appear apnoeic. This was demonstrated in a bronchoscopy case, where apnoea prior to the passage of the bronchoscope was followed by active diaphragmatic breathing during the examination. After the bronchoscope was removed, apnoea again occurred with momentary cyanosis, owing to upper respiratory obstruction. Thus upper respiratory paralysis occurred concurrently with *active* diaphragmatic breathing, in spite of doses of 50 mg. + 20 mg (= 70 mg) of Prestonal prior to bronchoscopy. This patient was reacting somewhat before his block had worn off but, on later questioning, remembered nothing before he was lifted onto his bed a few minutes later. The surgeon was pleased to have his patient breathing spontaneously during the examination

In the average intubation case, a minimum dose of 60 mg. of drug produced good conditions for intubation. In most of these cases apnoea and maximal relaxation occurred 2 or 3 minutes after injection and lasted from 6 to 8 minutes more.

2. *Abdominal Relaxation*

In all but one of the abdominal cases it was possible to obtain good relaxation of the abdominal muscles, if an adequate dose, either singly or by rapid drip, was given On the other hand, intermittent small doses of 10 or 15 mg, even if given repeatedly and at 3 or 4 minute intervals, might never produce good results. It seems that 30 or 40 mg. as the initial dose was necessary to obtain relaxation, whereupon additional doses of 20 mg intermittently usually proved adequate for maintenance. This finding was comparable to what we have found with d.T.c.

The dose of Prestonal approximates about six times the dose of d T.c which we were accustomed to use in similar cases.

3 *Pulmonary Ventilation*

To avoid the possibility of obstruction in the upper respiratory passages, an endotracheal tube is necessary. In addition the minimal amount of resistance to spontaneous ventilation is obtained. We could find no evidence of particular obstruction in the *lower* respiratory passages which might be considered to be spasm due to histamine-release. Such cases have been reported with d.T.c. but have been very rare in our experience with the latter drug.

Nevertheless, tracheal reactions from stimulation, such as mild cough or so called "bucking on the tube" did occur fairly often. However, such responses are probably not related to histamine.

In most of our abdominal cases, good relaxation was associated with very

depressed ventilation. Usually controlled ventilation was established either manually, or automatically with the Jefferson Ventilator.

However, in a few cases, and especially if nitrous oxide was used instead of cyclopropane, quite adequate spontaneous ventilation was maintained during the period of relaxation. It was difficult to gauge the dose just right to provide such a situation. Possibly if more cases were handled with nitrous oxide, spontaneous ventilation might be more frequently obtained.

4. *Changes in Pulse and Blood Pressure*

In over 90 per cent of cases, the systolic blood pressure remained steady within a range of 10 mm. of mercury and the pulse variation was within ten points per minute.

In one case, the pulse rose from 80 to 110 per minute after 100 mg. of 1 per cent Prestonal had been given within one minute. It soon returned to normal. Similarly, in a patient in a very light stage of anaesthesia (after only 100 mg. of Thiopental) Prestonal, in a dose of 70 mg. within two minutes, resulted in an increase of pulse rate from 84 to 124. In this case, the pulse rate was readily reversed to 80 with Tensilon (10 mg. + 10 mg.).

Thus it is fair to say that a relatively large dose of Prestonal, with or without very light anaesthesia, may result in tachycardia which is probably due to a block of the cardiac vagal fibres, as occurs very frequently with gallamine (Flaxedil).

There were no cases showing hypotension after this drug but an occasional one showed a mild *transitory* rise in blood pressure.

If the drug is not given faster than 2 mg. per second, there will seldom occur any change in pulse or blood pressure.

5. *Period of Action*

The drug seems to reach its peak action after about two minutes, at which time apnoea usually appears. Occasionally relaxation seemed maximal three minutes after the 1 per cent solution was given into the intravenous tubing of a previously set-up infusion.

Although the duration of action of a single dose was difficult to evaluate, it appeared to be about six to eight minutes.

Nevertheless, after repeated doses or after dilute solutions were given by continuous infusion and then stopped, the period of apnoea lasted for a further 25 or 30 minutes. Thus there may well have been some cumulative effect. During this apnoeic period there is usually persistently good relaxation. Near the end of the period it is common to see tight spastic jaw muscles before the respiration is spontaneously resumed.

We have not seen cases of very prolonged apnoea with Prestonal, such as have been seen many times associated with the combination of pentothal, succinylcholine, and controlled ventilation.

6. *Antagonists and Mode of Action*

Frey (5) has reported several cases where the myoneural block of Prestonal was reversed or antagonized by 5 mg. of pyridostigmine, rather more effectively

than by neostigmine (prostigmine). However, neostigmine produced some antagonism. Thus he concluded that the block was probably of the antidepolarizing or competitive type. Recently, other investigators have challenged this idea and suggest that it is probably the "mixed block" type of relaxant.

On six occasions we have tried to reverse the action of Prestonal with Tensilon, using an 1/V dose of 10 mg., repeated in 5 or 10 minutes.

Although tachycardia, when present after Prestonal, could be reversed by Tensilon, we could not see any sharp reversal of the block. However, it did seem that the apnoeic period after the last dose of Prestonal was somewhat shortened. This may indicate some interference with the block and possibly a larger dose of Tensilon would have produced more conclusive results.

Thus our experience with Tensilon as an antagonist is not very convincing.

On two occasions we have intubated after thiopental and succinylcholine and then proceeded to give Prestonal for abdominal relaxation. With one patient—age 14—50 mg. succinylcholine had been used initially, and after 60 mg. Prestonal the relaxation was still very poor. Then an infusion of 0 1 per cent succinylcholine was turned on and immediately excellent relaxation was obtained. With the other patient—age 74—40 mg succinylcholine had been used for induction. Prestonal in doses of 20, + 20, + 20 and 30 mg was then given before relaxation was obtained and this patient was a thin elderly man with advanced malignancy in the stomach.

It thus appears that succinylcholine, initially, definitely interferes with the Prestonal block but that subsequent doses of succinylcholine are still effective. Thus one might think that the Prestonal block is not of the depolarizing type. Otherwise these two drugs would probably by synergistic.

Consequently, our bit of evidence seems to support the theory that Prestonal belongs to the "mixed block" type of relaxant Clinically, it gives many of the responses which were seen after d.T c

7. *Other Observations*

(*a*) In no case did we see any muscle fasciculations after the injection of the drug, such as are commonly observed after injecting succinylcholine

(*b*) In several of the cases for abdominal surgery, the small bowel appeared to be well contracted, which may often facilitate the surgical procedure. This observation has also been made after succinylcholine.

(*c*) In contrast to the frequent occurrence of excessive salivary secretions after certain other relaxants, the patients receiving Prestonal were usually notably dry.

(*d*) The condition of the vocal cords was usually not completely quiescent, and there occasionally followed a minor stimulatory reaction in the cords and trachea after the endotracheal tube was placed. This reaction was never troublesome.

(*e*) There was no evidence in our cases of intravenous or perivenous irritation following the injection of Prestonal in the various concentrations mentioned. In one of our cases, the site of the infusion needle in the arm, during a hysterectomy, was completely covered with drapes and was not only out of sight but out of reach. After a total dose of over 80 mg. of 1 per cent Prestonal in amounts

of 10 or 15 mg each, the relaxation was still very unsatisfactory. Only then was it found that the needle was dislodged and the drug as well as the infusion fluid was passing extravenously. The area was infiltrated with 1 per cent procaine and there were no ill effects whatever.

(*f*) We were not too surprised to find, at least occasionally, some histamine-like patchy flushing in the skin of the face, neck, and chest areas of some of our patients. This response was associated with the larger doses of 1 per cent Prestonal given within a short period of a few minutes.

Conclusions

1. Prestonal is capable of producing good relaxation of skeletal muscles.
2. The duration of relaxation after a single dose is relatively short, probably between 6 and 8 minutes, but periods of relaxation up to 30 minutes may follow repeated doses or continuous infusion.
3. The block appears to be of the mixed type, and thus antagonists are not convincing.
4. The method of breakdown of the drug has not been established although hydrolysis by enzymes has been suggested.
5 No serious undesirable side-effects have been found thus far.
6. Although much more experience is necessary to evaluate this drug, Prestonal has some advantages over the currently popular relaxants. Only time can tell whether such advantages will overbalance the disadvantages and thus create a place for this relaxant in anaesthesia.

Résumé

Les auteurs présentent un rapport sur l'usage du prestonal comme myorésolutif dans 26 cas. Ce médicament peut produire un bon relâchement des muscles striés Après une dose unique, ce relâchement est d'une durée relativement courte, entre 6 et 8 minutes probablement, mais, si les doses sont répétées ou si la drogue est administrée en infusion continuelle, il peut exister des périodes de relâchement d'une durée allant jusqu'à trente minutes. Le type de blocage semble être varié aussi les antidotes ne sont pas efficaces. Les auteurs n'ont pas établi comment est métabolisé ce médicament, mais il semble qu'il serait hydrolysé par des enzymes. Jusqu'ici les auteurs n'ont pas, non plus, décelé d'effets indésirables.

Bien que, pour faire une bonne évaluation de ce médicament, il soit nécessaire d'en faire usage sur un nombre de cas beaucoup plus considérable, il est possible d'affirmer que le prestonal possède certains avantages sur les myorésolutifs employés couramment. Seul le recul du temps pourra permettre d'affirmer si ces avantages l'emporteront sur les désavantages et si ce médicament pourra se créer une place comme myorésolutif en anesthésie.

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