PANCURONIUM BROMIDE (PAVULON®) EVALUATION OF ITS CLINICAL PHARMACOLOGY*

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PANCURONIUM BROMIDE IS AN amino steroid muscle relaxant (Figure 1) which was synthesized in 1964 by Hewett and Savage and has been studied and evaluated clinically in Europe during the past four years.[1–5] It is an odourless, white, crystalline powder with a bitter astringent taste, melts at 215°C, with decomposition, and is soluble in 50 parts of chloroform and one part water at 20°C. The colourless solution is stable while sealed, but breaks down in a few hours after exposure to air. In Europe it is available in 2-ml ampoules containing 4 mg pancuronium bromide, 18 mg sodium chloride B.P. and water for injection B.P. to 2 mls. The preparation which was used in this study contains preservatives (acetic acid and sodium acetate) to buffer the solution to pH 4.0.

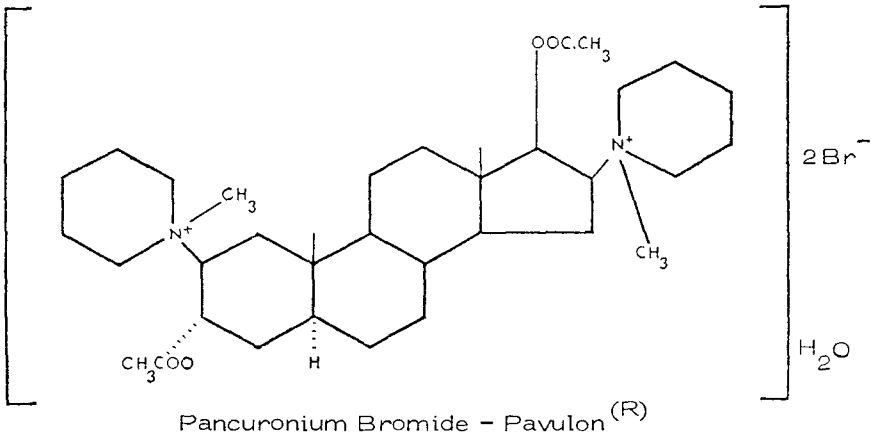

FIGURE 1. Structural formula for pancuronium bromide – Pavulon®.

Pharmacological studies have shown that it has no hormonal action but is a potent non-depolarizing skeletal muscle relaxant like tubocurarine and gallamine. It has a more rapid onset of action than tubocurarine with a similar duration of action. It has a somewhat longer action than gallamine. It has no significant effect on the blood pressure or the tracheobronchial tree due to the very slight ganglion-blocking action and the claim is that no histamine is released.[4] It does not affect

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the pulse rate. This is thought to be due to its observed stabilizing effect on the post-synaptic membrane of the cardiac vagus.[6] It is said to be about 5 times more potent than tubocurarine. Its effect is believed to be more readily reversed with atropine and neostigmine without appreciable cardiovascular reactions. This muscle relaxant is therefore recommended particularly for poor-risk patients, and those undergoing cardiac surgery.[5,7–9]

This report deals with a comprehensive clinical evaluation in 456 patients who required elective major operations.

Methods of Study

Clinical methods and monitoring

Consenting patients scheduled to undergo elective abdominal pulmonary, extremity (hip replacement), neurosurgical, radical neck dissection and major superficial operations (radical mastectomy) were selected for this study. Each patient was interviewed the previous day, a written informed consent obtained, and appropriate premedication was ordered, including a night time oral sedative which would ensure restful sleep and, one hour before surgery, intramuscular atropine and/or scopolamine alone, or with a moderate dose of a sedative or analgesic – whichever was considered appropriate for the patient.

These patients were divided into 4 groups which represented techniques of administering muscle relaxant drugs that are favoured by anaesthetists. This division helped to determine the response and efficacy of the different methods for using pancuronium.

Group A (251 patients) consisted of those in whom a sleep dose of thiopentone (4 to 5 mg/kg) was preceded (29 patients) or followed (222 patients) by approximately 0.1 mg/kg of pancuronium bromide. The patients' lungs were then ventilated with 100 per cent oxygen by bag and mask until there was minimal resistance to expanding the chest. Endotracheal intubation was then accomplished. The time from injection and the ease of intubation were noted. Pulmonary ventilation was then maintained with a mechanical respirator set to deliver 7.5 to 10 ml/kg at 12 to 18/minute using N_2O : O_2 (60 : 40) and a halogenated anaesthetic or parenteral analgesics, such as meperidine (Demerol®) or fentanyl (Sublimaze®), with non-barbiturate sedatives such as diazepam (Valium®) or droperidol (Inapsine®) termed "Balanced". Electrocardiogram lead 2 was monitored in all cases on an oscilloscope and direct-writer recordings were made in most cases just before induction of anaesthesia and before, during, and serially following injection of pancuronium bromide, as well as before and after atropine-neostigmine when these were required postoperatively to reverse persistent muscle relaxation. Changes in blood pressure, pulse rate, and airway resistance were also checked and recorded before and after injection of pancuronium. *No further muscle relaxant was given during any of these procedures.* Each of twenty-four patients in this group was given a relatively large dose of pancuronium (10 to 16 mg) to determine whether there would be any appreciable alterations in blood pressure, pulse rate, or ECG in combination with the inhalation agents.

Group B (65 patients). In these patients, anaesthesia was induced with thiopen-

tone (approximately 4 mg/kg) and pancuronium, as in Group A. During maintenance of anaesthesia, the procedures were also the same except, if relaxation was apparently wearing off, increments of pancuronium (0.5 to 2.0 mg) were given instead of increasing the halogenated anaesthetic concentration. With the "Balanced" technique, discretion was used in order to prevent the patient from becoming conscious during the operation. Four patients were given 10 mg pancuronium at the beginning and another four patients were given 4 mg later during the operation when stable conditions were present in order to test the cardiovascular response.

Group C (112 patients). In each instance, a sleep dose of thiopentone was given, followed by approximately 1.5 mg/kg succinylcholine, hyperventilation with 100 per cent oxygen for 1 to 2 minutes, endotracheal intubation and maintenance, as above. When signs that succinylcholine was wearing off became apparent (usually within 5 to 15 minutes), 3 to 6 mg pancuronium were given, depending upon the size and physique of the patient and the expected duration of operation. Further increments of 1 to 2 mg were given, as in Group B, if relaxation was evidently wearing off, rather than increasing the anaesthetic concentration. In 7 patients, in whom long surgery was expected, a relatively large, single dose of pancuronium was given (8 or 10 mg) to test the cardiovascular response.

Group D (28 patients). These patients were all to have pelvic surgery. Anaesthesia was induced with 6 mg tubocurarine, a sleep dose of thiopentone, and approximately 2 mg/kg succinylcholine, given intravenously in succession. After hyperventilation with oxygen for 1 to 2 minutes, endotracheal intubation was performed. Then, maintenance was carried out as in Groups B and C. In this group, the first dose of pancuronium was given 15 to 30 minutes after intubation. Subsequently, 1 to 2 mg additional injections of pancuronium were given as required. A large, single injection of pancuronium was not tested in this group.

Laboratory tests

In addition to routine measurements of blood chemistry, electrolytes, and organ panel studies, indicated by the patient's disease, a representative number of these patients had serial arterial and venous blood samples drawn and analyzed before and after the administration of pancuronium to determine blood gases, pH, oxygen saturation, plasma histamine, and serum potassium.

In the recovery room, the vital signs, ECG, body temperature, and urine output were closely observed and measurements were made of tidal volume, respiratory rate and effort, and grip-strength. Need for reversal of muscle relaxant with atropine/neostigmine was decided if the patient was making respiratory efforts but the tidal volume was less than 250 ml (< 4 ml/kg) and the patient was evidently not anaesthetized.

Results

The data collected from the anaesthetic record of each patient, study protocol and electrocardiogram tracing were transferred to IBM cards for tabulation and analysis. Figures 2 and 3 show the individual cases in Group A which required reversal and Figures 4 to 11 show all the cases in the other three groups. These

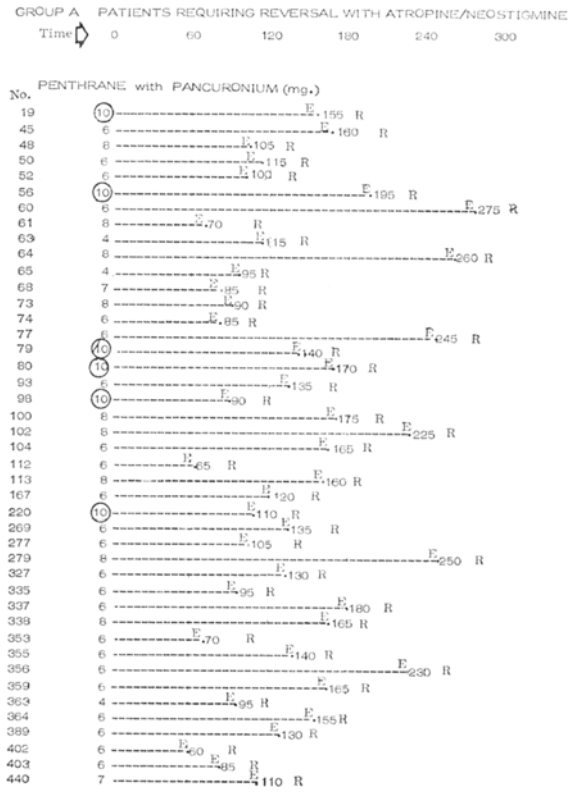

FIGURE 2. Patients from Group A requiring reversal with atropine/neostigmine after methoxyflurane (Penthrane®) anaesthesia showing from left to right: case number, dose of relaxant (large dose is circled), E = end of surgery, duration in minutes; R = is under time of reversal. (This code is used in all remaining figures.)

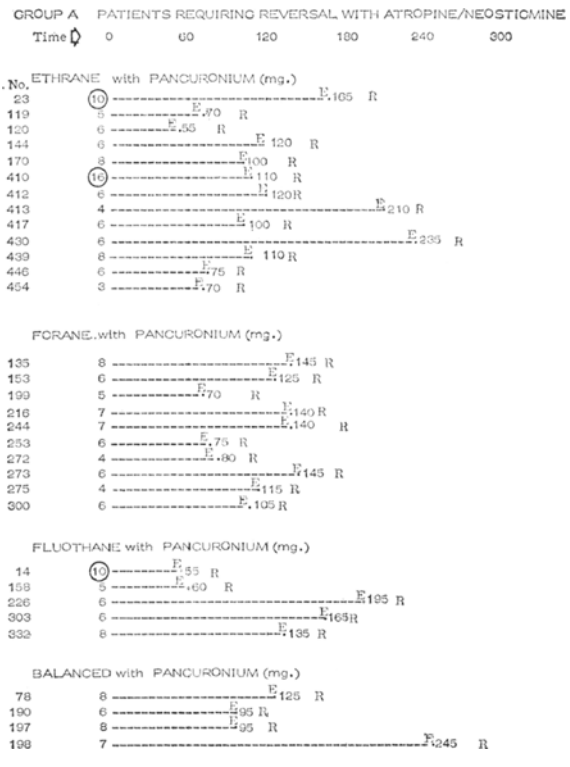

FIGURE 3. Patients from Group A requiring reversal with atropine/neostigmine after enflurane (Ethrane®), Forane, halothane (Fluothane®), and Balanced technique.

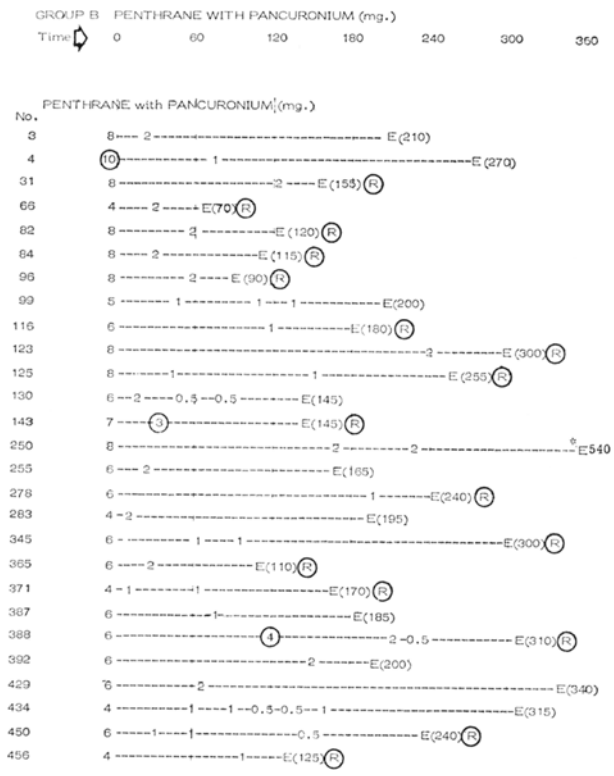

FIGURE 4. Patients from Group B (managed with methoxyflurane anaesthesia). Cases requiring reversal are shown with ®.

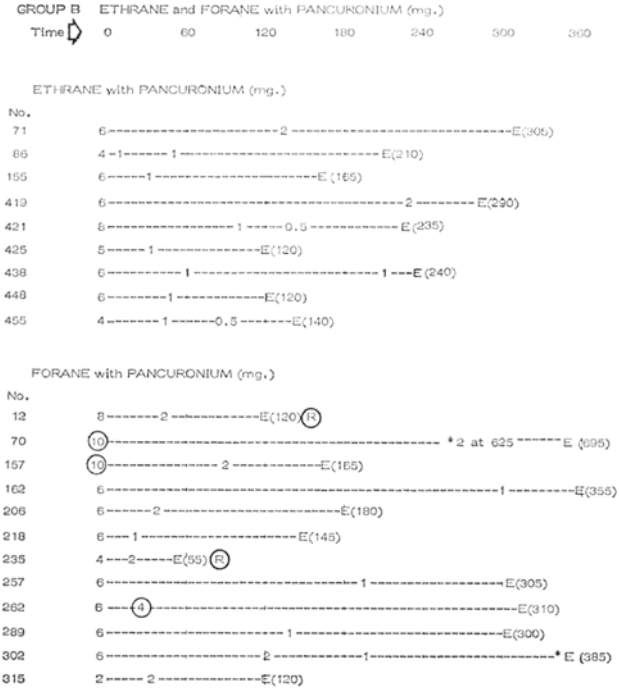

FIGURE 5. Patients from Group B (managed with enflurane and Forane).

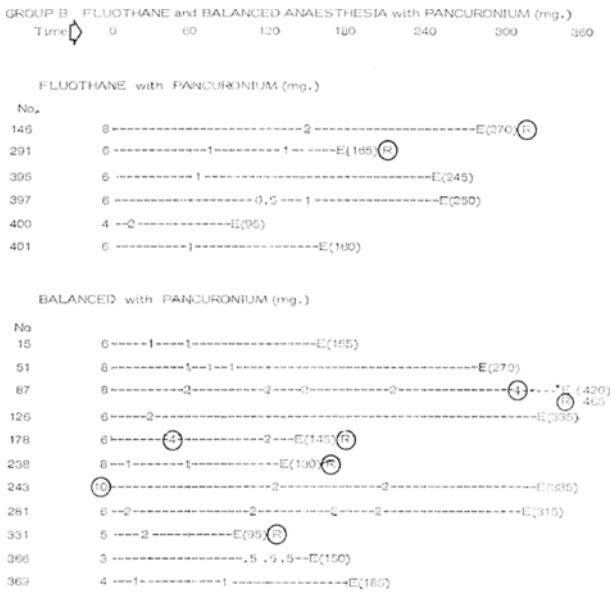

FIGURE 6. Patients from Group B (managed with halothane and Balanced).

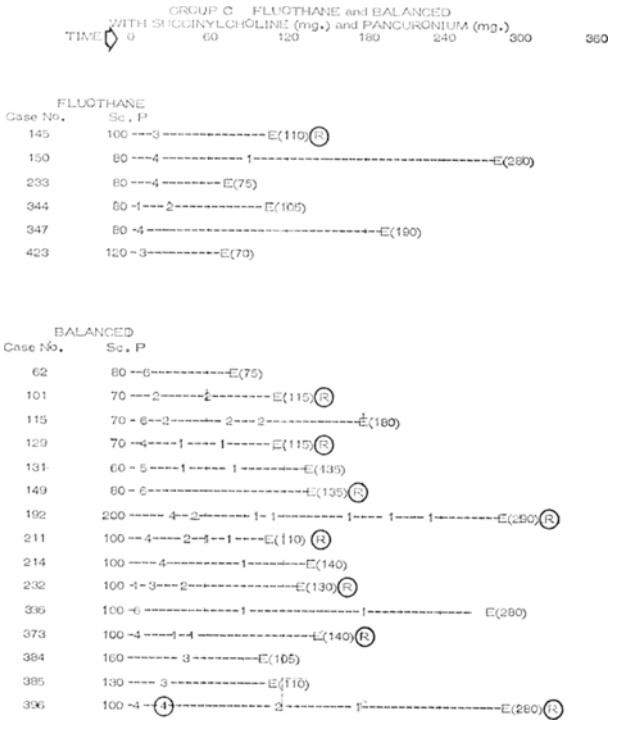

FIGURE 7. Patients from Group C (managed with halothane and Balanced).

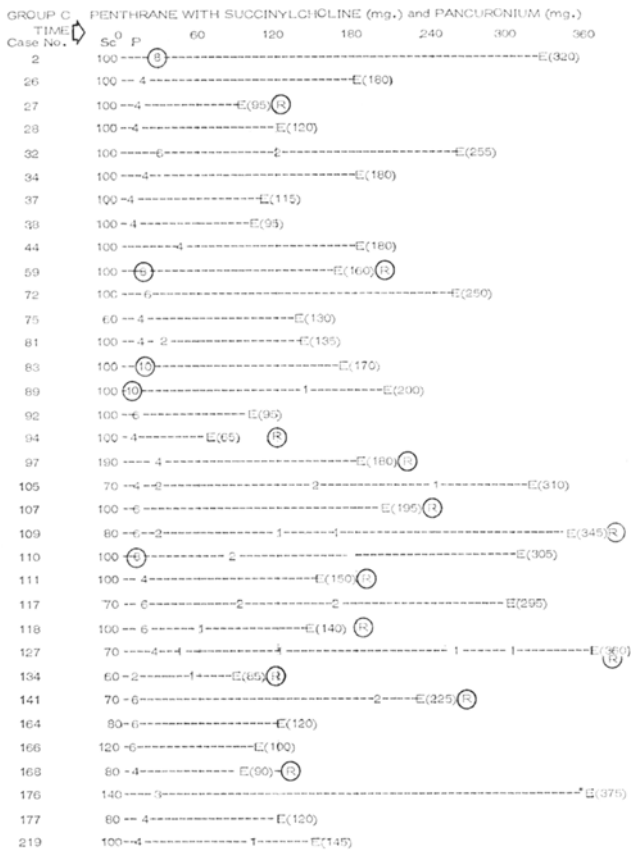

FIGURE 8. Patients from Group C (managed with methoxyflurane).

figures show the case numbers, primary anaesthetic agents, dose of relaxants, duration of surgery, and when reversal was required. The largest total dose of pancuronium was 20 mg (Group B, case 87). The operations varied in length from 55 minutes to 695 minutes, with an overall mean time of 176 minutes. Tables I and II summarize the vital statistics of the four groups of patients. Group D differed in that all but one patient were female, all had abdominal (pelvic) operations, the mean age was appreciably less (40 versus 50), and all but one patient were in good general health (ASA Class I & II). Groups A, B, and C had a relatively uniform distribution as to sex, mean age, physical state, and type of operation. The eldest patient was 83 years old. Less than 6 per cent of the patients were in ASA Class IV.

Table III summarizes the primary anaesthetics used. Non-explosive techniques were always employed, thus no patients were tested with cyclopropane, diethyl ether, or fluroxene. The primary anaesthetics used were selected preferentially by the attending anaesthetist. The fewest cases were done with halothane because it was elected not to use this agent in neurosurgical procedures, in the females in Group D who had halothane for a recent previous anaesthetic (for diagnostic D & C or radium insertions), and in a considerable number of patients for abdominal operations in whom jaundice was present or "liver profile" tests were abnormal.

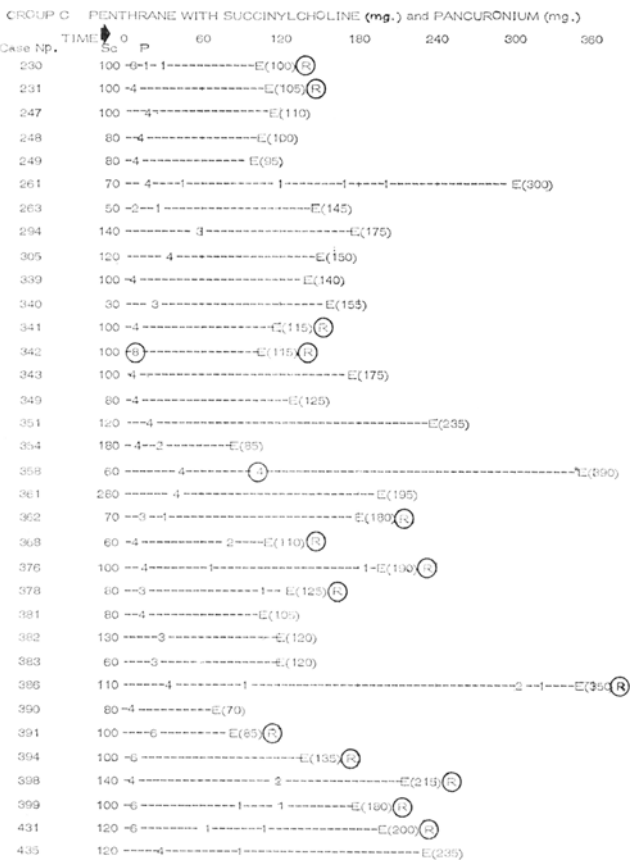

FIGURE 9. Patients from Group C (managed with methoxyflurane).

Table IV provides the mean dose of the drugs used for induction of anaesthesia. In Group A (23 of 29 patients), and Group B (3 of 4 patients), the initial injection of pancuronium caused complaints of burning along the vein but there was no skin flush along the vein. The remaining patients in these two groups were then given thiopentone first and we found that 18 of 221 (Group A) and 4 of 61 (Group B) patients complained of a stinging or burning during injection of thiopentone. Thirty-one other patients moved their arms as if in pain during the injection of pancuronium after a sleep dose of thiopentone had been administered, and we were reasonably sure the patients were in fact "asleep" (absence of eyelash reflex, snore, shallow breathing). Followup on these cases did not indicate that this response led to phlebitis. The cause of burning was not identified.

A diffuse skin flush developed on the chest usually but sometimes as well on the arm used for injection in 20 of 281 patients in Groups A and B who received thiopentone first. The flush first appeared after the injection of pancuronium in only one patient.

No stinging along the vein was evident when succinylcholine (Group C) or tubocurarine followed by succinylcholine (Group D) was administered after thiopentone induction but an appreciable number of patients complained about the

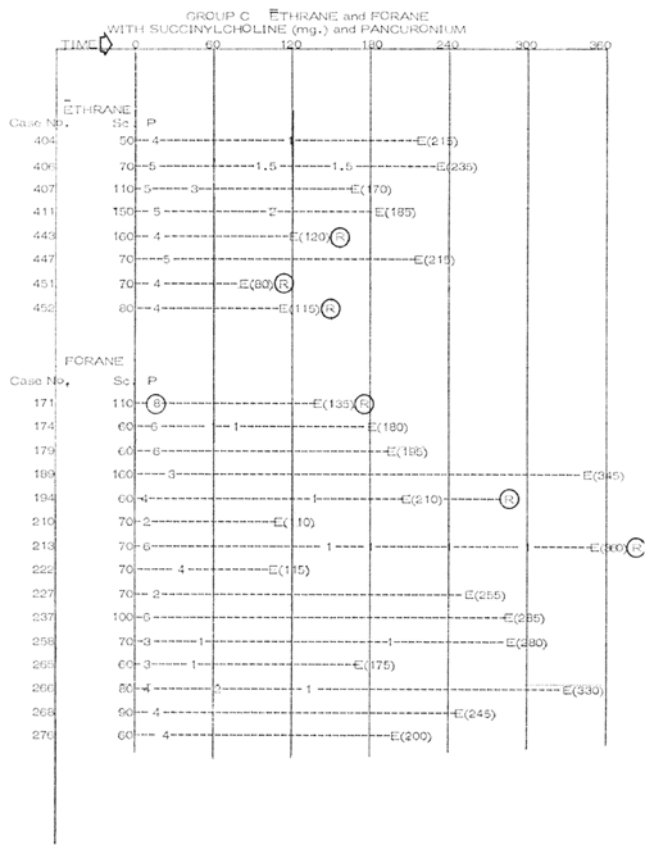

FIGURE 10. Patients from Group C (managed with enflurane and Forane).

thiopentone injection as occurred in Groups A and B, and several had a red skin flush on the thorax.

Ease of intubation

The rate, ease, and side effects during endotracheal intubation are summarized in Table V. In this study it appeared that the jaw and larnyx are not fully relaxed until the patient is unconscious and at least 150 seconds elapse after injection of 0.1 mg/kg pancuronium (Group A). Among the 10 patients in whom intubation proved difficult in this group, 6 were premedicated with atropine only and each received less than 5 mg of pancuronium, and/or the anaesthetist attempted intubation too soon. In Group B, of the four patients who were difficult to intubate, three had too little pancuronium initially, and the other patient was an extremely obese female who presented anatomical problems (no neck, no chin, small mouth, and large tongue). In none of these cases did we observe the release of excessive salivary or bronchial secretions, and none of the patients had bronchospasm.

It was our observation in Groups C and D that succinylcholine almost invariably provided far superior physical conditions for intubation in less than two minutes. Based on extensive experience with gallamine and tubocurarine, which pancuronium resembles closely in initial effect, the minimum dose for smooth intubation

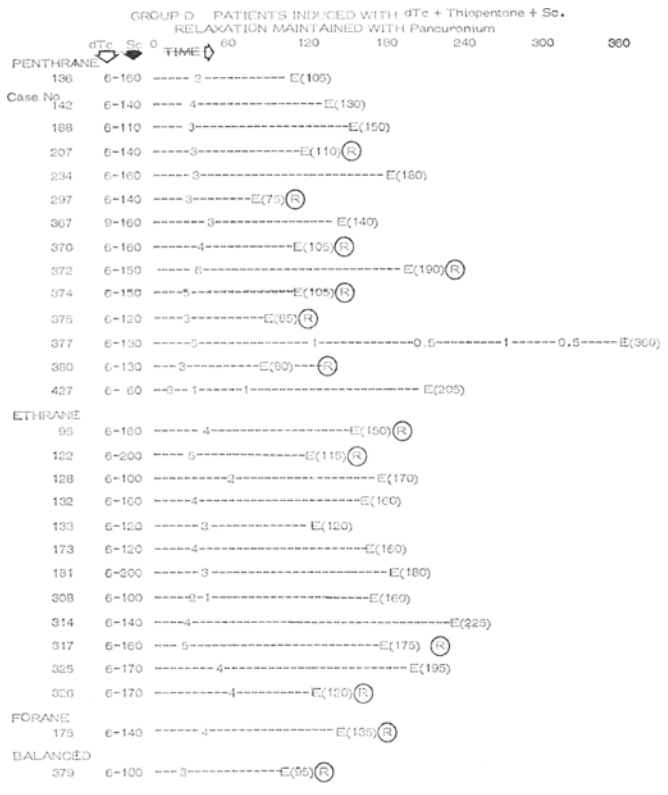

FIGURE 11. Patients from Group D (managed with methoxyflurane, enflurane, Forane, and Balanced).

should be at least 0.1 mg/kg given 3 full minutes before attempting to pass the endotracheal tube, in order to attain conditions that are routinely seen with succinylcholine.

Marked bucking occurred in a total of 12 patients in Groups A and B. In 5 patients, the dose of thiopentone was obviously too small and, in 4, insufficient pancuronium was given. The other three patients settled quickly when inhalation anaesthesia was added, so they were probably hypersensitive to tracheal stimulation.[10,11] Marked bucking was not seen in Groups C and D, apparently because a relatively large dose of succinylcholine was given, allowing profound laryngo-tracheal relaxation for sufficient time to suppress tracheal reflexes until adequate inhalation anaesthesia was established.

Effect on the cardiovascular system

ECG tracings done before anaesthesia and serially in 196 patients revealed that cardiac arrhythmias with a definitely abnormal electro-cardiogram were present in 33 patients. In these patients, no appreciable alteration in lead 2 occurred during or after injection of pancuronium, nor during endotracheal intubation. Aside from slight changes in the heart rate—usually an increase of <15 beats/minute after the pancuronium was injected—the only change of possible significance was the appearance of a brief run of premature ventricular contractions in 5 patients who received pancuronium only, and in 4 patients who received succinylcholine before-

TABLE I

DISTRIBUTION OF PATIENTS IN EACH GROUP ACCORDING TO SEX, AGE, AND ASA PHYSICAL STATE

CLINICAL EVALUATION of PANCURONIUM

VITAL STATISTICS

Number of Patients

	A	B	C	D
Sex				
M	108	31	46	1
F	143	34	65	27
Age				
< 50	127 (49)*	26 (52)*	51 (51)*	22 (40)*
> 50	124	39	61	6
Physical State				
I - II	205	50	88	27
III - IV	46	15	25	1

* mean age

TABLE II

DISTRIBUTION OF PATIENTS IN EACH GROUP ACCORDING TO SITE OF SURGERY

CLINICAL EVALUATION of PANCURONIUM

Site of Surgery

	Groups A	B	C	D	Totals
Abdominal	144	49	64	28	285
Thoracic	18	1	12	0	31
Extremity (orthopedic)	35	6	22	0	63
Head - Neck & Back (neurosur.)	49	8	13	0	70
Miscellaneous (superficial)	5	1	1	0	7
Totals	251	65	112	28	456

hand. This arrhythmia did not persist. In a few instances, arrhythmias present preoperatively disappeared upon the induction of anaesthesia. There was no significant change in blood pressure ($< \pm 30$ mm Hg) even when a large single dose of pancuronium was given both to healthy and to some debilitated patients. It also appeared as if the use of pancuronium had a stabilizing effect on the cardiovascular system when halothane anaesthesia was used; that is, marked hypotension, bradycardia and nodal rhythm did not appear when deep anaesthesia (>2 per cent halothane) was used with intermittent positive pressure breathing, as might occur when a relatively large dose of tubocurarine is given.[12] On the other hand, two of 28 patients in Group D had transient nodal rhythm during induction and blood pressure changes were $< \pm 30$ mm Hg before pancuronium was given.

TABLE III

DISTRIBUTION OF PATIENTS IN EACH GROUP SHOWING MAXIMUM VAPOUR CONCENTRATION OF INHALATION ANAESTHETICS AND NUMBER OF PATIENTS MANAGED WITH A BALANCED TECHNIQUE ALONG WITH 60 PERCENT NITROUS OXIDE

CLINICAL EVALUATION of PANCURONIUM PRIMARY ANAESTHETICS	A	B	C	D	Totals
<1.5 Forane(R) + N_2O	92	12	15	1	120
<2.0 Enflurane + N_2O	42	9	8	12	71
<1.0 Methoxyflurane + N_2O	98	27	68	14	207
<2.5 Halothane + N_2O	11	6	6	0	23
Balanced + N_2O	8	11	15	1	35
TOTALS	251	65	112	28	456

TABLE IV

MEAN DOSE OF DRUGS USED FOR INDUCTION OF ANAESTHESIA AND SIDE-EFFECTS SEEN DURING AND IMMEDIATELY FOLLOWING INJECTION (IV)

CLINICAL EVALUATION of PANCURONIUM	INDUCTION DRUGS				SIDE-EFFECTS	
	Thiopentone mg./kg.	Pancuronium	Tubo-curarine	Succinyl-choline	Sting along vein %	Skin flush %
GROUP A 251 Patients	4.74 ±1.24	6.60 ± 1.8 mg. 96 µg./kg.	-	-	16 * (41)	8 (19)
GROUP B 65 Patients	4.10 ±1.40	6.26 ± 1.7 mg. 84 µg./kg.	-	-	11 * (7)	3 (2)
GROUP C 112 Patients	4.07 ±1.30	-	-	1.5 mg./kg.	-	0
GROUP D 28 Patients	3.66 ±1.52	-	6 mg.	2.2 mg./kg.	-	-

* see text

Operating conditions and relaxation were good in approximately 90 per cent or more of the cases according to the primary anaesthetics. (Table VI) Among the groups, the technique employed in Group B had the most cases in which relaxation was not good. This was because the longest operations occurred in this group and there was a tendency not to give more relaxant near the end of a long procedure (see Table VII). Another reason was that less relaxant was given initially and it was difficult to judge the amount of relaxant to administer subsequently during prolonged surgery in order to maintain satisfactory relaxation and avoid postoperative respiratory depression. (see Figures 4, 5, & 6) This was the case particularly

TABLE V

SUMMARY IN EACH GROUP OF THE MEAN RATE, EASE, AND SIDE-EFFECTS DURING AND IMMEDIATELY FOLLOWING ENDOTRACHEAL INTUBATION (PER CENT AND NUMBER OF CASES SHOWN)

CLINICAL EVALUATION of PANCURONIUM									
INTUBATION CHARACTERISTICS									
Mean Time After Relaxant Given min. ± S.D.		Ease of Intubation Good* %	Fair** %	Poor %	Incidence of Bucking 0 %	Slight %	Marked %	Ventricular Arrhythmias %	
2.30	± 0.80	72 (181)	24 (60)	4 (10)	65 (165)	31 (77)	4 (9)	<2 (4)	a
2.32	± 0.99	57 (37)	37 (24)	6 (4)	63 (41)	32 (21)	5 (3)	<2 (1)	b
<1.5		>90%	-	-	>90%	-	0	<2 (2)	c
<2.0		>95%	-	-	>90%	-	0	<10 (2)	d

* relaxed jaw, larynx open
** relaxed jaw, larynx closed or moving

TABLE VI

OPERATING CONDITIONS (RELAXATION) ACCORDING TO THE PRIMARY ANAESTHETIC ADMINISTERED

CLINICAL EVALUATION of PANCURONIUM

Relaxation during Maintenance – All Groups by Anaesthetics

	No. Cases	Good	Fair-Poor
Forane(R) + N_2O	120	109 (91%)	11 (9%)
Enflurane + N_2O	71	68 (96%)	3 (4%)
Methoxyflurane + N_2O	207	186 (89%)	21 (11%)
Halothane + N_2O	23	21 (91%)	2 (9%)
Balanced + N_2O	35	33 (94%)	2 (6%)

when methoxyflurane was used during abdominal surgery (see Tables VIII and IX). Therefore to ensure good operating conditions for major prolonged operations, the best method is to administer an adequate dose of pancuronium for smooth intubation at the start, then to adjust the depth of the primary anaesthetic to maintain adequate conditions. Since three of the four inhalation agents employed have relatively high mobility and all the agents appeared to markedly prolong the effect of the relaxant or had sufficient relaxant properties themselves to ensure satisfactory conditions, this is the best method to use, when succinylcholine is not desired for intubation.

TABLE VII

SUMMARY IN EACH GROUP OF DURATION AND CHARACTER OF RELAXATION DURING SURGERY AND MEAN DOSE OF PANCURONIUM (TOTAL, PER KILOGRAM AND PER KILOGRAM PER MINUTE OF SURGERY)

CLINICAL EVALUATION of PANCURONIUM

Operating Conditions

	Duration of Surgery (min.)	Mean Total Dose of Pavulon	Character of Surgical Relaxation Good %	Fair %	Poor %
GROUP A 251 Patients	170 ±85	6.60 mg. 0.1 mg./kg. 0.58 μg./kg./min.	94 (236)	<6 (14)	<1 (2)
GROUP B 65 Patients	220 ±110	8.58 mg. 0.1 mg./kg. 0.54 μg./kg./min.	82 (53)	14 (9)	5 (3)
GROUP C 112 Patients	180 ±80	5.42 mg. .08 mg./kg. 0.43 μg./kg./min.	90 (101)	10 (11)	0 (0)
GROUP D 28 patients	150 ±55	3.82 mg. .06 mg./kg. 0.41 μg./kg./min.	96 (27)	4 (1)	0 (0)

TABLE VIII

INFLUENCE OF ANAESTHETICS ON DOSE OF PANCURONIUM AND SHOWING NUMBER OF PATIENTS THAT RECEIVED EACH ANAESTHETIC IN EACH GROUP

CLINICAL EVALUATION of PANCURONIUM

Influence of Anaesthetics on Dose of Pancuronium (All Cases)

	Total Dose mg.	Weight kg.	Anes. Time min.	Dose P μg./kg.	Dose P μg./min.	Dose P μg./kg./min.
GROUP A (251)	6.60	68.8	169	96	40	.58
Penthrane 98				97	50	.72
Forane 92				96	40	.69
Ethrane 42				96	51	.73
Fluothane 11				81	48	.66
Balanced 8				100	57	.89
GROUP B (65)	8.58	74.3	222	116	40	.54
Penthrane 27				114	48	.63
Forane 12				108	46	.60
Ethrane 9				107	38	.57
Fluothane 6				109	42	.60
Balanced 11				137	47	.61
GROUP C (112)	5.42	70.0	177	78	30	.43
Penthrane 68				78	34	.50
Forane 15				74	24	.36
Ethrane 8				72	35	.45
Fluothane 6				45	32	.39
Balanced 15				96	46	.64
GROUP D (28)	3.82	63.5	151	60	26	.41
Penthrane 14				62	29	.46
Forane 1				67	30	.50
Ethrane 12				57	24	.36
Balanced 1				67	32	.71

TABLE IX

INFLUENCE OF ANAESTHETICS ON DOSE OF PANCURONIUM USED DURING ABDOMINAL SURGERY—SHOWING THE NUMBER OF PATIENTS THAT RECEIVED EACH ANAESTHETIC IN EACH GROUP
NR = NOT REVERSED; R = REVERSED

CLINICAL EVALUATION of PANCURONIUM

Influence of Anaesthetics on Dose of Pancuronium (Abdominal Surgery)

	Total Dose mg.	Weight kg.	Anes. Time min.	Dose P µg./kg.	Dose P µg./min.	Dose P µg./kg./min.
GROUP A (144)	6.35	67.4	167	94	38	.56
Penthrane 29 NR				91	44	.61
Penthrane 27 R				102	53	.78
Forane 54 NR				98	38	.59
Forane 3 R				93	67	1.04
Ethrane 17 NR				86	47	.71
Ethrane 6 R				97	60	1.00
Fluothane 4 NR				53	36	.47
Fluothane 1 R				115	59	.85
Balanced 1 NR				75	67	.84
Balanced 2 R				113	64	1.03
GROUP B (65)	6.41	74.3	221	113	38	.52
Penthrane 5 NR				82	39	.42
Penthrane 14 R				121	51	.71
Forane 8 NR				120	35	.52
Forane 2 R				70	96	.84
Ethrane 7 NR				105	39	.59
Fluothane 3 NR				89	35	.42
Fluothane 2 R				157	42	.73
Balanced 5 NR				126	33	.47
Balanced 3 R				159	58	.71
GROUP C (112)	5.64	70.0	187	81	30	.43
Penthrane 21 NR				77	33	.48
Penthrane 14 R				92	40	.57
Forane 9 NR				67	23	.35
Forane 3 R				99	36	.49
Ethrane 4 NR				86	32	.42
Ethrane 2 R				53	42	.56
Fluothane 1 NR				49	21	.26
Fluothane 1 R				40	27	.36
Balanced 4 NR				70	34	.45
Balanced 5 R				110	49	.75
GROUP D (28)	3.82	63.5	151	60	26	.41
Penthrane 7 NR				65	22	.36
Penthrane 7 R				60	37	.58
Forane 1 R				67	30	.50
Ethrane 8 NR				54	20	.32
Ethrane 4 R				62	33	.45
Balanced 1 R				67	32	.71

Postoperative respiratory depression—requirement of reversal of relaxant

One-third of the patients (153) were either virtually apnoeic at the end of surgery or were not breathing adequately on arrival in the recovery room (tidal volume <300 ml). In analyzing the reasons it was first found that, of the patients by group (A, B, C, and D), the incidence of requiring reversal was 30, 37, 37, and 46 per cent respectively. A chi-square test of the data revealed that there was no significance in these differences from the mean for *all* patients (regardless of group). However, a close examination of the data revealed three factors that exerted a significant role on the incidence of reversal. The first factor became obvious in all groups, especially among the patients who had abdominal surgery: the patient who required reversal frequently *had a shorter operation.* Stated another way, they had a much larger dose/kg/min of pancuronium (see Table IX). For instance, whereas the mean duration of surgery in Group A where reversal was required was 132 minutes, that where reversal was not required was 184 minutes.

The second significant factor is evident in Table X, which shows that *the anaes-*

thetics used affected the incidence of reversal. Methoxyflurane clearly caused a high incidence of postoperative respiratory depression. This was not due to excessive administration of pancuronium (see Table VIII and IX), but occurred because methoxyflurane itself has a potent muscle relaxant activity, which persists for some time after its administration is discontinued. This analysis also revealed that all the halogenated anaesthetics used in this study either potentiate the action of non-depolarizing relaxants,[13] such as pancuronium,[14] or have a powerful muscle relaxant action of their own.[15] However, a persistent effect was least evident with Forane which has a low fat and low blood solubility and is eliminated rapidly but, while administered, markedly potentiates non-depolarizing relaxants, or itself relaxes skeletal muscles adequately.[16]

The third factor is less evident and is of borderline significance. Analysis of the data showed that the patients managed with a "Balanced" technique usually received and required a larger amount of muscle relaxant during surgery (see Tables VIII, IX, and X). There was also a relatively high incidence of reversal (50 per cent). The reason for this was that in most instances of postoperative respiratory depression in the "Balanced" group, the exact cause was obscured by the use of a combination of drugs each of which depresses respiration to a variable degree and interact to augment the effect of each other.[17] It is, of course, not as easy to reduce the blood level of these agents toward the end of surgery as is possible with inhalation anaesthetics of low solubility.

TABLE X

SUMMARY OF PATIENTS REQUIRING REVERSAL ACCORDING TO GROUP AND PRIMARY ANAESTHETIC

CLINICAL EVALUATION of PANCURONIUM – According to Primary Anaesthetics

	Reversal Required After Surgery								
	Group A		Group B		Group C		Group D		
	No. of Cases	Number Reversed	No. of Cases	Number Reversed	No. of Cases	Number Reversed	No. of Cases	Number Reversed	Percent Reversed
Forane	92	10	12	2	15	3	1	1	13%
Ethrane	42	13	9	0	8	3	12	4	28%
Penthrane	98	43	27	16	68	26	14	7	44%
Fluothane	11	5	6	2	6	1	0	0	39%
Balanced	8	4	11	4	15	8	1	1	49%
Totals	251	75 (30%)	65	24 (37%)	112	41 (37%)	28	13 (46%)	

Ease of reversal and cardiovascular effects (see Table XI)

Among the 153 patients that were reversed, only a few were so treated immediately. In all cases of apnoea, ventilation was controlled mechanically until some respiratory effort was evident clinically and low body-temperature was restored to approximately 37°C. In no case did apnoea persist beyond 30 minutes of the end of surgery. Atropine 0.4 to 2 mg was given intravenously, followed in a few minutes by approximately twice the amount of neostigmine (0.5 to 4 mg) given slowly in divided doses. The initial dose of atropine/neostigmine given was judged by the anaesthesiologist to be sufficient to develop an adequate tidal volume. In only 3

TABLE XI

SUMMARY OF PATIENTS REQUIRING REVERSAL, SHOWING MEAN DOSE OF ATROPINE AND NEOSTIGMINE REQUIRED TO RESTORE PERSISTENT ADEQUATE BREATHING AND THE EFFECT ON THE PULSE RATE AT 10 MINUTES AFTER REVERSAL DRUGS WERE GIVEN

CLINICAL EVALUATION of PANCURONIUM

Recovery of Breathing

	Postanaesthetic Reversal Required		Effective Dose of Atropine / Neostigmine Mean Dose Used		Alterations in Pulse Rate at 10 min.		
	No %	Yes %	Atropine mg.	Neostigmine mg.	0 %	+ %	- %
GROUP A 251 Patients	70 (176)*	30 (75)*	0.8	1.6	30 (21)*	30 (21)*	40 (33)*
GROUP B 65 Patients	63 (41)	37 (24)	1.0	2.0	42 (10)	33 (8)	25 (6)
GROUP C 112 Patients	63 (71)	37 (41)	0.8	1.6	25 (11)	35 (14)	40 (16)
GROUP D 28 Patients	54 (15)	46 (13)	0.7	1.4	31 (4)	15 (2)	54 (7)

* number of patients

cases were supplementary doses given to augment an inadequate response. Two of these cases had been managed with "Balanced" anaesthesia. In no case did excessive salivation, bronchospasm, or marked hypotension occur after the injection of neostigmine.

Electrocardiograms taken before, during, and following the administration of atropine and neostigmine did not reveal marked changes in the heart rate observed up to 10 minutes after. In most instances the pulse rate rose within 2 minutes after atropine (bradycardia was not seen), then often fell within 4 minutes after neostigmine.[18,19] At 10 minutes after the injections, 46 patients had no net change in heart rate, 45 patients had a drop, and 62 had a rise. Tachycardia over 130/minute and bradycardia below 56/minute did not occur. Some patients (9) had transient extrasystoles but significant arrhythmias not present previously were not observed.[19] In Table XI we have summarized the mean doses of atropine and neostigmine required to restore an adequate tidal volume (>300 ml) and the effect observed on the pulse rate. No cardiovascular effects occurred probably because the dominant cholinergic effect of the anaesthetics was balanced by atropine.

Laboratory data (see Table XII)

Laboratory tests on patients who received pancuronium with Forane revealed no effect. Serum potassium tended to decrease slightly as is always seen during anaesthesia managed in the manner employed here. Plasma histamine levels did not alter significantly. This is being studied more extensively. Even the patients who received a relatively large dose of pancuronium during induction (35 patients), during maintenance (4 patients), or when we found intubation difficult (14 patients, Groups A and B), there were no clinical signs pointing to histamine

TABLE XII

BLOOD GAS, OXYGEN SATURATION, PLASMA HISTAMINE, AND PLASMA POTASSIUM BEFORE ADMINISTRATION OF PANCURONIUM, AT END OF OPERATION AND 60 MINUTES AFTER ANAESTHESIA

CLINICAL EVALUATION of PANCURONIUM

Mean Blood Gases, Oxygenation, Plasma Histamine and Potassium

GROUP A (30 Patients)

		Before	After	+ 60 min.
pH		7.47	7.43	7.45
pCO_2	mm.Hg.	35	35	33
HCO_3^-	mM/L	24	22	22
pO_2	mm.Hg.	71	302	74
SaO_2	%	95	98	94
Hgb.	Gm	12.6	13.9	13.7
Hct	%	36	37	37
K	mEq./L	3.8	3.5	
Histamine	µg./L	18.4	17.5	

release, such as the wheezing of bronchospasm, a skin flush, or hypotension, as occurs sometimes with tubocurarine.

Serial blood gas, pH and oxygen saturation estimations showed no appreciable change, so no alteration in the muscle relaxant action was expected, since changes in blood pH within the clinical range have no effect on plasma distribution of the muscle relaxants.[20,21]

DISCUSSION

For smooth endotracheal intubation, 0.1 mg/kg pancuronium is required intravenously, followed by artificial respiration for at least 2½ minutes prior to attempting laryngoscopy. Anaesthesia can then be maintained with 60 per cent N_2O and a clinically safe vapour concentration of halogenated anaesthetics for as long as 3 hours without more relaxant drug. The variation in the muscle relaxant response to pancuronium, however, was no more predictable in an individual patient than with an equivalent dose of tubocurarine or gallamine.[22]

It appeared that the response to pancuronium was as good with halothane, without an excessive amount of either agent, as it was with methoxyflurane, enflurane, and Forane, without augmenting a ganglionic blocking action of the anaesthetics.

The smoothest anaesthesia, using this technique, was with N_2O + Forane, which was followed by rapid, quiet recovery and uncommon need (<15 per cent) for reversal as well. (See Table XIII) When "Balanced" anaesthesia was used, the effect of pancuronium appeared to be appreciably shorter. This was undoubtedly due to the lack of potentiating inhalation agents and also may have been due to a cholinergic effect on the skeletal muscles of fentanyl, and to a relatively lighter level of unconsciousness produced by such sedatives as droperidol and diazepam. However, when surgery was finished we found that more patients (50 per cent)

TABLE XIII

RATE OF RECOVERY OF WAKEFULNESS, PULMONARY VENTILATION, BLOOD PRESSURE AND PULSE RATE AFTER PANCURONIUM + FORANE ANAESTHESIA IN PATIENTS NOT REVERSED

CLINICAL EVALUATION of PANCURONIUM

Rate of Recovery from Pancuronium with Forane(R) Anaesthesia (means)

Patients Not Requiring Reversal

	Eyes Open (min.)	Tongue Out (min.)	Radford Predicted M.V. L/min.	Recovery Room M.V. on arrival L/min.	Recovery Room M.V. on +30 min. L/min.	Blood Pressure and Pulse Rate Before Induction B.P. mm.Hg.	Before Induction Pulse /min.	Recovery Room B.P. mm.Hg.	Recovery Room Pulse /min.
GROUP A (82)	17	28	6.20	9.17	9.65	139/85	65	142/88	87
GROUP B (10)	11	14	7.80	8.10	7.50	153/93	84	163/100	89
GROUP C (12)	19	33	6.47	6.95	6.65	135/64	65	141/90	87

had to be reversed, undoubtedly due to the much faster recovery from the analgesic and the persistent respiratory depression accompanying heavy psychosedation.

For longer procedures, an additional amount of pancuronium is required but, to avoid the need for reversal, the increments should not exceed 1 mg, and none should be given if the end of surgery appears to be within 30 minutes. In Group B, it appeared that repeated doses of pancuronium cause a cumulative effect, i.e., the dose/kg/min needed became much less as the procedure lengthened (see Table IX and Figures).

In Group C we found that the use of 1.5 mg/kg succinylcholine, followed by artificial respiration for up to 2 minutes before intubation provided a smooth, rapid induction. The subsequent total requirement for pancuronium was *reduced by approximately 25 per cent* when compared to Groups A and B (see Tables VIII and IX).

In Group D the number of patients was too small to allow for valid statistical comparison, but the use of tubocurarine (6 mg) and succinylcholine (approximately 2 mg/kg) during induction appeared to reduce the subsequent amount of pancuronium required per kg/min by at least 30 per cent when compared to Groups A and B (see Tables VIII and IX). However, all but one of these patients were females having pelvic surgery, which usually does not require as much relaxant as upper abdominal surgery, hence less was given, especially because of the expected added effect of tubocurarine.

We recognised that apnoea or severe respiratory depression at the end of these major operations, in which muscle relaxants were used either at the beginning only (as in Group A) or as judged necessary (as in Groups B, C, and D), could be cause-and-effect or by coincidence. The latter occurs frequently due to hyperventilation (hypocarbia), reflex inhibition of breathing by a cuffed endotracheal tube,[11] prolonged effect with lowered body temperature (when succinylcholine is used), electrolyte imbalance, severe renal disease, and synergistic action with narcotic analgesics and antibiotics, among others.[17] In most cases, it was possible to manage the anaesthetic and pulmonary ventilation so that, by the time surgical dressings were applied, mechanical control of ventilation was no longer required. After careful suctioning of the oral pharynx and trachea, the cuff on the endotra-

cheal tube was released, but the tube was usually left in place until the patient was settled in the recovery room and pulmonary ventilation and effort was assessed or measured. Monitoring of body temperature, urine output and blood gases, estimating other laboratory data, and avoiding neomycin and related antibiotics during surgery, helped us eliminate some extraneous factors that might have led to prolonged apnoea not related to an overdose of the anaesthetic and/or muscle relaxants. Even so, one-third of the patients required reversal. However, it takes considerable experience to become proficient in the use of a new muscle relaxant during anaesthesia. We were therefore pleased that an overdose of pancuronium could be reversed without difficulty or provoking undesirable side effects, and none of the patients who received atropine/neostigmine became "recurarized".

The original report on the use of tubocurarine (Intocostrin, Squibb), mostly in a single dose the equivalent of <15 mg in the course of light cyclopropane anaesthesia, carried little of note on the cardiovascular system[23] because this combination is fairly stable. Pancuronium is the first new relaxant that may be used with virtually all the currently widely used and in-development anaesthetic agents that does not cause significant undesirable changes in the blood elements or in the blood pressure, pulse rate, or electrocardiogram, even when 2 to 3 times the clinical dose is injected. It also appears to be wholly compatible with the slow separate administration of a moderate amount of atropine/neostigmine in a 1:2 ratio when reversal is necessary.[22] In this relatively limited study, no difficulty was encountered when tubocurarine and succinylcholine were used judiciously along with pancuronium. Based on these observations, the new relaxant appears to be worthy of extensive use to further substantiate the European reports of its efficacy.

Conclusions

Our overall impression of pancuronium was that it is similar to tubocurarine, except that development of peak action is slightly faster and it is at least 4 times more potent based on milligram consumption rates. Its duration of action is variable but lasts at least 90 minutes in an average size, fit adult, when 0.1 mg/kg is given with a sleep dose of thiopentone preceding halogenated anaesthetics including halothane. Repeated small doses of pancuronium appear to have some cumulative effect during clinical anaesthesia. When an operation lasts less than 120 minutes, reversal is usually required.

Pancuronium may be used following induction with succinylcholine or with that preceded by a small dose of tubocurarine (6 mg) to avoid fasciculation, but the total dose should be 20 to 30 per cent less than if pancuronium is used alone. When used with methoxyflurane or with a "Balanced" technique, approximately half the patients require reversal. Although it is claimed that pancuronium does not release histamine, and we have no clinical evidence that it does, there is no proof for this claim in man aside from our limited observations with halogenated anaesthetics.[15,16] Although untoward reactions were not observed in this study, there is still limited information on the effect of pancuronium in man suffering from severe liver disease, kidney disease, and/or electrolyte imbalance—each of which deserves special study. The outstanding feature of this non-depolarizing

muscle relaxant is that it has little influence on the cardiovascular system and it can be reversed safely with atropine/neostigmine.

Summary

Pancuronium bromide is a new non-depolarizing muscle relaxant with a steroidal structure but no hormonal activity. It was evaluated clinically in 456 adult consenting patients who underwent major elective operations, including abdominal (285), neurosurgical (70), thoracic (31), extremity (63), and superficial (7) procedures. In most of the operations (Group A) a single dose was given (251 operations, mean duration 170 minutes) but in others (Group B) supplementary doses were given because the procedure was prolonged (65 operations, mean duration 220 minutes). Intubation was often performed with succinylcholine (Group C, 112 patients, mean duration 180 minutes) or a small dose of tubocurarine (6 mg) preceding succinylcholine (Group D, 28 patients, mean duration 150 minutes) followed by pancuronium during maintenance.

In virtually each case anaesthesia was induced with a sleep dose of thiopentone and after intubation was managed with inhalation of 60:40 nitrous oxide: oxygen with <1.0 per cent methoxyflurane (Penthrane®) in 207 cases, <1.5 per cent Forane in 120 cases, <2 per cent enflurane (Ethrane) in 71 cases, and <2.5 per cent halothane (Fluothane®) in 23 cases. In 35 other cases, a balanced technique with 60:40 nitrous oxide: oxygen and fentanyl (Sublimaze®), droperidol (Inapsine®), and/or diazepam (Valium®) were used.

The vital signs, electrocardiogram, urine output, and body temperature were monitored and detailed records were kept on the character of induction, maintenance, and recovery from anaesthesia along with laboratory evaluations, particularly with respect to blood gases, pH, oxygen saturation, plasma potassium, and histamine.

As was shown in the original laboratory reports and clinical evaluations in Europe, this muscle relaxant is similar in its action to tubocurarine, except that it is at least four times more potent on a milligram dose basis and it has a slightly faster onset of producing full relaxation of the jaws and larynx (three minutes).

Pancuronium appears to have much less ganglion blocking and histamine releasing properties than tubocurarine when a relatively large dose is used, so hypotension and bronchospasm are not seen. These observations were confirmed in our clinical study. We were particularly impressed with the stability of the blood pressure, pulse rate, and electrocardiogram when halothane was used for maintenance. However, the injection of pancuronium before thiopentone was sometimes painful ("burning"), probably due to the buffer that was added.

The duration of adequate muscular relaxation during major surgery is difficult to predict with pancuronium as is the case with other non-depolarizing agents, but atropine/neostigmine reversed its relaxant action without producing appreciable cardiovascular effects as long as atropine immediately preceded or was given along with neostigmine in approximately 1:2 dose ratio. No case of recurarization occurred after a moderate dose of neostigmine, although a few cases required supplementation to ensure restoration of adequate pulmonary ventilation.

Based on this study, pancuronium indeed appears to be an effective muscle relaxant. For poor risk patients requiring major surgery in which skeletal muscle relaxation is important to facilitate exposure and reduce the amount of inhalational or parenteral anaesthetic agents, it is especially safe and useful.

RÉSUMÉ

Le bromure de Pancuronium est un nouveau relâchant musculaire non-dépolarisant, possédant une structure de stéroide, mais dépourvue d'activité hormonale.

Il a été évalué cliniquement chez 456 adultes malades qui ont subi des opérations chirurgicales majeures, à savoir 285 abdominales, 70 neurochirurgicales, 31 thoraciques, 63 sur les extrémitiés, et 7 superficielles.

Dans la majorité des opérations (Groupe A) une dose unique a été administrée (251 interventions, d'une durée moyenne de 170 min); dans d'autres cas (Groupe B) des doses supplementaires étaient données à cause de la durée de l'opération (65 interventions d'une durée moyenne de 220 min).

L'intubation était souvent pratiquée avec la succinylcholine (Group C, 112 malades, durée moyenne 180 min), ou bien une petite dose de tubocurarine (6 mg) précédait la succinylcholine, suivie de Pancuronium pendant le maintien de l'anésthesie (Groupe D, 28 malades, durée moyenne 150 min).

Dans pratiquement tous les cas l'induction se faisait au Pentothal et après l'intubation l'anesthésie était conduite au Protoxyde d'azote: Oxygène (60:40) plus: <1 pour cent Methoxyflurane (Penthrane) dans 207 cas, <1.5 pour cent Forane dans 120 cas, <2 pour cent Enflurane (Ethrane) dans 71 cas, ou bien <2.5 pour cent Halothane (Fluothane) dans 23 cas.

Dans 35 autres cas une technique "balancée" au Protoxyde d'azote: O_2(60:40) avec Fentanyl (Sublimaze), Droperidol (Inapsine), ou bien Diazepam (Valium) était utilisé.

Les signes vitaux, le tracé électrocardiographique, la quantité d'urine et la température du malade étaient suivis régulièrement; les détails concernant l'induction de l'anesthésie, le maintien et le réveil étaient scrupuleusement enregistrés, ainsi que les résultats des analyses de laboratoire, concernant particulièrement les gaz sanguins, le pH, la saturation de l'O_2, le K et l'histamine plasmatique.

Comme cela a été demontré dans les rapports de laboratoire et les évaluations cliniques en Europe, ce relâchant musculaire est similaire dans son action à la tubocurarine, sauf qu'il est au moins quatre fois plus puissant à poids égal et qu'il produit un peu plus rapidement le relâchement complet des mâchoires et du larynx (3 min).

Pancuronium semble avoir beaucoup moins d'action gangio-plégique et la sécrétion d'histamine paraît être plus faible qu'avec la tubocurarine quand une dose relativement élevée est employée, ainsi hypotension et bronchospasme n'ont pas lieu. Ces observations ont été confirmées dans nos études cliniques.

Nous avons été particulièrement impressionnés par la stabilité de la tension artérielle, du pouls et de l'électrocardiogramme, quand l'halothane était employé pour le maintien de l'anesthésie. L'injection du pancuronium était parfois douloureuse ("brulure") quand le produit Américain a été utilisé probablement dû

au stabilisant qu'il contient (lequel est absent dans le produit Européen qui ne cause pas de brulure à l'injection).

La durée du relâchment musculaire pendant une grande intervention est difficile à prédire avec pancuronium, comme c'est la cas avec d'autres agents non-dépolarisants, mais atropine/néostigmine renversait son action sans produire des effets cardiovasculaires appréciables pourvu qu'atropine précédait ou était administrée avec la néostigmine dans la proportion approximative de 1:2. Il n'y a pas eu de cas de recurarisation après une dose modérée de néostigmine, bien que quelques cas ont nécessité une quantité additionnelle pour assurer la restoration d'une ventilation pulmonaire adéquate.

En se basant sur cette étude, pancuronium semble vraiment être un relâchant musculaire utile, particulièrement pour des grands malades à subir des interventions chirurgicale majeures dans laquelle le relâchement musculaire est important pour faciliter l'opération et pour permettre de réduire la quantité des agents anesthésiques.

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