CARDIOVASCULAR EFFECTS OF PANCURONIUM IN PATIENTS ANAESTHETIZED WITH ENFLURANE AND FLUROXENE

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ABSTRACT

The effects of pancuronium on the blood pressure and pulse rate were investigated in patients anaesthetized with either fluroxene or ethrane prior to the surgical procedure. At surgical levels of fluroxene anaesthesia, pancuronium increased the blood pressure and pulse rate significantly. In the patients anaesthetized with ethrane, the blood pressure did not change and the pulse rate rose only temporarily and to a less significant level. Analysis of the changes in pulse rate shows that the greater increase produced by fluroxene was due in part to the initial bradycardic effect of this anaesthetic. However the consistent elevation of blood pressure in this group can only be explained by sympathetic stimulation produced by fluroxene and unmasked by pancuronium. Previous administration of atropine suppresses the effect of pancuronium regardless of the anaesthetic in use.

KEY WORDS: ANAESTHETICS, VOLATILE; Enflurane, Fluroxene; NEUROMUSCULAR RELAXANTS; Pancuronium, cardiovascular effects.

IT HAS BEEN SHOWN that pancuronium bromide, a non-depolarizing neuromuscular blocking agent, produces a moderate increase in pulse rate and blood pressure in patients and animals anaesthetized with thiopentone, nitrous oxide,¹ halothane-nitrous oxide,^{2,3} or nitrous oxide-fentanyl.⁴ It has been demonstrated that this drug does not change the isometric contraction of rabbit atria or cat papillary muscle⁵ although at 1000 times the clinical doses it blocks the uptake of noradrenaline in the rat heart muscle preparation,⁶ the cardiovascular changes being produced by a muscarinic effect⁷ which can be obliterated by pretreatment with atropine, both in animals⁸ and in man.^{4,8,9}

Since the cardiovascular effects of this drug seem to depend on the unmasked sympathetic tone of the preparation when vagal blockade is produced, it is of interest to study them during fluroxene anaesthesia, where sympathetic activity is increased¹⁰ and during ethrane anaesthesia

where it is decreased.¹¹ We did this evaluation by studying the blood pressure and pulse rate changes produced by pancuronium in patients before surgical stimulation. We also investigated the possibility that the changes produced by this muscle relaxant could be prevented by prior administration of atropine.

METHODS

Thirty-one patients of the American Society of Anesthesiologists physical status I and II, 27 to 61 years of age, free from cardiopulmonary disease, scheduled for lumbar laminectomy and fusion or total hip replacement were the subjects of this study.

At the time of the study, fluroxene or ethrane were the anaesthetics of choice for these surgical procedures in this institution. Pancuronium was used for the maintenance of anaesthesia and suxamethonium for tracheal intubation. Cannulation of the radial artery for direct blood pressure measurement and monitoring of blood gases was also part of the anaesthetic management. The study was carried out before the surgical procedure. The study was approved by the Committee for Human Studies and the Institutional Research Committee of the Hahnemann Medical College and Hospital of Philadelphia.

All patients were premedicated with hydro-morphone 0.5 mg, diazepam 5 mg and scopolamine 0.3 mg intramuscularly, given 60 to

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90 minutes prior to the start of anaesthesia. Patients were assigned to receive either fluroxene or ethrane by chance selection of the first anaesthetic to be given, which was fluroxene, followed by ethrane, fluroxene, ethrane, etc. in consecutive order until all 31 patients were studied.

The blood pressure, electrocardiogram lead II and expired carbon dioxide concentration were recorded continuously on a Grass M 7 polygraph; end tidal carbon dioxide concentration was monitored with an infrared analyzer.* The pulse rate was counted from the blood pressure tracings. The output of the anaesthetic vaporizers was checked frequently during the study. Spot checks of end tidal anaesthetic concentrations were carried out by gas chromatography. Blood gases were determined before the administration of pancuronium and at 4–6 minutes afterwards.

Anaesthesia was induced with methohexitone $1\text{--}2\text{ mg}\cdot\text{kg}^{-1}$ intravenously and tracheal intubation was facilitated by decamethonium $0.1\text{ mg}\cdot\text{kg}^{-1}$ of body weight. Anaesthesia was then continued with either ethrane 3.4 per cent or fluroxene 7 per cent in oxygen. Normocarbic ventilation was maintained with a respirator set at 10 b.p.m. and $7\text{--}10\text{ ml}\cdot\text{kg}^{-1}/\text{min}$ tidal volume. After 15 minutes of anaesthesia, pancuronium $0.1\text{ mg}\cdot\text{kg}^{-1}$ was given intravenously and observation continued for 16 minutes on 10 patients anaesthetized with fluroxene (Group I) and 10 anaesthetized with ethrane (Group II). Two additional patients in each group were monitored for 10 minutes after 15 minutes of anaesthesia without being given pancuronium. Three patients anaesthetized with fluroxene (Group IA) and four with ethrane (Group IIA) were given atropine 0.4 or 1 mg intravenously, observed for four minutes, then given the standard pancuronium dose and monitored for 4–6 minutes.

Statistical evaluation was performed by analysis of variance with significance at $P < 0.05$, and then by the Duncan's Multiple Range Test.

RESULTS

Eleven of the 31 patients were female. There was no apparent difference in male and female response to anaesthesia or pancuronium; the small number in each group precluded valid statistical comparisons. There was no intergroup significant difference as to weight, height or

FIGURE 1 Mean $\pm$ SE of mean blood pressure and pulse rate of groups I and II.

PaCO_2 . The mean PaCO_2 was $4.96 \pm 0.11\text{ kPa}$ ($37.3 \pm 0.8\text{ torr}$).

The effects of premedication, anaesthesia and pancuronium administration on Groups I and II are shown in Table I and Figure 1.

Blood Pressure

Group I. Fluroxene produced no significant change in mean arterial pressure; pancuronium increased it significantly ($P < 0.01$) both in relation to anaesthetic and preanaesthetic levels. This increase persisted throughout the observation.

Group II. Neither ethrane anaesthesia nor pancuronium produced significant changes in blood pressure in this group.

Pulse Rate

Group I. Premedication did not change the pulse rate. Fifteen minutes of fluroxene produced a 16 per cent decrease, significant at $P < 0.05$, while pancuronium increased it significantly ($P < 0.01$) in relation to the anaesthetic and preanaesthetic readings. This increase lasted throughout the observation.

Group II. Ethrane produced a significant increase in pulse rate ($P < 0.01$) in relation to the preanaesthetic value and when compared to that before preanaesthesia ($P < 0.05$). Pancuronium

*Capnograph, Godart-Statham N.V. U.S.A. Operations. 2230 Statham Boulevard, Oxnard, CA 93030.

TABLE I

Before Premed.	After Premed.	After 15 min. Anaesth.	Effect of Pancuronium 0.1 mg · kg ⁻¹ at							
			2 min.	4 min.	6 min.	8 min.	10 min.	12 min.	14 min.	16 min.
Group I-Blood Pressure mmHg										
$\bar{x}$	89.8	84.6	101.2	102.4	102.2	101.7	101.2	100.0	98.7	
$\pm$	3.32	4.3	6.8	6.2	4.9	5.1	4.5	4.3	4.4	
		NS	**	**	**	**	**	**	**	
Group II										
$\bar{x}$	87.2	81.7	84.7	84.2	83.4	83.3	81.4	84.1	82.8	
$\pm$	3.7	3.5	3.6	3.6	3.7	3.1	3.2	3.3	3.0	
		NS	NS	NS	NS	NS	NS	NS	NS	
Group I-Pulse Rate										
$\bar{x}$	70.4	58.7	86.0	88.6	87.1	87.7	87.9	88.7	87.2	87.0
$\pm$	2.3	2.0	4.1	3.4	3.8	3.9	3.8	3.5	3.0	3.2
	NS	1*	**	**	**	**	**	**	**	**
Group II										
$\bar{x}$	71.3	77.2	85.2	84.0	84.6	82.9	82.9	82.9	82.3	81.6
$\pm$	3.7	4.0	5.0	4.3	4.6	4.1	4.3	4.7	4.4	4.5
	NS	1**	*	*	*	NS	NS	NS	NS	NS

$\bar{x}$ mean of 10 patients, $\pm$ SE.

NS non-significant difference.

*P < 0.05, **P < 0.01 compared to 15 minutes under anaesthesia.

1*; 1** preanaesthetic comparisons.

TABLE II

Pte	Sex	Age	Wt. kg	Blood Pressure (mmHg)						Pulse Rate (per minute)										
				Anaes.			Atropine			Pancuronium			Anaes.	Atropine			Pancuronium			Atropine mg
				Pre-Anaesth.	15 min.	2 min.	4 min.	2 min.	4 min.	6 min.	15 min.	2 min.	4 min.	6 min.	2 min.	4 min.	6 min.			
Fluroxene (Group IA)																				
AF	M	45	70	76.7	86.7	113.3	105.0	103.3	103.3	101.7	58	48	92	88	92	94	96	0.4		
RR	M	35	72	85.0	101.7	129.3	125.3	116.7	113.7	110.0	67	64	118	122	126	126	126	1.0		
HR	F	40	75	101.7	108.0	119.7	116.7	115.0	110.0	110.0	58	72	119	122	122	122	119	1.0		
Ethrane (Group IIA)																				
AC	F	43	61	101.7	80.0	87.3	81.3	81.3	81.3	—	82	96	103	104	100	98	—	0.4		
LS	F	48	60	88.0	81.7	90.0	85.0	91.3	92.7	88.3	76	78	97	99	100	98	98	0.4		
CP	M	59	70	83.0	72.7	75.0	75.0	71.3	68.3	—	72	76	92	92	89	90	—	0.4		
JB	M	27	76	103.3	98.7	97.7	98.3	97.3	98.3	98.3	88	100	130	130	134	136	134	1.0		

Effects of Ethrane 3.4% or Fluroxene 7% inspired, Atropine and Pancuronium 0.1 mg·kg⁻¹.

FIGURE 2 Effect of pancuronium on mean blood pressure and pulse rate following atropine 0.4 or 1.0 mg. Groups IA and IIA.

produced significant increase in pulse rate ($P < 0.05$) in relation to the preanaesthetic reading and lasted 6 minutes.

Table II and Figure 2 show the effect of pancuronium on blood pressure and pulse rate following atropine 0.4 or 1.0 mg (Groups IA and IIA).

Blood Pressure

Group IA. Fluroxene increased the blood pressure by 13 per cent, while atropine, independently of the dose, increased it another 22 per cent. However, this level was not maintained by the 4th minute and continued to decrease following the administration of pancuronium.

Group IIA. Ethrane produced only a slight decrease in blood pressure. Atropine or pancuronium had no effect.

Pulse Rate

Group IA. Fluroxene produced no change in pulse rate, while atropine caused an 80 per cent increase. Pancuronium had no effect.

Group IIA. Ethrane produced a 10 per cent

increase in pulse rate and atropine added another 20 per cent. Pancuronium produced no changes after atropine.

The four patients who were observed for 25 minutes without receiving pancuronium showed only a slight decrease in blood pressure between the 15th and 25th minutes of fluroxene or ethrane anaesthesia. Pulse rate remained unchanged.

Because of technical limitations, the end tidal anaesthetic concentration was determined by gas chromatography in only two patients of groups I and II after 15 minutes of exposure. Ethrane showed 2.5 and 2.7 per cent, while fluroxene gave 5.6 and 5.7 per cent concentrations.

Four patients in the fluroxene group and six in the ethrane group were evaluated for changes in blood pressure and pulse rate produced by the surgical stimulation; four minutes after the operation had started, neither the blood pressure nor the pulse rate had changed in the fluroxene group. However, in the ethrane group there was an increase in blood pressure ranging from 6 to 20 per cent in five of the six patients; the pulse rate increased from 7 to 16 per cent in three.

DISCUSSION

The object of this study was to compare the cardiovascular response as judged by changes in blood pressure and pulse rate produced by pancuronium in two groups of patients, in one of which sympathetic nervous activity had been increased by fluroxene anaesthesia and in the other where it had been decreased by ethrane anaesthesia. Analysis of the results showed that when pancuronium was given to patients exposed to fluroxene, the blood pressure increased; it had no effect on those anaesthetized with ethrane. The effect on the pulse rate was a marked increase from the anaesthetic level in the fluroxene group and a moderate increase in the ethrane group; both groups showed almost identical pulse rates after the relaxant was given. When this parameter was evaluated by analysis of variance, it showed a difference at $P < 0.05$ level only at the time of exposure to the anaesthetics before pancuronium was given.

Under the conditions of the present study fluroxene is a mild myocardial depressant^{12,14} and ethrane a strong one;¹³ both decrease the vascular resistance slightly. It is therefore difficult to establish categorically the role of sympathetic tone on the cardiovascular response elicited by pancuronium. However, at this level of

fluroxene anaesthesia¹² the cardiac output is unchanged, the pulse rate is slightly decreased and the stroke volume slightly increased. Any increase in pulse rate brought about by a vagolytic agent will increase the cardiac output and the blood pressure. This change would be significant if the sympathetic system had been previously stimulated, as in the present study, by fluroxene. When pancuronium is added to 1.5 MAC ethrane anaesthesia (approximate figure in our study) no change in cardiac output or blood pressure should be expected since at this stage there is pronounced myocardial depression, moderately decreased vascular resistance, moderately elevated heart rate¹³ and depressed sympathetic tone.¹¹ A further moderate increase in pulse rate caused by the vagolytic action of pancuronium will have no effect on cardiac output and blood pressure as seen in the present study.

In this kind of clinical study, although the insult of surgery is avoided, it is impossible to preclude the circulatory effects of the emotional stress¹⁸ elicited by the expectation of major or minor surgery.¹⁹ For this reason, preanaesthetic medication was given. The standardized form of its administration produced mild sedation as reflected by the moderate decrease in pulse rate. No over-sedation was seen, as attested by the control P_{aCO_2} values.

The degree of hypotension seen in this study was not as marked as that reported in young volunteers by Calverly *et al.*¹³ and Cullen *et al.*¹² for ethrane and fluroxene at similar end tidal concentrations.

The fluroxene-induced decrease in pulse rate was similar to that reported by Cullen¹² at a comparable anaesthetic level. This decrease could be related to vagal stimulation since it was readily antagonized by both pancuronium and atropine; it could be postulated that anaesthetics which increase sympathetic output would also increase vagal output. The opposite effect has been shown for isoflurane,¹⁵ an anaesthetic that decreases the sympathetic and vagal output. The moderate but consistent increase in pulse rate produced by ethrane is in agreement with previous reports.^{13,16} It is possible that ethrane also depresses the vagal system in a similar way but to a lesser extent than isoflurane.¹⁵

Atropine was given to groups IA and IIA in doses of 0.4 or 1.0 mg to determine whether it would suppress the effects of pancuronium on the blood pressure and pulse rate. It did, as had been previously reported under comparable cir-

lated with the dose of atropine given regardless of whether fluroxene or ethrane was the anaesthetic, but the blood pressure increased in the fluroxene group.

Although we did not measure the sympathetic output or the plasma or urine levels of catecholamines and, therefore, can not document that our patients were in a state of elevated or depressed sympathetic tone when subjected to the action of pancuronium, Skovsted found sympathetic depression in cats at enflurane end tidal 0.9 per cent; therefore it is likely that our patients had achieved at least that degree of depression at 2.5 per cent end tidal concentration of this anaesthetic. Skovsted also found that the sympathetic stimulation produced by fluroxene was moderately elevated at 4.5 per cent end tidal, being marked at 8.2 per cent. It is highly likely that end tidal fluroxene of 5.5 per cent would produce sympathetic stimulation which, through its cardiac inotropic and/or chronotropic effect, would increase the cardiac output and consequently the blood pressure. However, the lack of factual information on the state of sympathetic tone during the present study makes this comment only speculative.

The lack of cardiovascular response to surgical stimulation in the patients anaesthetized with fluroxene indicates that the cardiovascular effects of pancuronium were those seen at a surgical anaesthetic level.

The response to surgical stimulation seen in the patients anaesthetized with ethrane would indicate that the peripheral vascular response to sympathetic stimulation was preserved as was shown previously in cats by Skovsted.¹¹

This study seems to show that the cardiovascular effects of pancuronium are greater during a state of sympathetic stimulation than during sympathetic depression; however, this reaction does not seem to be universal for all sympathetic stimuli.¹⁷

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RÉSUMÉ

L'influence de l'administration de pancuronium sur la tension artérielle et la fréquence cardiaque a été étudiée sur des patients anesthésiés au fluroxène ou à l'enflurane avant la chirurgie. Au niveau chirurgical de l'anesthésie au fluroxène, le pancuronium a augmenté la tension artérielle et la fréquence cardiaque de façon significative. Chez les malades anesthésiés à l'enflurane, la tension artérielle n'a pas été modifiée et la fréquence n'a augmenté que temporairement et à un degré moindre. L'analyse des modifications de la fréquence a montré que l'augmentation plus marquée produite par le fluroxène est due en partie à l'effet initial bradycardisant de cet anesthésique. Cependant, l'augmentation consistante de la pression artérielle dans ce groupe ne peut s'expliquer que par la stimulation sympathique produite par le fluroxène et dévoilée par le pancuronium. L'administration préalable d'atropine supprime l'effet du pancuronium quelque soit l'anesthésique employé.