THE EFFECT OF PANCURONIUM ON REFLEX REGULATION OF HEART RATE IN MAN*

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PANCURONIUM BROMIDE (NA-97, Pavulon-Organon) is a new non-depolarizing competitive neuromuscular blocking agent. Its clinical blocking properties are similar to d-tubocurarine and are associated with hypotension, ganglionic blockade, and histamine release.^{3,5-14} Despite some variation most studies report that cardiovascular stability is maintained with pancuronium in the presence of cardiovascular depressing anaesthetic agents.^{1,2,5,13,15-17} This cardiovascular stability has been attributed to a vagolytic effect on the heart resulting in increased heart rate and cardiac output.^{16,17} This vagolytic effect may be due to a ganglionic^{3,13} or a post-ganglionic muscarinic blocking effect,^{13,18} but these have not been investigated in man. Further, there have been no reports on the interaction of this agent with homeostatic cardiovascular reflex mechanisms, in particular, the baroreflex.

The purpose of this study is to measure the effect of pancuronium on vagal slowing of the heart, reflexly induced by an acute elevation of systemic blood pressure. By using this Pressor Test (PT) as described by Smyth, Sleight & Pickering,¹⁹ we were able to observe the vagolytic effect of pancuronium as well as its effects on the baroreflex.

METHOD

The quantitation of baroreceptor reflex function (BRF) in terms of cardiac slowing to a pressor stimulus has been described in detail elsewhere.^{19,20} Only a brief summary will be presented here. The test is based on the observation that a hypertensive stimulus to the baroreceptor areas reflexly induces cardiac slowing. Direct arterial blood pressure and electrocardiogram are recorded simultaneously. Graded doses of a smooth muscle vasoconstrictor (angiotensin) sufficient to produce a transient increase in systolic blood pressure in the range of 20 to 30 torr or a significant lengthening of the pulse interval on the electrocardiogram are injected intravenously. By plotting the R-R interval change in response to the appropriate systolic pressure pulses, a plot is obtained (see Figure 1). By using the least square technique, a linear relationship is found from which a slope can be calculated. The slope is expressed in milliseconds of R-R interval change per torr increase in systolic blood pressure and is an expression of baroreflex sensitivity.

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FIGURE 1. Systolic blood pressure (abscissa) plotted against the succeeding R-R interval (ordinate) for one subject. The relationship between the two parameters is represented by the computed line. The slope of this line expressed in milliseconds of R-R interval change per Torr rise in systolic pressure is a quantitation of BRF.

Six healthy unpremedicated patients ranging in age from 21 to 24 years and undergoing minor surgical operations were studied. The subjects arrived in the operating room two hours before operation. An intravenous infusion was established in a large forearm vein. The radial artery was cannulated percutaneously under local anaesthesia. Direct arterial blood pressure was measured with a Statham 23 De strain gauge and recorded on a Hewlett-Packard polygraph simultaneously with lead 2 of a standard three-limb electrocardiogram. A pneumograph was placed about each subject's thorax to allow for exclusion of the effects of respiration on baroreceptor sensitivity.^{19,20} Thus R-R intervals and the corresponding systolic pressure during inspiration are excluded from calculations. Each subject's ventilation was then controlled with an Ohio anaesthetic ventilator (Model 300) in a semi-closed anaesthetic circuit. Air leaks were prevented by a nose clamp and a tightly fitting mouthpiece. A Pressor Test (PT) was performed once the subject was stabilized. The dose of angiotensin administered ranged between 2 and 7.5 micrograms. This period of study was designated as the "awake control" (AC).

Anaesthesia was then induced by mask with methoxyflurane in oxygen. Once the subjects were anaesthetized, 1 milligram/kilogram of succinylcholine was administered to facilitate tracheal intubation. Ventilation was then controlled at values similar to the awake control period. End-tidal methoxyflurane concentrations were monitored using a Beckman IR-215A infra-red analyzer. Once anaesthetic equilibration had occurred, the end-tidal methoxyflurane concentration was maintained between 0.20 and 0.22 per cent. This represents a minimal alveolar concentration or MAC of approximately 1.25.^{21,22} To ensure adequate equilibration between blood, lungs and brain, adequate time was allowed until the inspired to end-tidal methoxyflurane difference was 0.02 per cent or less. We

FIGURE 2. Typical "hockey stick" pressor test plot for one subject following the administration of pancuronium. Slope is computed from the "blade" of the "hockey stick" (see text for details).

had previously determined that this alveolar concentration of methoxyflurane does not alter baroreceptor reflex function.²³ A Pressor Test was then performed on each subject. This period of study represents the methoxyflurane control study (MC).

Once the blood pressure and heart rate had returned to baseline values (usually within 5 minutes), pancuronium 0.11 milligrams/kilogram was administered intravenously. Pressor Tests were performed at 4-, 10-, and 15-minute periods after the injection of pancuronium. This period represents the pancuronium study (PS).

For comparison arterial blood samples were drawn during each study period for determination of PaO_2 , PaCO_2 and pH. All subjects were excluded for whom slopes of correlation coefficients were below 0.68 or where a probability value derived from the correlation coefficient was more than 0.05. The mean, with or without the standard deviation of each Pressor Test performed during the three study periods, were compared to one another by utilizing the analysis of variance technique and the least significant difference test (LSD) to the 5 per cent level.

RESULTS

Figure 2 is a typical Pressor Test response in one subject following the administration of pancuronium. The plot configuration represents a "hockey stick." There is initially a pressure rise following the administration of angiotensin

TABLE I
PATIENT DATA AND PRESSOR TEST SLOPES

Sub- ject	Age	Wt. (kg)	Awake Control (AC)			Methoxyflurane Control (MC)			Pancuronium 0.11 mg/kg (PS)					
			4 min.			10 min.			15 min.			4 min.		
			S.B.P.	HR.	$\frac{\Delta R - R}{\Delta SBP}$	S.B.P.	HR.	$\frac{\Delta R - R}{\Delta SBP}$	S.B.P.	HR.	$\frac{\Delta R - R}{\Delta SBP}$	S.B.P.	HR.	$\frac{\Delta R - R}{\Delta SBP}$
S.G.	22	60	125	52	14.88	105	70	19.25	148	104	15.80	146	96	20.30
B.L.	24	56	130	75	8.55	85	62	6.17	116	83	11.85	114	92	6.03
J.P.	23	81	155	55	18.20	112	50	17.35	137	67	3.10	148	67	5.04
M.H.	21	68	126	55	39.70	93	67	15.50	116	67	5.50	135	62	9.70
R.J.	24	56	145	69	32.30	135	63	4.48	105	71	3.10	118	77	3.70
B.R.	23	78	137	67	23.37	85	85	20.70	114	85	6.15	149	85	7.60
Mean	22.83	66.5	136.3	62.1	22.83	102.5	66.1	13.91	117.6	73.2	8.54	135.0	79.8	8.72
± SD	1.17	11.0	11.8	9.4	±11.52	19.3	11.5	±6.90	11.7	9.1	±4.84	15.6	13.6	±6.03

SD: Standard deviation.

FIGURE 3. Comparison of the means of all the study periods. The three mean slopes calculated after the administration of pancuronium are significantly different from the AC ($p < 0.05$) and only significantly different from the MC at the 0.10 level.

with little change in the R-R interval (the handle of the hockey stick). When a certain pressure elevation is reached, the R-R interval lengthens with a systolic pressure increase (the blade of the hockey stick). This "hockey stick" effect was observed in all subjects who had Pressor Tests performed after the administration of pancuronium. The calculated slope of each subject is derived from the blade of the hockey stick. One subject's slope (SG) was excluded during the 4-minute pancuronium study on the basis of a poor correlation coefficient. Pertinent data and the slopes calculated during the three observation periods are shown in Table I. The mean slopes obtained during the various study periods are shown in Figure 3. The slopes obtained during the "awake" and "methoxyflurane" controls are significantly different from one another ($p < 0.05$). This is not in accordance with previous data from our laboratory²³ where we reported no significant change in slope after methoxyflurane. The three mean slopes obtained during the pancuronium study are significantly different at the 0.05 level when compared to the awake controls, but are significantly different from the methoxyflurane controls only at the 0.10 level.

Arterial blood gases and pH studies varied little from control values throughout the study and are not reported. Systolic blood pressures and heart rates listed in Table I are baseline values obtained just prior to the administration of angiotensin.

DISCUSSION

We have previously reported that methoxyflurane at 1.5 and 2 MAC does not depress baroreflex activity when compared to awake controls using the same Pressor Test. The discrepancy between our awake and anaesthetized controls can be explained on the basis that too few subjects were studied. We felt that increasing the number of subjects in our studies was not warranted because of the frequent reports of nephrotoxicity of methoxyflurane.²⁴ Consequently we pooled the awake and anaesthetized control slopes from our previous study²³ with our present awake and methoxyflurane control slopes, and found no significant difference between the mean values of the two control groups (AC = 22.9 and MC = 19.6).

We have shown that as systolic blood pressure increases initially there is no change in heart rate until a particular pressure is reached. The latter phenomena can be explained on the basis that although the baroreceptors are being stimulated, the reflex heart rate response is initially antagonized by the muscarinic and possibly ganglionic blocking effect of pancuronium. With additional pressure rise and hence enhanced baroreceptor stimulation, the partial vagal blockade is overcome and the heart rate slows as depicted by the blade of the hockey stick. It is well known that the heart is under sympathetic as well as parasympathetic control. Baroreceptor responses to acute blood pressure elevation results in an augmentation of parasympathetic impulse with a paradoxical inhibition of sympathetic impulses to the heart.^{25,26} We are unaware of any studies of the effect of pancuronium on sympathetic nervous function; therefore, we cannot comment on the action of the drug on this aspect of reflex autonomic cardiac rate regulation.

Because there is some preservation of the baroreflex in the presence of high doses of pancuronium, hypertensive or hypotensive responses occurring during similar anaesthesia should be partially counteracted. In subjects who have some defect in their baroreflex pathways, such as the hypertensive,²⁰ the elderly, or subjects under halothane anaesthesia,^{27,28} this benefit of preservation of the reflex with pancuronium will not be apparent.

It should be noted that the dosage of pancuronium used in this study was large (0.11 milligram/kilogram). Similar studies with comparable doses of d-tubocurarine in the same model were difficult to interpret. There was a marked variation in blood pressure, especially during controlled ventilation. This made it extremely difficult to relate heart rate and pressure changes to one another following the administration of the vasopressor.

SUMMARY

We have shown that the baroreflex is partially maintained in patients anaesthetized with methoxyflurane following the administration of pancuronium. Initially heart rate responses are counteracted by the vagolytic effect of pancuronium, which might be explained by a muscarinic and/or ganglionic blocking property of the drug.

RÉSUMÉ

Nous avons montré que la réponse à la stimulation des barorecepteurs est partiellement maintenue chez les patients anesthésiés au Méthoxyflurane suivant l'administration de Pancuronium. Initialement la réponse cardiaque est contre-carrée par l'effet vagolytique du Pancuronium, ce qui peut s'expliquer par la propriété muscarinique et/ou la propriété ganglioplégique du médicament.

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