SOME EFFECTS OF PROPRANOLOL ON THE CARDIOVASCULAR
RESPONSES OF THE MONKEY TO SIMULATED
SUBARACHNOID HAEMORRHAGE*

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SUBARACHNOID HAEMORRHAGE HAS BEEN ASSOCIATED with electrocardiographic changes in man and in the experimental animal.^{1,2} These may vary greatly in character and amongst them have been changes consistent with increased activity of the sympathetic nervous system. Structural changes in the myocardium have been described that could be produced by a period of sympathetic nervous system over-activity³ and increased tissue catecholamine levels have been measured following subarachnoid haemorrhage and other forms of stimulation of the brain in the laboratory animals.⁴ The importance of the catecholamines is also suggested by the abolition of encephalogenic cardiac arrhythmias in dogs following treatment with reserpine.⁵ The portion of sympathetic nervous activity mediated by β -receptor stimulation has received some attention, not only because of the intrinsic interest in the mechanism of these arrhythmias, but because of the effect of rapid arrhythmias on cardiac output and the possible reduction of cerebral blood flow. Accordingly it seemed of interest to study the effects of the prior administration of propranolol on such changes in cardiac rhythm and cerebral blood flow as might occur following simulated subarachnoid haemorrhage in the monkey.

METHOD

Rhesus monkeys were sedated with intraperitoneal sodium pentobarbital 50 mg/kg body weight and the trachea was intubated. Anaesthesia was maintained with a mixture containing thirty per cent of oxygen in nitrous oxide. The animals were paralyzed with d-tubocurarine, artificially ventilated with a Harvard variable phase ventilator and then surgical preparations were made for measurements of cerebral blood flow, intracranial pressure, and systemic arterial pressure. During this period fluid balance was maintained, blood gases were measured at regular intervals, and normal body temperature was maintained. Four to six hours later, at which time cerebral blood flow was stable and a multichannel Grass encephalograph indicated brain activity consistent with light nitrous oxide anaesthesia, arrangements were made to simulate a subarachnoid haemorrhage. This was done by inserting a needle through a hole in the midline of the skull at a point 0.5 cm cephalad to the nasion and manipulating its tip along the floor of the anterior fossa to a point about 0.75 cm anterior to the tuberculum sellae so that it lay in the

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subarachnoid space dorsal to the planum sphenoidale. This is the region which would be contaminated by blood released from an aneurysm in the vicinity of the Circle of Willis. The position of the needle was confirmed by fluoroscopy and by leakage of cerebrospinal fluid. The manoeuvre produced no electroencephalographic, arterial pressure, or electrocardiographic changes. Either saline or propranolol 0.03 mg/kg was administered intravenously at a rate of 0.01 mg/kg/min. Five minutes later a subarachnoid haemorrhage was simulated by injecting 4.0 ml of fresh autogenous blood through the needle over a period of twenty seconds. At autopsy the gross characteristics closely resembled the pathological state in patients succumbing from rupture of an aneurysm.

Cardiac rhythm and femoral arterial pressure were continuously monitored on Electronics for Medicine equipment. The technique employed for measuring cerebral blood flow was that described by Ingvar Lassen and Hoedt Rasmussen.^{6,7,8} $^{133}\text{Xenon}$ (0.5–1.0 mCi) dissolved in 0.5 ml of sterile saline was injected during a two to three second period through a small catheter inserted into the lingual artery. Extra-cerebral contamination with $^{133}\text{Xenon}$ was minimized by ligation of the external carotid artery distal to the origin of the lingual artery. The clearance of $^{133}\text{Xenon}$ from the brain was measured simultaneously for a ten-minute period by each of two collimated scintillation detectors placed symmetrically over the right and left parietal regions. The signal output from each one inch diameter, half inch thick, integral line NaI(Tl) crystal was amplified, analyzed and stored over multiplexed high speed time sequential inputs (multiply buffered device) into a 400 word magnetic core memory. Punched paper tape data output from the 400 word memory allowed immediate access to calculated flows through an on-site laboratory computer system.

Calculation of CBF by compartmental, stochastic, and initial slope index methods was made. The compartmental analysis (c) assumes that the semilogarithmic replot of the clearance curve can be represented by two exponential components. From these two phases blood flow in the gray and white matter is calculated. The relative weights of the two components are determined from the intercepts of the two slopes at zero time. Utilizing the perfusion rates and relative weights of each tissue, the weighted mean cerebral blood flow for the tissue under observation can be calculated by the formula:

$$F_c = W_g \times f_g + W_w \times f_w \quad \text{ml/100 gm/min.}$$

The stochastic method (H/A) formulated mathematically by Zeirler⁹ can be applied to calculate the mean flow values from the linear washout curve according to the formula:

$$F_{H/A} = \frac{(H_0 - H_{10}) \times \lambda \times 100}{A_{10} - \text{Background}} \quad \text{ml/100 gm/min}$$

where H_0 corresponds to all the indicator particles to be cleared and H_{10} the number of particles remaining after ten minutes of clearance. A_{10} is determined by integrating the counts recorded during ten minutes and λ denotes the mean tissue: blood solubility for $^{133}\text{Xenon}$.

The initial slope index (is) method utilizes the gradient of the first 1.5 to 2 minutes of the logarithmic clearance curve.^{10,11} An estimate of mean cerebral blood flow can be rapidly assessed by the equation:

$$F_{is} = \lambda g \times 2.30 \times D \quad \text{ml 100 gm/min}$$

λg corresponds to the ¹³³Xenon partition coefficient for gray matter and D represents the numerical value of the slope of the curve.

The computer programme employed for calculation of the pre-haemorrhage flows incorporated a correction factor (c) for P_{CO_2} .⁸ In view of the uncertainty regarding the effect of arterial P_{CO_2} on cerebral circulation following acute apoplexy this factor was omitted from calculation of the post-haemorrhage flows. Every endeavour was made to maintain the arterial P_{CO_2} within the normal range during this period, although some of the animals were in a state of slight metabolic acidosis during the course of the experiment.

RESULTS

Some data regarding the state of the animals prior to the introduction of subarachnoid blood and approximately forty-five minutes later appear in Table I. There was a significant difference in the temperature of the two groups at the forty-five minute period but in other respects the two groups are comparable.

The cardiac rhythm was analyzed for a two-minute period following the introduction of blood and in two animals in the propranolol group no alterations in rhythm occurred. Details of the arrhythmias that did develop appear in Table II. Sinus arrhythmia was frequent and in the propranolol group the RR intervals differed by periods of up to 0.8 seconds. T-wave changes were common and usually

TABLE I

	Prior to subarachnoid haemorrhage		45 minutes after subarachnoid haemorrhage	
	Saline group n6	Propranolol group n6	Saline group n6	Propranolol group n6
pH				
Mean	7.39	7.34	7.39	7.37
SD	±0.04	±0.09	±0.01	±0.01
P_{CO_2} (mmHg)				
Mean	42	41	40	40
SD	±4	±4	±4	±5
P_{O_2} (mmHg)				
Mean	153	134	131	144
SD	±48	±33	±32	±34
Esophageal temperature C°				
Mean	36.8	36.4	37.4	36.3
SD	±0.5	±0.9	±0.6	±0.4

TABLE II
INCIDENCE OF CARDIAC ARRHYTHMIAS DURING TWO MINUTES
FOLLOWING THE BEGINNING OF INTRODUCTION OF
SUBARACHNOID BLOOD

	Saline n6	Propranolol n6
No change	0	2
Sinus arrhythmia	2	4
A-v junctional rhythm		
<5 isolated complexes	3	2
multiple complexes	1	0
Premature ventricular systoles		
<5 isolated complexes	1	0
bigemini	0	1
sequences of more than 3 complexes	1	1
U waves	0	1
T elevation or inversion	3	5

consisted of an increase in amplitude. The monkey in the propranolol group that developed sequential ventricular extrasystoles received propranolol twenty-eight minutes before the simulated haemorrhage, because of technical difficulties. The other five animals were subjected to haemorrhage within five to ten minutes of the injection of the drug.

The changes of pulse rate and systemic blood pressure that occurred in the two groups appear in Tables III to VI. There was a transient decrease in pulse rate in the group that did not receive propranolol. The propranolol group also exhibited cardiac slowing, but this appeared to be of greater magnitude and longer duration. There was an increase in systemic blood pressure following the haemorrhage in both groups, but this was significantly greater after one minute had elapsed, and during the ensuing four minutes, in the propranolol group.

The prehaemorrhage cerebral blood flow measurements, with which the posthaemorrhage blood flows were compared, were made prior to the injection of propranolol. These, together with the posthaemorrhage flows, appear in Table VII. In the saline group there was no significant difference between the pre- and posthaemorrhage flows. In the propranolol group there was a significant reduction in the posthaemorrhage blood flow, calculated by the compartmental ($p < 0.025$, $p < 0.025$), and stochastic ($p < 0.25$, $p < 0.005$) methods.

The monkeys exhibited electroencephalographic changes beginning approximately 10 seconds following the start of blood injection. The EEG became flat at 15–20 seconds and remained isoelectric for 30–120 seconds. Giant amplitude slow waves then appeared and lasted up to 5 minutes. Electrical activity gradually reverted towards normal, although there was generally increased sporadic delta and theta activity as compared to the baseline trace. In the animals showing a progressive reduction in CBF, progressive loss of amplitude and decreased frequency was exhibited.

Satisfactory measurement of intracranial pressure was not achieved during the course of these experiments but in previous experiments, using a similar technique, lumbar cerebrospinal fluid pressure reached a mean value of 120 mm Hg (sd 76) at the termination of the injection of blood.¹²

TABLE III
HEART RATE PER MINUTE ASSOCIATED WITH SUBARACHNOID HAEMORRHAGE IN MONKEYS THAT DID NOT RECEIVE PROPRANOLOL

M#	PRE SAH	+20 sec	+40 sec	+60 sec	+3 min	+5 min	+10 min	+30 min	+60 min
1	160	90	75	75	105	120	125	125	130
2	200	150	130	145	180	210	210	210	200
3	200	78	80	80	160	180	140	120	220
4	170	210	195	175	200	200	200	200	200
5	210	210	190	150	175	200	200	220	180
6	210	170	135	115	220	225	230	225	225
7	240	190	100	145	220	240	260	245	255
8	250	260	200	250	230	240	260	290	300
Mean	205	170	138	142	189	201	201	204	214
sd	±31	±62	±52	±56	±44	±38	±47	±58	±51
t =		3.15	2.79						
t =		<0.01	<0.02						
		NSC			NSC	NSC	NSC	NSC	NSC

TABLE IV
HEART RATE PER MINUTE ASSOCIATED WITH SUBARACHNOID HAEMORRHAGE IN MONKEYS THAT RECEIVED PROPRANOLOL

M#	PRE SAH	+20 sec	+40 sec	+60 sec	+3 min.	+5 min.	+10 min.	+30 min.	+60 min
9	162	110	105	108	96	108	126	104	130
10	180	138	88	88	136	145	160	172	180
11	176	172	155	140	148	144	170	176	192
12	180	148	96	108	160	160	170	190	190
13	180	132	180	120	110	140	160	190	190
14	160	100	100	100	150	80	65	150	210
Mean	173	133	108	111	133	130	148	162	182
SD	±9	±26	±24	±18	±25	±30	±41	±31	±27
t =		3.51	6.20	7.57	3.62	3.42			
p =		<0.01	<0.001	±0.005	<0.01	<0.01	NSC	NSC	NSC

TABLE V
SYSTEMIC BLOOD PRESSURE (mmHg) ASSOCIATED WITH SUBARACHNOID HAEMORRHAGE IN MONKEYS THAT DID NOT
RECEIVE PROPRANOLOL

M#	PRE SAH	+20 sec	+40 sec	+60 sec	+3 min	+5 min	+10 min	+30 min	+60 min
1	95	140	125	117	110	100	100	95	90
2	70	42	126	106	70	75	70	63	72
3	150	110	206	175	150	140	138	180	170
4	75	60	90	95	70	73	75	70	70
5	115	—	150	75	90	110	112	118	120
6	70	130	95	100	70	70	70	75	75
7	120	110	160	160	110	120	125	120	110
8	120	—	225	205	—	120	115	135	105
Mean	102	99	147	129	96	101	101	107	102
SD	±29	±38	±49	±45	±30	±26	±26	±39	±33
t =		2.25							
p =	NSC	<0.05	NSC	NSC	NSC	NSC	NSC	NSC	NSC

TABLE VI
SYSTEMIC BLOOD PRESSURE (mmHg) ASSOCIATED WITH SUBARACHNOID HAEMORRHAGE IN MONKEYS THAT RECEIVED PROPRANOLOL

M#	PRE SAH	+20 sec	+40 sec	+60 sec	+3 min	+5 min	+10 min	+30 min	+60 min
9	105	195	205	195	163	190	100	45	40
10	140	180	215	190	190	170	140	140	140
11	90	160	175	192	150	140	105	85	135
12	95	140	155	170	120	110	95	135	150
13	150	145	215	195	160	195	155	150	155
14	110	175	150	135	120	105	120	125	110
Mean	115	166	186	180	151	146	119	113	122
SD	±25	±21	±30	±24	±27	±34	±24	±40	±43
t =	3.38	4.50	4.63	2.38					
p =	<0.02	<0.002	±0.001	±0.05	NSC	NSC	NSC	NSC	NSC

TABLE VII

CEREBRAL BLOOD FLOWS (ML/100 GM/MIN) ASSOCIATED WITH SUBARACHNOID HAEMORRHAGE IN MONKEYS THAT DID AND DID NOT RECEIVE PROPRANOLOL

	Prehaemorrhage CBF			Posthaemorrhage CBF					
	CC	H/AC	ISC	C	+5 min. H/A	IS	C	+45 min. H/A	IS
Saline									
Monkey No. 2	56 ±11	83	87	55	76	82	42	54	51
4	47 ±4	57 ±6	57 ±10	92	110	121	40	64	67
5	51 ±12	74 ±3	78 ±5	60	76	76	72	69	67
6	54 ±8	62 ±3	59 ±4	44	44	43	43	44	43
7	44 ±14	61 ±18	70 ±18	54	57	56	50	63	60
8	40 ±8	39 ±8	41 ±6	26	22	20	11	13	14
Propranolol									
Monkey No. 9	38 ±6	45 ±12	48 ±10	7	7	15	4	3	9
10	48 ±2	68 ±2	79 ±4	41	49	47	33	37	43
11	47 ±7	55 ±12	55 ±18	38	34	34	30	22	14
12	61 ±9	78 ±14	85 ±16	51	65	76	48	51	51
13	59 ±8	69 ±4	69 ±10	38	34	39	43	32	31
14	59 ±2	70 ±6	82 ±11	26	27	33	22	28	40

DISCUSSION

A relationship between some of the cardiac arrhythmias associated with subarachnoid haemorrhage and an effect of the sympathetic nervous system on the heart is well documented.^{5,13,14} Many of these arrhythmias are likely to be mediated by β -receptor mechanisms and propranolol is an effective drug in the prophylaxis and treatment of such arrhythmias.^{15,16} Thus it seems likely that the failure to abolish arrhythmias of ventricular origin in the propranolol group of monkeys was, at least in part, due to insufficient quantity of the drug rather than inappropriate selection of the drug. Coltart *et al.*¹⁷ have measured the plasma propranolol associated with suppression of automatically occurring ventricular ectopic beats in adult humans. The drug was infused at a rate of 1.0 mg/minute (a quantity similar on a body weight basis to that used in the experiments reported here) – but for suppression of arrhythmias for a two-minute period dosages up to 29 mg were required in eight out of twelve cases. The dosage of propranolol employed in the present experiments was limited to 0.03 mg/kg because preliminary observations showed that higher dosage was likely to produce a significant difference in systemic blood pressure between the two groups. Offerhaus and Van Gool⁴ noted the effectiveness of 1.0 mg/kg in abolishing existing arrhythmias for five minutes in rabbits, but also noted that pretreatment of the animals with the dosage apparently necessary to block the arrhythmias produced a gradual fall in systemic arterial pressure. This

could be of a magnitude sufficient to threaten the maintenance of normal cerebral blood flow. Although the half life of propranolol in the body is two hours¹⁵ no attempt was made to measure such effect as the drug in the dosage used may have on cerebral blood flow, because the simulated haemorrhage would have been unduly delayed. Little inference of a reduction in cerebral blood flow can be drawn from the reports of clinical use of the drug and Solti *et al.*¹⁸ have demonstrated in dogs that propranolol 0.2 mg/kg has no effect on cerebral blood flow. Thus the assumption is made that the reduction in cerebral blood flow following the simulated haemorrhage in the propranolol group is due to an altered response to the injection of blood rather than a pre-existing reduction in flow produced by propranolol. Introduction of blood into the subarachnoid region as employed in these experiments has rapid cardiovascular effects derived from tactile and pressure events within the cranium and responses to these occurring in the rest of the body. The limited number of physiological functions measured in these experiments precludes more than speculation regarding the reason for the reduction in flow of the animals that had received propranolol. The peripheral actions of the drug may be the most important in this context, if maintenance of cerebral blood flow under adverse circumstances of subarachnoid haemorrhage is in its initial stage due in part to adequate sympathomimetic responses of the heart. Propranolol would impair this homeostatic mechanism. Alternatively, or perhaps in addition, propranolol may have a role in modifying the local responses of the cerebral vasculature and indirectly influencing cerebral blood flow. The complexities of β -adrenergic mechanisms and vascular smooth muscle form part of a recent review by Somlyo *et al.*¹⁹

In conclusion, it appears that propranolol used in the manner described fails to ensure protection against ventricular arrhythmias induced by subarachnoid haemorrhage and may increase the danger of vagal stimulation. The changes in cerebral blood flow indicate the need for further elucidation of the effects of various forms of intracranial stimulation on cerebral blood flow in the presence of propranolol. During neurosurgical anaesthesia the effect of rapid arrhythmias on cardiac output²⁰ may make their correction mandatory, but it seems possible that propranolol has a significant effect on intracranial haemodynamics during surgery and in the postoperative period.

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