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Research Article

THE EFFECT OF INTRAVENOUS PAPAVERINE HYDROCHLORIDE ON THE CEREBRAL CIRCULATION [1, 2]

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Papaverine, one of the benzylisoquinoline derivatives of opium, has found its primary usefulness as a relaxer of the smooth muscle of blood vessels (1). Numerous reports are to be found in the literature as to its effectiveness in the treatment of occlusive and spastic conditions of the pulmonary (2), coronary (3) and peripheral arteries (4–6). In recent years, Russek and Zohman have reported clinical studies in which they felt papaverine had been demonstrated to be an effective therapeutic agent in the treatment of vasospastic conditions involving the cerebral vessels (7). Experimental demonstration of the effect of papaverine hydrochloride on the cerebral vessels has been limited to a report by Shenkin of the effect of 0.06 gm. of the drug intravenously in four patients judged to have decreased cerebral circulation (8). He noted no significant change in cerebral circulatory functions other than a reduction of mean arterial blood pressure and cerebral vascular resistance. The purpose of this paper is to report our findings on the effects of intravenous papaverine on cerebral blood flow and metabolism in 18 subjects, as measured by the nitrous oxide technique (9).

METHOD

Eighteen hospital patients were chosen, the two largest component groups being patients with acute and chronic liver disease (seven), and normal middle-aged and elderly people (five). There was no purpose in this selection of patients except that the cerebral metabolism of these groups was under study for other purposes. The remainder of the subjects (six) were chosen at random. All patients were males and ranged in age from 25 to 79 years. A control cerebral blood flow was performed using the modification of the original nitrous oxide technique previously described (10), in which continuous simultaneous samples of blood are drawn from the internal jugular bulb and femoral artery over the ten-minute period of nitrous oxide inhalation to measure mean arterio-venous nitrous oxide difference. The papaverine was administered intravenously in doses of 0.2 gm. in 200 cc. normal saline over a period of about 15 to 20 minutes. The second blood flow measurement was begun approximately five to eight minutes after the intravenous solution had been started. Arterial pressure measurements were made by the auscultatory method every two minutes throughout the procedures, with the arm held at heart level. Mean pressures were calculated from the formula MP = Diastolic pressure + ⅓ pulse pressure. These readings were checked on several patients by direct pressure readings on a U tube mercury manometer. In all instances calculated and direct pressures agreed closely. Blood samples for oxygen determinations were drawn before and after each blood flow measurement, and the average was used as the final arterial-cerebral venous oxygen difference. The oxygen measurements were done by the spectrophotometric method of Hickam and Frayser (11). Cerebral oxygen consumption and cerebral vascular resistance were calculated in the usual manner. Cerebral venous oxygen tension was not measured directly, but was computed from cerebral venous oxygen content by means of an oxygen dissociation curve drawn for pH 7.4.

RESULTS

The data obtained from these studies are presented in Table I. As may be seen, there was a statistically significant increase in cerebral blood flow (CBF) from a mean of 56.6 to 63.9 ml./100 gm. brain/min. ($p = 0.013$), an increase of 13%. This was associated with a statistically significant decrease in cerebral vascular resistance (CVR), from a mean of 1.67 to 1.40 mm. Hg/ml. blood/100 gm. brain/min. ($p = < .01$). The mean

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arterial-cerebral venous oxygen difference decreased from 6.64 to 5.86 vol.% ($p = < .01$), commensurate with the increase in CBF, so that cerebral oxygen consumption showed no significant change. Mean arterial pressure fell from 98 to 85 mm. Hg, a statistically significant decrease. Mean cerebral venous oxygen tension increased slightly but significantly ($p < 0.01$), from 30.5 to 32.1. As can be seen from Figure 1, cerebral blood flow actually decreased slightly in five of the 18 subjects. The reasons for this cannot be stated with surety, but it seems likely that it was due to experimental error in the procedure, perhaps in the analysis of the blood samples for nitrous oxide, because in four of these five patients, the arterial-cerebral venous oxygen difference decreased, and in the fifth it was unchanged. Since the determination of the arteriovenous oxygen difference is subject to less error than measurement of the cerebral blood flow, it is probable that the blood flow determinations were inaccurate. In only one of these five (R. W., Table I) was the difference between the control and papaverine determination outside experimental error. The subjects in whom this phenomenon occurred had no physiological similarity

TABLE I

Comparison of cerebral functions (controls and after i.v. papaverine)

Pt.	Age	Diagnosis	Cerebral blood flow (*ml./min./100 gm. brain*)		Arterial-cerebral venous O_2 difference (*vol. %*)		Cerebral O_2 consumption (*ml. O_2/min./100 gm. brain*)		Mean arterial pressure (*mm. Hg*)		Cerebral vascular resistance (*units*)		Cerebral venous O_2 tension (*mm. Hg*)	
			Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
A. G.	34	Homologous serum jaundice	53	74	5.99	5.56	3.15	4.12	81	76	1.54	1.03	27	28
D. H.	42	Arthritis, infectious	51	60	7.73	7.03	3.93	4.21	85	84	1.67	1.40	26	29
M. R.	79	Normal old age	40	53	9.32	7.27	3.73	3.85	94	95	2.35	1.79	25	29
C. B.	40	Laennec's cirrhosis	63	71	5.80	4.73	3.65	3.36	101	85	1.60	1.20	31	33
H. M.	38	Laennec's cirrhosis	45	44	4.78	3.30	2.15	1.45	87	80	1.93	1.82	38	44
P. M.	58	Laennec's cirrhosis	64	68	4.90	4.70	3.13	3.19	90	85	1.41	1.25	25	26
C. B.	58	Normal middle age	47	74	6.54	5.21	3.08	3.86	90	68	1.91	0.92	31	36
R. L.	33	Viral hepatitis	55	59	7.76	6.96	4.27	4.11	93	80	1.69	1.29	29	32
M. S.	50	Normal middle age	66	79	6.66	5.66	4.40	4.47	97	91	1.47	1.15	32	34
G. O.	56	Laennec's cirrhosis	55	54	5.12	4.13	2.81	2.23	81	72	1.47	1.33	34	38
C. C.	53	Normal middle age	59	67	7.13	6.54	4.21	4.37	79	78	1.34	1.16	30	32
R. E.	51	Cerebral vascular disease	47	45	6.98	5.55	3.28	2.50	92	98	1.96	2.16	30	34
J. R.	44	Normal middle age	60	64	6.15	5.58	3.69	3.57	104	88	1.74	1.37	32	33
M. D.	31	Idiopathic epilepsy	63	83	6.31	6.18	3.95	5.13	102	97	1.62	1.17	33	33
R. G.	47	Multiple sclerosis	59	54	7.64	7.16	4.50	3.85	85	79	1.44	1.46	30	30
R. W.	34	Essential hypertension	65	46	7.46	7.30	4.85	3.36	145	132	2.23	2.87	32	33
P. B.	25	Viral hepatitis	51	73	8.36	7.57	4.27	5.53	83	70	1.63	0.96	29	30
L. R.	53	Mild bronchial asthma	75	82	4.94	4.81	3.70	3.94	79	78	1.05	0.95	36	35
		Mean values	56.6	63.9	6.64	5.86	3.72	3.74	98	85	1.67	1.40	30.5	32.1
		P values	0.013		<0.01		>0.5		<0.01		<0.01		<0.01	

$$t = \frac{\text{Mean difference}}{\text{Std. error of mean difference}}.$$

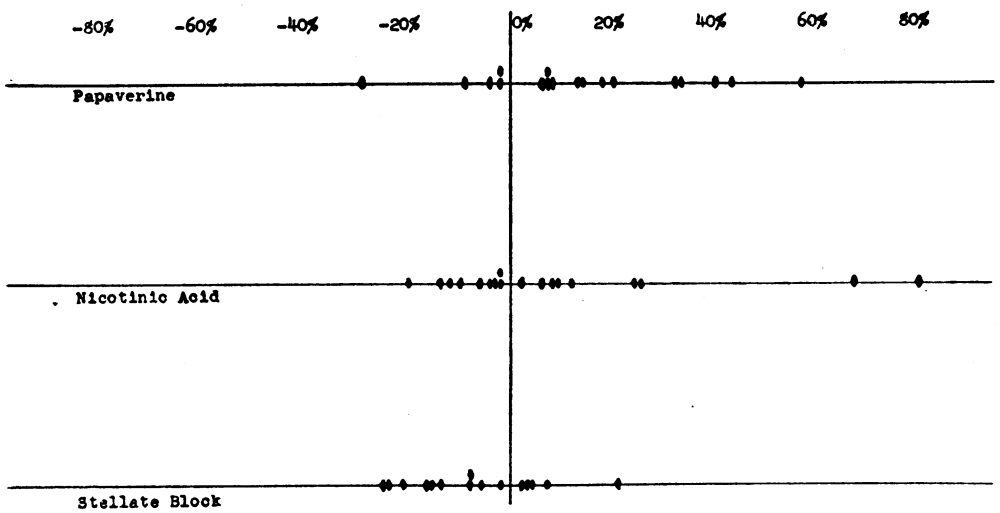

FIG. 1. INDIVIDUAL DETERMINATIONS OF CEREBRAL BLOOD FLOW, EXPRESSED AS PERCENTAGE CHANGE FROM THE CONTROL VALUES RESULTING FROM THE ADMINISTRATION OF PAPAVERINE, NICOTINIC ACID AND PROCAINE BLOCK OF THE STELLATE GANGLION

to explain it. Figure 1 also compares the percentage change in cerebral blood flow due to papaverine as compared to that due to nicotinic acid and stellate block, which were previously reported. The great preponderance of increases in blood flow following papaverine, as compared to the other two, is evident. The mean cerebral blood flow in the control series is somewhat below the value established for normal young men (mean of 65) (10) and is probably due to the fact that this study included a heterogeneous population of various disease states, as well as normal elderly subjects, for whom no normal mean value has been established.

DISCUSSION

In light of our past knowledge of papaverine, its action in causing relaxation of the smooth muscle of arteries and arterioles seems the best explanation for the decreased cerebral vascular resistance and increased cerebral blood flow noted is this study. There was no reason to suspect anoxia or decreased blood pH (12) of playing a role in these results for arterial O_2 content was unchanged after papaverine, as was blood pH in the several patients in whom it was measured. Although CO_2 tension of the blood was not measured, there was no reason to suspect that it was increased as a result of papaverine administration. The decrease in arterial pressure is suggestive evidence that the papaverine probably causes arteriolar dilatation, although this is certainly not localized to the brain. The possibility of contamination of internal jugular blood by extracerebral blood from increased blood flow to the skin of the face, thus causing abnormally high values for cerebral blood flow, must be considered just as with the intravenous administration of nicotinic acid (13). In none of the patients reported, however, was any facial flush noted during the administration of the papaverine. In six of the patients in whom cerebral blood flow was increased, the cerebral arteriovenous oxygen difference was measured after 100 mgm. nicotinic acid were given intravenously. In only one subject did the results indicate the presence of facial contamination, and these data were therefore discarded.

It is worthy of note that much of the repute gained by papaverine as a vasodilator is based on clinical rather than experimental studies. In coronary artery disease it is reported as being highly effective in relieving angina (3). In occlusive diseases of the peripheral arteries, many authors have reported papaverine as being a highly effective agent (5, 6), especially in relieving the vasospasm associated with acute obstructive episodes.

A recent study in normal subjects wherein the effect of various drugs on the peripheral vessels was recorded by use of venous occlusion plethys-

mography, skin temperatures and radioactive sodium uptake from the gastrocnemius muscle has shown that intravenous papaverine has a moderate vasodilating effect on the vessels in the skin and subcutaneous tissue in some individuals (14). The drug was not as effective as priscoline as a vasodilator and less than 50% of the subjects showed any significant vasodilatation. It is understood by the authors that laboratory studies of this sort may have no specific bearing on purely clinical data.

In recent years clinical studies have reported papaverine to be an effective drug in the treatment of diseases of the cerebral vessels. Russek and Zohman reported 46 cases of vascular encephalopathy due to hypertension, acute glomerulonephritis and similar disease states, all of whom showed definite beneficial effects from the administration of papaverine (7). It does not seem that the small increase in cerebral blood flow produced by papaverine would result in the profound clinical changes reported by these authors. On the other hand it should be pointed out that in none of our subjects was there reason to suspect acute cerebral vascular changes which might have been reversed by a cerebral vasodilating agent. For that reason final conclusions on the clinical efficacy of papaverine as a vasodilator must be reserved until such time as appropriate subjects can be studied.

These studies also indicate that just as in other portions of the vascular tree, a pronounced individual variability of response to papaverine is seen. It is of interest that papaverine does increase cerebral blood flow, since it is one of the few agents of those thus far reported that does so.

SUMMARY

1. Intravenous papaverine hydrochloride, in doses of 0.2 gm. administered in 20 minutes, results in a 13% increase in cerebral blood flow, a commensurate decrease in arterial-cerebral venous oxygen difference, with no change in cerebral oxygen consumption, and a decrease in cerebral vascular resistance and cerebral venous oxygen tension.

2. It is thought that the mechanism whereby papaverine increases cerebral blood flow and decreases cerebral vascular resistance, is its direct vasodilating effect on cerebral vessels.

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