THE EFFECTS OF INTRAVENOUS PRISCOLINE ON CEREBRAL CIRCULATION AND METABOLISM[1]

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Priscoline hydrochloride (2-benzyl-imidazoline-hydrochloride) is a drug of many pharmacologic actions. The effects of the drug in man apparently depend upon the dosage and method of administration. It is reported to produce peripheral vasodilatation by: *1*) adrenergic blockade, inhibiting the effects of circulating adrenalin on smooth muscle cells of blood vessels; *2*) sympathetic blockade at the terminations of the sympathetic nerves in the blood vessels; *3*) direct action on peripheral vessels; and *4*) epinephrine-reversal. There may be sufficient increase in cardiac output to elevate arterial pressure even in the presence of generalized peripheral vasodilatation (1–7). The drug also has other actions not specifically related to the cardiovascular system. Clinically, priscoline has been used widely in the treatment of occlusive and spastic peripheral vascular disease because of its ability to produce an increased cutaneous and muscle blood flow (8–11). Several enthusiastic reports have appeared on the beneficial effects of priscoline on cerebral vessels in the treatment of cerebral vascular disease (12–14), and D. Engel has observed dilatation of pial vessels by capillary microscopy through a window in the skull of cats following intravenous priscoline (15). The present study was undertaken in an effort to measure the effects of large doses of intravenous priscoline on cerebral blood flow, metabolism, and other cerebral metabolic functions in man.

METHOD

Twenty-four patients, chosen from the hospital wards, were studied. Most were essentially normal, middle-aged or elderly individuals and the others had a variety of disease states. The mean age of the group was 48 years, but only 5 were under the age of 40, whereas 9 were 55 years or over. None of the subjects had acute cerebral vascular accidents. A control blood flow was performed using the modification of the original nitrous oxide technique previously described (16). The priscoline was then administered intravenously in doses of 50 to 100 mgm. in 200 ml. of normal saline over a period of 15 to 20 minutes. Thirteen patients received 100 mgm. of priscoline, 2 received 50 mgm., and 9 received 75 mgm. The second blood flow measurement was begun five to eight minutes after the intravenous solution had been started, during the period of maximal drug action. All patients developed facial flushing, conjunctival suffusion, moderate pupillary constriction, nasal stuffiness, pilomotor erection, and tachycardia. Blood pressure responses were variable. Arterial pressure measurements were made by the auscultatory method every two minutes during the procedure, with the arm held at heart level. Mean pressures were calculated from the formula

$$\text{MP} = \text{diastolic pressure} + \tfrac{1}{3} \text{ pulse pressure},$$

and agreed with mean pressures measured directly by a mercury U tube manometer in most patients. Blood samples for oxygen determinations were drawn before and after each blood flow measurement, and the average was used as the final value for arterial-cerebral venous oxygen difference and arterial oxygen saturation. The oxygen measurements were done by the spectrophotometric method of Hickam and Frayser (17). Arterial and venous oxygen tensions were estimated from the pH and the per cent oxyhemoglobin saturation, using the dissociation curves of Dill. (The values for oxygen tension when oxyhemoglobin saturation was above 90 per cent were obtained from a chart of interpolated values, using the figures of Dill, since it was impossible to read the curves accurately above this point.) Carbon dioxide content of whole blood was measured by the method described by Peters and Van Slyke (18). Carbon dioxide tension was estimated from the nomograms of Peters and Van Slyke (18). Whole blood pH was measured with the glass electrode of a Cambridge Model R pH meter at 33° C., and corrected to 38° C. by Rosenthal's factor. Samples for blood glucose were collected similarly to the oxygen samples, but the average arterial-cerebral venous glucose difference represents four arterial and four venous glucose determinations. Blood

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TABLE I—*Effects of intravenous priscoline on cerebral metabolic functions*

Pt.	Age	Diagnosis and dose	Cerebral blood flow		Arterial-cerebral venous O_2 diff.		Cerebral O_2 consumption		Arterial O_2 saturation		Arterial O_2 tension		Cerebral venous O_2 tension		Arterial CO_2 content		Arterial CO_2 tension		Arterial pH		Venous pH		Arterial-cerebral venous glucose diff.		Cerebral glucose consumption		Mean arterial pressure		Cerebral vascular resistance	
			ml./min./100 gm. brain		*Vol. %*		*ml. O_2/min./100 gm. brain*		*%*		*mm. Hg*		*mm. Hg*		*Vol. %*		*mm. Hg*						*mgm. %*		*mgm. glucose/min./100 gm. brain*		*mm. Hg*		*mm. Hg/ml. blood/min./100 gm. brain*	
			ā	p̄	ā	p̄	ā	p̄	ā	p̄	ā	p̄	ā	p̄	ā	p̄	ā	p̄	ā	p̄	ā	p̄	ā	p̄	ā	p̄	ā	p̄	ā	p̄	ā	p̄
RP	19	Inf. Hepatitis—100 mgm.	47	41	7.3	8.0	3.4	3.3	94	98	75	110	32	31	47.5	47.9	41	36	7.39	7.45	7.36	7.39	7.3	7.6	3.4	3.1	82	85	1.74	2.07
CK	55	Pul. Emphysema—100 mgm.	54	64	7.3	7.2	4.0	4.6	90	86	62	53	30	30	49.1	49.6	43	40	7.39	7.42	7.34	7.33	8.5	13.0	4.9	8.3	74	54	1.37	0.84
NC	30	Normal—100 mgm.	94	—	5.0	6.4	4.7	—	97	97	102	97	43	36	45.1	41.2	44	36	7.35	7.42	7.31	7.37	8.3	12.5	7.8	—	81	84	0.86	—
DC	64	Normal—100 mgm.	79	39	4.7	5.2	3.7	2.0	91	92	69	74	38	41	52.3	51.0	49	50	7.34	7.32	7.31	7.21	7.0	9.3	5.5	3.6	80	70	1.01	1.80
FB	53	Normal—100 mgm.	45	37	5.2	5.0	2.3	1.8	95	93	—	—	35	36	49.7	48.3	—	—	—	—	—	—	7.0	9.0	3.2	3.3	83	87	1.84	2.35
WK	61	Normal—100 mgm.	36	39	4.7	5.3	1.7	2.1	91	90	67	61	38	33	51.6	50.4	46	40	7.37	7.42	7.33	7.37	5.4	5.6	2.0	2.2	93	91	2.58	2.33
ER	67	Normal—100 mgm.	100	77	5.8	7.2	5.8	5.5	90	93	63	73	33	31	44.8	42.8	39	37	7.38	7.38	7.34	7.32	8.9	10.0	8.9	7.7	93	95	0.93	1.23
EM	43	Normal—100 mgm.	78	77	5.7	6.2	4.4	4.8	98	98	111	106	36	31	47.8	46.1	43	37	7.36	7.42	7.33	7.37	—	—	—	—	94	88	1.21	1.14
WP	46	Normal—100 mgm.	61	52	6.4	7.3	3.9	3.8	96	94	97	79	43	36	47.3	45.4	49	43	7.30	7.35	7.27	7.29	—	—	—	—	91	93	1.49	1.79
MB	54	Normal—75 mgm.	55	53	6.2	6.0	3.4	3.2	95	96	81	90	33	34	51.0	50.0	43	44	7.39	7.37	7.36	7.35	—	—	—	—	84	94	1.53	1.72
HH	40	Amyotrophic lateral sclerosis—75 mgm.	43	51	8.6	9.0	3.7	4.6	97	94	101	76	32	28	44.9	44.2	40	39	7.38	7.38	7.31	7.32	—	—	—	—	96	93	2.23	1.82
EN	36	Cerebral Vasc. Dis.—75 mgm.	54	—	4.8	3.6	2.6	—	93	93	71	73	35	46	47.6	45.5	40	41	7.40	7.37	7.38	7.35	—	—	—	—	96	100	1.78	—
GV	58	Normal—75 mgm.	54	42	5.8	—	3.1	—	—	—	—	—	—	—	—	—	—	—	7.38	7.45	7.34	7.42	—	—	—	—	117	99	2.17	2.36
JD	54	Cirrhosis—75 mgm.	67	48	6.0	6.1	4.0	2.9	92	92	68	63	32	29	—	—	—	—	7.39	7.46	7.35	7.40	—	—	—	—	88	77	1.31	1.60
CO	41	Rh. Arthritis—100 mgm.	77	—	7.6	8.2	5.9	—	96	96	—	—	30	30	—	—	—	—	—	—	—	—	—	—	—	—	87	83	1.13	—
CM	41	Normal—100 mgm.	73	—	5.7	6.8	4.2	—	99	98	—	—	34	30	—	—	—	—	—	—	—	—	—	—	—	—	94	91	1.29	—
MR	36	Emphysema—75 mgm.	49	—	7.7	8.1	3.8	—	92	94	—	—	32	32	—	—	—	—	—	—	—	—	—	—	—	—	84	86	1.72	—
LA	38	Normal—100 mgm.	57	—	4.9	4.2	2.8	—	97	97	—	—	40	44	—	—	—	—	—	—	—	—	—	—	—	—	97	93	1.70	—
EH	41	Normal—100 mgm.	40	—	6.5	6.4	2.6	—	91	89	—	—	30	30	—	—	—	—	—	—	—	—	—	—	—	—	110	92	2.75	—
IW	62	Normal—75 mgm.	33	—	7.3	8.5	3.1	—	99	99	—	—	33	30	—	—	—	—	—	—	—	—	—	—	—	—	101	85	3.06	—
RM	43	Cirrhosis—75 mgm.	46	—	4.6	4.6	2.1	—	86	87	—	—	30	31	—	—	—	—	—	—	—	—	—	—	—	—	98	95	2.13	—
FH	58	Dx. Unknown—75 mgm.	44	—	6.3	7.0	2.8	—	98	97	—	—	34	32	—	—	—	—	—	—	—	—	—	—	—	—	100	97	2.28	—
GH	55	Normal—50 mgm.	57	60	7.4	7.0	4.2	4.2	99	97	—	—	31	31	—	—	—	—	—	—	—	—	—	—	—	—	110	102	1.93	1.70
JF	62	Cirrhosis—50 mgm.	50	47	5.1	5.4	2.6	2.5	96	94	—	—	33	29	—	—	—	—	—	—	—	—	—	—	—	—	97	81	1.94	1.72
		MEAN VALUES	59	52	6.12	6.47	3.62	3.50	94.4	94.1	80.6	79.6	34.2	33.1	48.2	46.9	43.4	40.3	7.37	7.40	7.33	7.35	7.8	9.6	4.7	4.7	93	88	1.66	1.75
		p values	$0.05 < p < 0.1$		$p = 0.02$		$p > 0.4$		$p > 0.5$		$p > 0.5$		$p > 0.5$		$p < 0.01$		$p < 0.01$		$p < 0.01$		$p > 0.3$		$p < 0.02$		$p > 0.5$		$p < 0.01$		$p > 0.5$	

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

ā = Before priscoline.
p̄ = After priscoline.

glucose was measured by the sodium thiosulfate titration method of Somogyi (19).

Cerebral oxygen consumption (CMR O_2)
= cerebral blood flow (CBF) × arterial − cerebral venous oxygen difference (A − V O_2)

Cerebral glucose consumption (CMR Gl.)
= CBF × arterial − cerebral venous glucose difference (A − V Gl.)

Cerebral vascular resistance (CVR)
$$= \frac{\text{mean arterial pressure (MAP)}}{\text{CBF}}$$

RESULTS

The data obtained in this study are presented in detail in Table I. There is an apparent reduction in CBF from a mean of 59 to 52 ml./min./100 gm. brain. Though strictly speaking this is not a statistically significant change, it is felt that it represents a definite trend for reduction of CBF following priscoline. This feeling is strengthened by the statistically significant increase in A–V O_2 from 6.1 to 6.5 vol. %, with no alteration in CMR O_2. Though glucose observations were made on only 7 patients, there is a statistically significant increase in A–V Gl. from a mean of 7.8 to 9.6 mgm. %, with no change in CMR Gl.

In almost all subjects the administration of priscoline was followed by a mild increase in respiratory rate and depth. The fall in arterial CO_2 content (48.2 to 46.9 vol. %), the increase in arterial pH (7.37 to 7.40), and resultant drop in arterial CO_2 tension (pCO_2) (43.4 to 40.3 mm. Hg), all of which are statistically significant changes, seem to confirm the visual observation that the patients were over-ventilating. There was no significant change in cerebral venous pH, arterial O_2 saturation, arterial or cerebral venous O_2 tension, or cerebral vascular resistance. There was a small but significant drop in arterial pressure from a mean of 93 to 88 mm. Hg.

It is of interest that some of the earliest observable clinical effects of priscoline in these patients, aside from tachycardia, were the conjunctival suffusion, nasal congestion, mild pupillary constriction, facial flushing, and increased facial heat and dryness, which closely resembled the effects of a bilateral stellate ganglion block. The known effect of priscoline in producing sympathetic blockade was probably responsible for this phenomenon. The intense pilomotor reaction of priscoline usually occurred later, and the resultant sensation of chilliness did not appear until the measurements on cerebral metabolism had been completed. All patients suffered mild to severe postural hypotension which persisted for at least 30 minutes after administration of the drug was completed.

DISCUSSION

The data indicate that priscoline apparently has an effect on cerebral vessels that differs from that on the vessels of skin and muscle. Unfortunately the data do not permit a final interpretation of the manner in which priscoline seems to produce a slightly diminished CBF and widened A–V O_2. It is possible that administration of the drug induced moderate hyperventilation, with reduction of arterial pCO_2, and subsequent decrease of CBF, since hyperventilation is known to diminish CBF (20), although the absence of evidence of active vasoconstriction and the relatively small reduction in arterial pCO_2 make this concept doubtful. Priscoline may produce a chain of events similar to that postulated for aminophylline (21); it may produce mild cerebral vasoconstriction causing a decrease in CBF, with mild anoxia of cerebral tissue (decreased O_2 content of cerebral venous blood), and resultant increase of cerebral CO_2 tension. This may in turn produce hyperventilation, with resultant diminution in arterial pCO_2. The complete lack of correlation between changes in arterial pressure and CBF indicates that the apparent reduction in CBF is not due to the fall in arterial pressure, as seems to be the case with histamine (22).

Though the effects of priscoline on cerebral metabolic functions are somewhat variable, there is no evidence that priscoline produces cerebral vasodilatation. The ineffectiveness of the sympathetic blocking effect of priscoline on cerebral circulation could have been anticipated by the known lack of response of CBF to stellate ganglion block (23, 24).

The apparent clinical effects of priscoline which have been attributed to its action on cerebral circulation or metabolism (13–15) are difficult to explain on the basis of the results obtained in this study. It would seem that such doses of prisco-

line are actually prejudicial to CBF and that the drug should be used with caution in cerebral vascular disease. Although in none of our subjects was there reason to suspect acute cerebral vascular changes which might have been reversed by a vasodilating agent, most of these subjects were in the age group in which "subclinical" cerebral vascular disease is almost uniformly found (25). Final conclusions concerning the possible efficacy of priscoline in the treatment of cerebral vascular disease must depend upon carefully controlled clinical observations.

SUMMARY

1. Intravenous priscoline, in doses varying from 50 to 100 mgm., administered in 15 to 20 minutes, results in an apparent, though not statistically significant, decrease in CBF, an increase in A–V O_2 and A–V Gl., a slight decrease in mean arterial pressure, a decrease in arterial CO_2 content and arterial pCO_2, a rise in arterial pH, with no alteration in CMR O_2, CMR Gl., CVR, arterial O_2 saturation, arterial pO_2, and cerebral venous pO_2.

2. It is postulated that priscoline produces mild cerebral vasoconstriction and slight hypoxia of brain tissue, though its effects are variable.

3. This study does not offer a satisfactory explanation for the reported beneficial clinical effects of priscoline in the treatment of cerebral vascular disease.

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