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The Effect of Vincamine on the Regional Cerebral Blood Flow in Man

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Abstract. The cerebral hemodynamic action of Vincamine is measured in 17 patients with primary or secondary cerebral circulation disorders, by use of the multiregional ^{133}Xe clearance technique. The statistical analysis of the results justifies the grouping of all the cases and the distinction between reference, ischemic and hyperemic zones by determining for each subject a range of + or −15% of his own mean regional cerebral blood flow.

The drug, in a single injection in the internal carotid artery, shows a significant beneficial hemodynamic effect on the ischemic regions of the brain. No steal phenomenon is recorded in the middle cerebral artery territory.

The action of the drug leads to a decrease and an equalization of the hemodynamic resistances of the cerebral vascular bed.

Introduction

It is a somewhat intricate problem to assess the cerebral action of vasoactive drugs in man. This is due to several factors, namely the difficulty of using aggressive methods in a conscious individual, the complexity of the cerebral vascular bed, formed by areas which may show different sensitivities to a drug, and finally the fact that the blood flow perfusing a region of the brain depends not only on local vascular conditions, but also of the level of hemodynamic resistance in the neighboring areas (*McHenry et al.*, 1970; *Olesen and Paulson*, 1971). The variety of pathological conditions also increase the difficulty.

The technique using ^{133}Xe for the measurement of the regional cerebral blood flow (rCBF), makes it possible to solve some of these problems; this method is used here for studying the cerebral hemodynamic effects of Vincamine, a synthetic alkaloid of Vinca minor (*Scheindlin*, 1955; *Kuehne*, 1964).

Material and Method

The study concerns 17 patients with neurological affections accompanied by cerebral circulatory dis-

Table I. Cases, with diagnosis and side of the study of rCBF

Case No.	Sex	Age	Diagnosis	Studied hemisphere
1	F	65	right hemisphere cerebral infarct	right
2	M	53	left hemisphere cerebral infarct	left
3	F	35	left hemisphere cerebral infarct	left
4	F	45	left hemisphere cerebral infarct	left
5	F	37	right hemisphere cerebral infarct	right
6	M	38	right hemisphere cerebral infarct	right
7	F	59	atherosclerotic dementia	right
8	M	59	atherosclerotic dementia	right
9	F	52	diffuse cerebral atrophy	left
10	M	58	diffuse cerebral atrophy	left
11	F	42	diffuse atherosclerosis	right
12	M	68	atherosclerotic dementia	left
13	M	17	posthemorrhage hydrocephalus	left
14	F	68	normal pressure hydrocephalus	left
15	F	62	normal pressure hydrocephalus	left
16	F	57	normal pressure hydrocephalus	left
17	M	54	right hemisphere cerebral infarct	right

orders (table I). The cerebral infarcts under concern are 1 week to 1 month old. All the cases of normal pressure hydrocephalus are surgically derived and clinically stabilized.

Following a local anesthesia without any vasoconstrictive substance, an internal carotid artery is catheterized from the common carotid. The patient receives no premedication and remains in dorsal decubitus, in a quiet environment with shaded lights, during the entire procedure.

After injection of 5 mCi ^{133}Xe in 1 ml saline through the catheter, the radioactivity of the corresponding cerebral hemisphere is detected by a scinticamera and recorded by successive 2-sec countings for 20 min, with a Tridac-Multi 8 Intertechnique device. 20–32 zones of interest are index-outlined on the scintigraphic projection of the hemisphere. The Xe desaturation curves of each region are reconstituted and analyzed according to the bicompartmental model (*Lassen and Ingvar,* 1961; *Glass and Harper,* 1963; *Lassen et al.,* 1963), with computation of the flows of both compartments, fast and slow, for each region (*Depresseux et al.,* 1976).

Measurements are made twice in each patient: prior to any treatment, and 5 min after the injection of 5 mg Vincamine (Pervincamine Dausse) into the internal carotid of the cerebral hemisphere concerned.

The stability of operational conditions is ensured by repeated measurements of the arterial blood pressure and of the arterial partial pressure in CO_2 at the beginning of both tests. A patient (case No. 17) whose arterial partial pressure in CO_2 varied during the test, is eliminated from the analysis of the results. The arterial partial pressure values in CO_2 of the other patients are 38.1 ± 0.1 mm Hg.

Results

The analysis of the results bears only on the rCBF of the fast compartment. This value is indeed the most representative component of the superficial blood flow of the cerebral convexity and it is the less liable to methodological incertainty.

The classical weighted arithmetic mean of the fast and slow flows was rejected: indeed,

the main weighting factor between the cortical grey and the superficial white substances is mainly linked to the uneven detection geometry of both compartments and, as such, is devoid of physiological significance (*Depresseux,* 1972).

The CBF of the slow compartment was not considered in the statistical study because of the lack of precision of its measurement due to the fact that many regional curves of Xe activity assume a monoexponential profile after Vincamine. It is presumable that, in these occurrences, rCBF slow = rCBF fast, but nothing permits to exclude that rCBF slow = 0.

Accuracy of the Method

The precision of the method was tested: two measurements of rCBF are performed in the same subject in stable psychophysiological conditions, without any intercurrent injection of drug and without any alteration in MABP nor in $paCO_2$; they show differences between paired rCBF that are normally distributed; the expectation of these differences does not differ significantly from zero (mean difference = −0.19 ml/min·100 g; 95% confidence limits of the mean = −0.49 and + 0.89 ml/min·100 g).

Mode of Grouping of the Results for the Analysis

The differences between paired values of rCBF, before and after the injection of Vincamine, are widely dispersed in each subject and from one case to another.

The statistical analysis is performed on the basis of the hypothesis that this dispersion may be partially linked to disturbances in the regional distribution of blood and/or to the diversity of the pathological conditions of the different patients.

On the one hand, three kinds of regions are distinguished in each patient, as *reference, ischemic* and *hyperemic* zones. On the other hand, the subjects are partitioned into the 3 subgroups of cerebral *infarcts* (6 cases), *dementia* (6 cases) and *hydrocephalus* (4 cases).

The mode of distinction between reference, ischemic and hyperemic zones is based on the fact that most of the hemispheric rCBF of a normal subject at rest lie between + or −15% of his own mean rCBF. The interval of ± 15% is about 2 times the coefficient of variation.

The individual mean rCBF of each patient is chosen as a reference for this classification to take into account that, in pathological cases, diffuse alterations of the flow, owing for instance to a lowered consciousness level or to a loss of autoregulation, are superimposed to the alterations in distribution. So the pattern of distribution of rCBF of each subject was analyzed by the distinction of the following areas (*Kohlmeyer,* 1973): (1) the reference areas, in which the flow is situated in an interval of 15% on either side of the mean rCBF of the patient; (2) the ischemic areas, in which the blood flow is less than 85% of the mean rCBF of the patient; (3) the hyperemic areas, in which the flow is higher than 115% of the average flow. Of course, this hyperemia may only be relative, since it is conventionally defined in relation to a reference flow which is that of the patient and which, as such, can be decreased. Table II shows an example of the rCBF in 1 case (No. 16).

The regions in which rCBF was determined are thus distributed into nine classes (table III). The first purpose of the statistical analysis is to test if this empirical distinction is suitable and to try to reduce the number of classes in the study of the effect of Vincamine on CBF.

The distributions of the differences between the paired values of rCBF before and after Vincamine may be considered as Gaussian-like for the ischemic, hyperemic and reference

Table II. Example of values of rCBF fast, in ml/min·100 g, before (F_1) and after (F_2) intracarotid injection of Vincamine, in case No. 16

Hyperemic zones			Reference zones			Ischemic zones		
F_1	F_2	d	F_1	F_2	d	F_1	F_2	d
71	41	−30	47	43	−4	43	57	+ 14
83	73	−10	59	59	0	36	51	+ 15
79	71	−8	58	69	+ 11	43	66	+ 23
63	59	−4	51	67	+ 16	41	64	+ 23
69	69	0	59	75	+ 16	39	63	+ 24
70	71	+ 1	51	69	+ 18	41	71	+ 30
73	74	+ 1	53	73	+ 20	40	74	+ 34
65	74	+ 9	53	73	+ 20	37	72	+ 35
						42	79	+ 37
						31	71	+ 40
n		8			8			10
$\bar{d}$		−5.1			+ 12.1			+ 27.5
s_d		11.7			9.2			9.1

The zones are grouped in hyperemic, reference and ischemic areas by setting a range of +/− 15% on each side of the mean rCBF of the patient (53.7 ml/min·100 g). The differences d are $F_2 - F_1$.

Table III. The nine subgroups of rCBF values as defined following the diagnostic criteria and the distinction between ischemic, reference and hyperemic zones

		Infarcts	Dementia	Hydrocephalus	Total
Ischemic zones	n	39	27	24	90
	$\bar{d}$	22.3	26.5	33.8	
	s_d	2.8	4.6	5.4	
Reference zones	n	83	78	58	219
	$\bar{d}$	5.1	14.7	12.6	
	s_d	1.3	2.0	3.0	
Hyperemic zones	n	37	34	15	86
	$\bar{d}$	−3.9	1.1	−10.7	
	s_d	2.9	3	6.8	
Total	n	159	139	97	395

n = Number of zones; $\bar{d}$ = mean difference rCBF after Vincamine minus rCBF before Vincamine, in ml/min·100 g; s_d = standard deviation of the mean $\bar{d}$.

Table IV. The comparison between the rCBF fast prior to and following the intracarotid injection of 5 mg Vincamine: reference and relatively ischemic and hyperemic values are separately considered

	Ischemic zones	Reference zones	Hyperemic zones
Mean rCBF before Vincamine (1) (ml/min·100 g)	32.6	50.0	64.6
Mean rCBF after Vincamine (2) (ml/min·100 g)	59.2	60.5	61.5
Mean difference (2) – (1) (ml/min·100 g)	+ 26.6	+ 10.5	– 3.1
Number of regions	90	219	86
t test of paired data	t = 11.20	t = 8.71	t = – 1.49
Significance	$p < 0.001$	$p < 0.001$	no

areas, in each subject (Rankits method). For each of the 3 zones of 1 diagnostic group, the analysis of variance shows no statistically significant differences between subjects in each group. Another analysis of variance reveals no significant differences between the 3 subgroups of infarcts, dementias and hydrocephalus.

On the other side, a very significant difference (F = 28.2, DF: 2 and 40) appears between the dispersion inter and the dispersion intra when the analysis is performed between the reference, the ischemic and the hyperemic areas, all the cases being grouped.

This preliminary statistical study justifies to maintain the distinction between reference, ischemic and hyperemic areas, as defined previously, and to group all the subjects in the application of the t test to the paired differences of rCBF.

Statistical Comparison Between CBF Before and After Vincamine

The comparatively ischemic zones show an important enhancement of flow after Vincamine (mean difference $\bar{d}$ = + 26.6 ml/min·100 g), and this increase is highly significant (see the t test, table IV). The confidence limits at 95% of the mean difference are 22.0 and 31.2 ml/min·100 g.

The same comparison with regard to reference zones also shows a significant flow increase, but its average amplitude is less than that of ischemic zones, with a mean value $\bar{d}$ = 10.5 ml/min·100 g and a 95% confidence interval from 8.1 to 12.8 ml/min·100 g. Lastly, the relatively hyperemic zones show no significant variation of rCBF.

The examination of the individual values of rCBF shows no regional steal phenomenon to the prejudice of the ischemic zones, which might have been concealed by only considering the mean flows. On the contrary, the mean flow of the relatively hyperemic zones shows widely varying modifications after Vincamine in each patient, and it appears difficult to correlate these differences with any clinical feature.

The Action of Vincamine on the Hyperemic Zones

In view to elaborate a model permitting to account for the wide variation of comportment of the relatively hyperemic zones, a comparison is performed between the mean individual rCBF

values after Vincamine, respectively in these hyperemic zones (1) and in the remainder of the hemisphere (2). The paired differences of CBF (2) – (1) have Gaussian distribution (Rankits method), with a mean value not diverging significantly from zero (t = –0.07, DF = 14). In the same way, the differences between the rCBF of the ischemic and reference areas are not significant (t = 1.78, DF = 14).

The rCBF tend thus to equalize after the injection of Vincamine (fig. 1). This redistribution effect is presumably the result of a decrease and of an equalization of the cerebral hemodynamic resistances under the action of Vincamine.

The Action of Intracarotid Vincamine on the Occipital Region

Moreover, this study stresses a general methodological difficulty which may occur in these pharmacological studies using an intracarotid administration of drug. If the distribution of the rCBF in each patient is considered, the flow increase following an injection of Vincamine is not so marked in the posterior

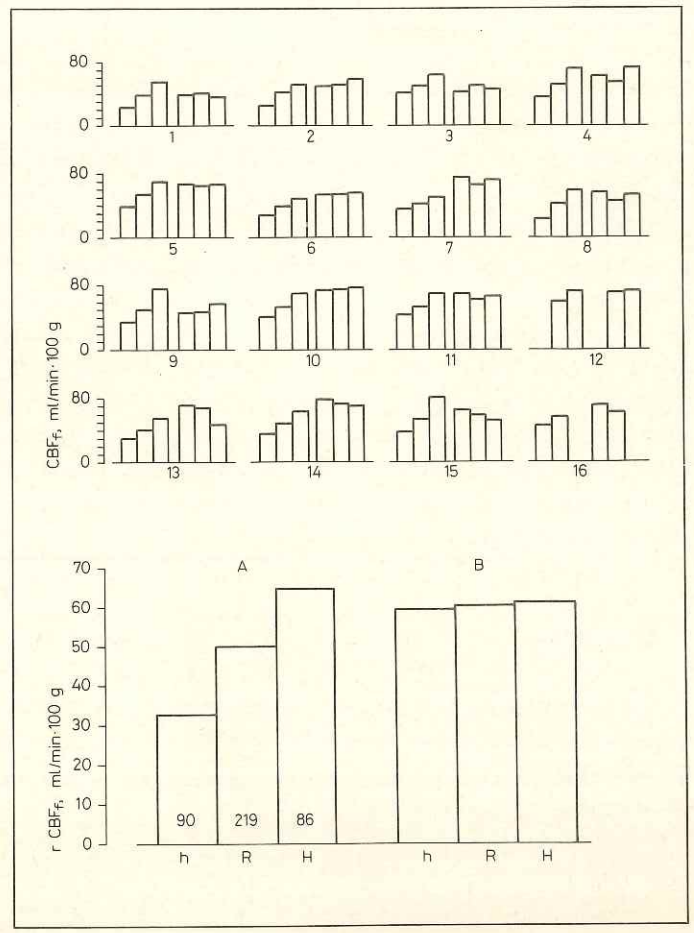

Fig. 1. The individual and global values of the mean rCBF fast of the reference (R), ischemic (h) and hyperemic (H) zones, before (A) and after (B) the intracarotid injection of 5 mg Vincamine: the hyperemic value tends to equalize with the two other values.

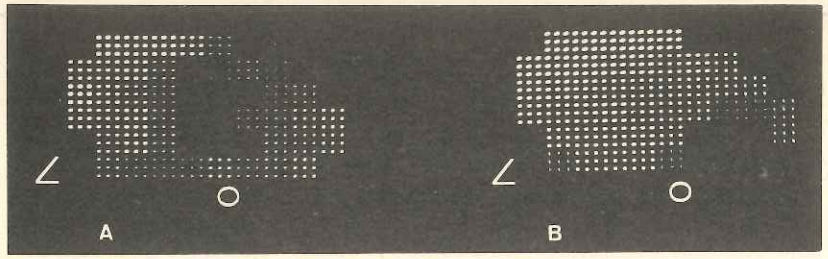

Fig. 2. Brilliance representation of the left rCBF of patient No. 1 before (A) and after (B) the intracarotid injection of 5 mg Vincamine.

and occipitotemporal regions as in the anterior regions. In some cases, there may even occur an intracerebral steal phenomenon at the expense of the former regions. Figure 2 shows a particularly striking example of such a modification of the cerebral perfusion. This disturbance in blood distribution may be related to a lower concentration of Vincamine in these regions, due to the elective carotid mode of injection used for this study. Of the methods used for studying the effect of drugs on the cerebral flow, those which involve an elective carotid injection of the substance, have therefore the advantage of decreasing systemic vascular effects, but do have the drawback of not ensuring a homogenous concentration of the drug in all the cerebral hemisphere under study, thus making it difficult to establish any dose-effect relation.

Conclusion

This investigation objectivates the action of a single injection of 5 mg Vincamine into the internal carotid artery on the blood flow of the corresponding cerebral hemisphere in patients who have primary or secondary cerebral circulatory disorders.

A preliminary statistical study permits to clear up the apparent diversity of response to Vincamine of the cerebral zones under study. The cases with the different diagnosis of cerebral infarcts, dementia and hydrocephalus may be grouped for the analysis of the results, and the distinction between reference, ischemic and hyperemic zones before Vincamine reveals a very useful procedure.

In the conditions of this study, Vincamine increases the regional flows in the zones which, initially, are most ischemic; this increase is very significant and is observed in all individual cases. On the other hand, no characteristic steal phenomenon from the ischemic zones was registered.

The enhancing effect on the perfusion is also significant for higher flows, close to normal values, but its average amplitude is lower.

The action of the drug on the blood flow of the relatively hyperemic zones varies widely with each case, but the statistical study reveals that the flow of the previously hyperemic zones tends to become equal to the remainder of the cerebral hemisphere. As a conclusion of this study, it may be stated that Vincamine induces a decrease and an equalization of the hemodynamic resistances of the cerebral vascular bed.

As there was no intercurrent modification in the gas content of the arterial blood, or any variation in arterial blood pressure, the modifications in cerebral blood flow may therefore be interpreted as the result of the vasomotor effect or of the local metabolic action of the drug.

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References

Depresseux, J.C.: Principes généraux de la mesure de débits d'organe par radio-isotopes. Application à l'étude du débit sanguin cérébral. Nucl. Med. *11:* 101–131 (1972).

Depresseux, J.C.; Merchie, G.; Champarnaux, J.F., and Haglund, M.E.: Description of a computer program for the determination of regional cerebral blood flow. Int. J. biomed. Comput. *7:* 241–249 (1976).

Glass, H.I. and Harper, A.M.: Measurement of regional blood flow in cerebral cortex of man through intact skull. Br. med. J. *i:* 593 (1963).

Kohlmeyer, K.: Messungen der regionalen Hirndurchblutung mit Xenon 133 vor und nach intravenöser Verabfolgung verschiedener sogenannter vasoaktiver und zerebralstoffwechselaktiver Pharmaka im Akutversuch. Verh. dt. Ges. KreislForsch. *39:* 95–101 (1973).

Kuehne, M.E.: The total synthesis of Vincamine. J. Am. chem. Soc. *86:* 2946 (1964).

Lassen, N.A.; Hoedt-Rasmussen, K.; Sørensen, S.C.; Skinkøj, E.; Cronquist, S.; Bodforss, B., and Ingvar, D.H.: Regional cerebral blood flow in man determined by krypton 85. Neurology *13:* 719–731 (1963).

Lassen, N.A. and Ingvar, D.H.: Blood flow of the cerebral cortex determined by radioactive krypton 85. Experientia *17:* 42–43 (1961).

McHenry, L.C.; Jaffe, M.E.; Kawamura, J., and Goldberg, H.I.: Effect of papaverine on regional blood flow in focal vascular disease of the brain. New Engl. J. Med. *282:* 1167–1170 (1970).

Olesen, J. and Paulson, O.B.: The effect of intraarterial papaverine on regional blood flow in patients with stroke or intracranial tumors. Stroke *2:* 148–159 (1971).

Scheindlin, S.: Isolation of an alkaloid from Vinca minor. J. Am. pharm. Ass. *44:* 331 (1955).

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