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Pharmacokinetics of vinpocetine and its metabolite, apovincaminic acid, in plasma and cerebrospinal fluid after intravenous infusion

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Abstract: The pharmacokinetics of vinpocetine (ethyl apovincaminate, Cavinton) and its metabolite, apovincaminic acid, was studied in patients with cerebrovascular disorders. Vinpocetine (1 mg/kg) was infused intravenously over 25 min. The elimination half-life of the parent drug in plasma was 4.7±2.13 h. Total clearance of vinpocetine was 0.79±0.1 l h^{-1} kg^{-1}. The presence of vinpocetine in cerebrospinal fluid shows that the drug is able to pass through the blood–brain barrier and reach the central nervous system which is a possible site of action. The maximum increase of cerebral blood flow (25%) was measured at 32 min after the start of the infusion.

Keywords: *Vinpocetine; apovincaminic acid; pharmacokinetics in patients; cerebrospinal fluid; cerebral blood flow.*

Introduction

Vinpocetine (ethyl apovincaminate, Cavinton) is a new drug applied with success in the treatment of cerebrovascular disorders. Results of earlier studies on the pharmacological behaviour of the drug have been summarized [1]. It was shown that vinpocetine dilates cerebral blood vessels, increases cerebral blood flow (CBF), improves cerebral utilization of oxygen, inhibits phosphodiesterase and inhibits uptake of adenosine into erythrocytes. Since vascular and cerebral monoaminergic systems are thought to play an important role in the regulation of CBF, biological experiments were carried out to obtain information on the effect of vinpocetine on these systems [2]. It was found that vinpocetine accelerates the turnover of cerebral noradrenaline; hence noradrenergic mechanisms may have a role in mediation of the vascular or neural or both effects of the drug.

The pharmacokinetics of the drug in healthy volunteers after oral and bolus intravenous administration have been studied previously [3, 4]. The aim of the present study was to obtain information on the ability of vinpocetine to pass through the blood–brain barrier and reach the central nervous system (CNS), which is a possible site

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of action. The next task was to determine the profile of the concentration–time curves of vinpocetine in plasma and in cerebrospinal fluid (CSF) after intravenous infusion and establish whether there was any correlation between the magnitude of the effect of the drug on the CBF and the concentration of the drug in plasma and CSF.

Studies on the metabolism [5] and kinetics [6] of vinpocetine in the rat and a preliminary study of human plasma samples [7] showed that the parent drug is extensively metabolized in both species and that apovincaminic acid (AVA) is one of the main metabolites. As AVA itself is thought to have vasodilator activity [5] its concentrations in plasma and CSF were also determined.

Since the treatment of cerebrovascular disease is the main application of vinpocetine, the present study was carried out on patients with this type of disorder.

Experimental

One female (No. 5) and 11 male patients were selected for the study. Either stenosis or occlusion of the internal carotid arteries was demonstrated in all cases. The ages of the patients were 35–56 years and their weights were 60–100 kg. A 100 ml volume of physiological saline containing vinpocetine in a concentration to give a dose of 1 mg/kg was administered at 4 ml/min.

CBF was monitored in patients Nos 1–9 by the ^{133}Xe inhalation method described by Obrist *et al.* [8] and previously applied in measuring the effect of vinpocetine [9]. Two or three control measurements were carried out before administration of the intravenous infusion. ^{133}Xe was inhaled for 1 min and a subsequent 10 min washout of the tracer was monitored by two large collimated detectors placed over the fronto-temporal and parietal regions on each side of the head. The first CBF assessment was performed 10 min after the start of the infusion and was followed by two consecutive measurements at times recorded in Table 4.

In addition, blood samples (4.5 ml) for full pharmacokinetic studies were taken from patients Nos 1–6 after 5, 10, 20, 25, 30, 45, 60 and 90 min and 2, 3, 4, 8, 10, 12 and 24 h from the start of the infusion. An aliquot of 0.5 ml of a solution of sodium citrate (3.8% m/m) and sodium fluoride (1% m/m) was used for each sample as an anticoagulant and esterase inhibitor.

Both CSF and blood samples were obtained from patients Nos 10 and 11 at the times mentioned above up to 1 or 1.5 h from the start of the infusion. In one case (No. 12) CSF and blood were only drawn at 45 min. Because of technical difficulties CBF was not measured in these three cases.

The concentrations of vinpocetine and AVA in plasma and CSF were measured by the gas–liquid chromatographic (GLC) methods published previously [7, 10]. In the second part of the work where concentrations of vinpocetine and AVA in CSF were measured, these methods were slightly modified; i.e. 0.2 M KOH was used for pH adjustment instead of glycine–NaOH buffer. This modification resulted in purer samples, in improvement of sensitivity and hence in an increase of the reliability of the assay of samples that contained vinpocetine in low concentrations.

Results from the GLC assay were subjected to mathematical analysis on a TPA 1140 digital computer (Central Research Institute for Physics, Hungarian Academy of Sciences). The work of Wagner [11] on clinical pharmacokinetics was used as a guide in this part of the study. The post-infusion part of the graphs of plasma concentration of vinpocetine against time can be described by a multiexponential function:

$$C_{(t)} = \Sigma C_n e^{-\lambda_n(t-t_i)}$$

where t_i is the time of duration of the infusion (25 min) and n is the number of exponentials involved. Both di- and triphasic approaches were tried. Back projection (by the stripping technique) was used for the estimation of C_n and λ_n values.

The rate constant of the terminal disposition phase (λ) for AVA was calculated from the slope of the regression line fitted to the last three or four measured points of the semi-logarithmic graphs of plasma concentration against time.

The total plasma clearance (CL) was calculated as the Dose/$AUC^{0-\infty}$ ratio, where $AUC^{0-\infty}$ is the total area under the graph of plasma concentration against time. The $AUC^{0-\infty}$ of vinpocetine was calculated by application of the trapezoidal rule for the period of the duration of the infusion and by integration of the triexponential expression from zero to infinity for the post-infusion period. The $AUC^{0-\infty}$ for AVA was calculated by application of the trapezoidal rule up to the last measured point and then by extrapolation to infinity.

The apparent volume of distribution (V_d) was obtained from the $CL/\lambda_{terminal}$ ratio, and the half-life was calculated from the equation $t_{1/2} = 1n2/\lambda$.

Results

The pharmacokinetic curves of vinpocetine and AVA obtained from eight patients are shown in Figs 1, 2 and 4. In seven out of eight cases, where the blood samples were pooled immediately after the end of the infusion, measured concentrations at 25 min were about 10–15% lower than those measured at 20 min. No fall in concentration at 25 min was experienced in the eighth case (Fig. 4B), where the end of blood sampling at 25 min coincided with the end of the infusion. To diminish the consequences of this experimental error in the calculations it was assumed that $C_{t=25} = C_{t=20}$.

The RMS values (root mean square) for the di- and triexponential approaches are shown in Table 1. Since the RMS values for the triexponential expression are better and because previous studies [3, 6] showed that the 'first-pass' effect plays an important role in the metabolism of vinpocetine, it was decided to apply the 'first-pass' three compartment open model of Fig. 3 [11]. The model parameters and the pharmacokinetic characteristics of vinpocetine are summarized in Table 2. With these parameters the theoretical C_t values for the infusion part of the graphs of plasma concentration against time were calculated; the RMS data for measured and calculated values are shown in Table 1.

Table 3 shows the pharmacokinetic parameters calculated for AVA. Previous study of the metabolism of vinpocetine on healthy volunteers [4] showed that 30.2±10.4% of the dose is converted to AVA and excreted via the kidney. If the same extent of conversion of vinpocetine to AVA is assumed in the present work, the estimated CL value for AVA is 0.09 1 h^{-1} kg^{-1}.

Figure 4 illustrates the concentrations of vinpocetine and AVA in plasma and CSF of two patients. The peak concentration of vinpocetine in CSF (5.7 ng/ml in patient No. 4 and 3.9 ng/ml in No. 11) was measured 30 min after the start of the infusion. A concentration of 3.6 ng/ml of vinpocetine and 5 ng/ml of AVA was found in the single CSF sample from patient No. 12 at 45 min. The elimination half-life of vinpocetine in the CSF was 35 min in patient No. 10 and 70 min in patient No. 11.

Table 4 shows the CSF:plasma concentration ratios of vinpocetine and AVA. Within

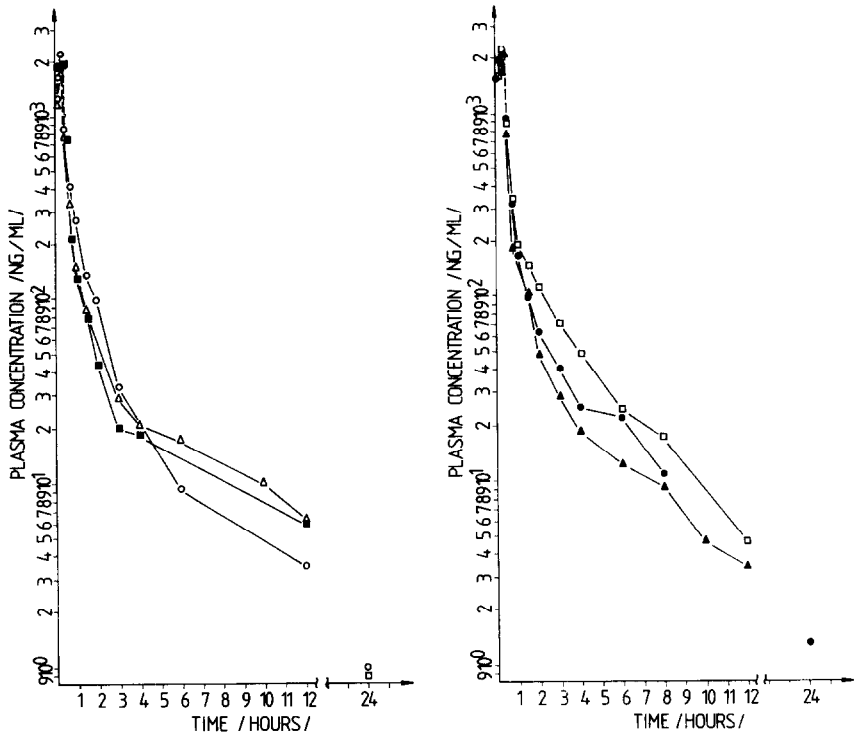

Figure 1
Graphs of plasma concentration of vinpocetine against time after 25 min intravenous infusion at a dose of 1 mg/kg. Patients: No. 1, ○; No. 2, △; No. 3, ■; No. 4, ●; No. 5, ▲; No. 6, □.

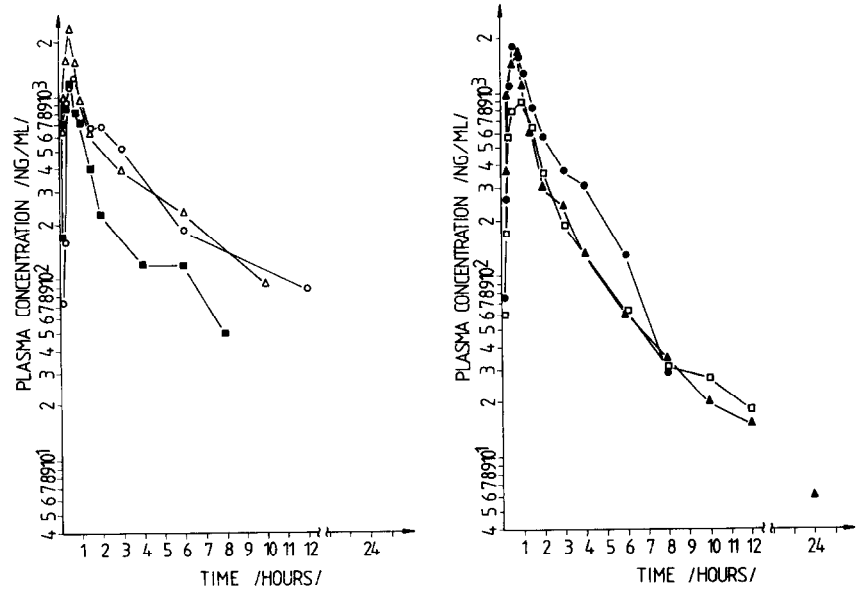

Figure 2
Graphs of plasma concentration of AVA against time after 25 min intravenous infusion of vinpocetine at a dose of 1 mg/kg. Patients: No. 1, ○; No. 2, △; No. 3, ■; No. 4, ●; No. 5, ▲; No. 6, □.

Table 1
Root mean square values for biexponential (n = 2) and triexponential (n = 3) curve fittings

Subject	Post-infusion part $n = 2$	Post-infusion part $n = 3$	Infusion part $n = 3$
1	338.8	43.1	284.5
2	204.1	66.7	282.8
3	128.3	14.5	685.0
4	196.6	65.0	285.5
5	104.5	10.3	94.2
6	141.8	76.9	241.5

Table 2
First-pass three-compartment open model parameters and pharmacokinetic data of vinpocetine

Parameter*	Subject (body weight, kg) 1(100)	2(64)	3(60)	4(70)	5(70)	6(67)	Mean ± S.D.
C_1	1679	1250	1598	1794	1445	1838	1600 ± 222
C_2	547	450	314	310	401	243	377 ± 110
C_3	12	37	31	41	41	132	49 ± 42
λ_1	18.67	15.38	15.13	13.6	16.77	15.30	15.8 ± 1.72
λ_2	1.22	1.88	1.74	1.33	1.79	1.40	1.56 ± 0.276
λ_3	0.08	0.14	0.15	0.15	0.22	0.28	0.17 ± 0.069
$t_{1/2}^{\lambda 1}$	0.037	0.045	0.046	0.051	0.041	0.045	0.044 ± 0.00
$t_{1/2}^{\lambda 2}$	0.57	0.37	0.40	0.52	0.39	0.49	0.456 ± 0.08
$t_{1/2}^{\lambda 3}$	8.6	4.9	4.6	4.6	3.1	2.5	4.71 ± 2.129
k_{20}	1.224	1.836	1.717	1.292	1.771	1.291	1.521 ± 0.28
k_{12}	16.717	12.140	12.526	11.183	14.110	11.555	13.038 ± 2.06
k_{21}	0.886	1.075	0.594	0.519	0.837	0.525	0.739 ± 0.22
k_{13}	1.052	2.168	1.999	1.903	1.797	3.204	2.02 ± 0.696
k_{31}	0.089	0.181	0.183	0.188	0.264	0.412	0.219 ± 0.10
$AUC^{0-\infty}$	1373	1125	1206	1364	1086	1462	1269 ± 151
CL	0.72	0.89	0.83	0.73	0.92	0.68	0.79 ± 0.10
V_d	910	406	331	342	293	160	407 ± 259
V_1	7.26	7.35	5.68	6.57	6.53	5.49	6.48 ± 0.774

* Units: concentration, ng ml^{-1}; rate constant, h^{-1}; half-life, h; AUC, ng h ml^{-1}; CL, l h^{-1} kg^{-1}; V_d and V_1, l; weight, kg.

Table 3
Pharmacokinetic parameters of apovincaminic acid

Parameter*	Subject 1	2	3	4	5	6	Mean ± S.D.
$\lambda_{terminal}$	0.12	0.23	0.15	0.59	0.14	0.19	0.24 ± 0.18
$t_{1/2}$	5.8	3.0	4.6	1.2	5.0	3.6	3.9 ± 1.6
$AUC^{0-\infty}$	4862	4589	2539	3525	2734	2065	3386 ± 1143

* Units: rate constant, h^{-1}; half-life, h; AUC, ng h ml^{-1}.

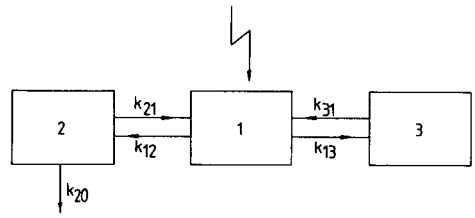

Figure 3
Three-compartment open model.

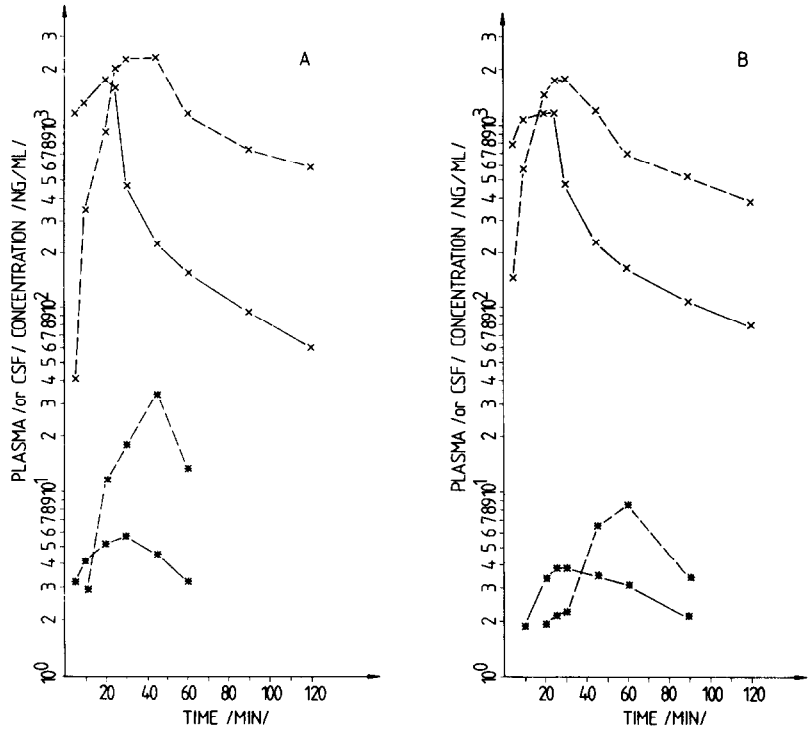

Figure 4
Graphs of concentration against time of: vinpocetine in plasma, —×—; AVA in plasma, --×--; vinpocetine in CSF, —*—; AVA in CSF, --*--; A, patient No. 10; B, patient No. 11.

Table 4
CSF:plasma concentration ratios (%) of vinpocetine (VP) and apovincaminic acid (AVA)

Subject		Time (min)							
		5	10	20	25	30	45	60	90
10	VP	0.28	0.31	0.30	—	1.2	2.0	2.7	
	AVA	—	0.84	1.2	—	1.4	2.6	1.2	
11	VP	—	0.15	0.31	0.34	0.8	1.1	2.0	2.0
	AVA	—	—	0.14	0.12	0.13	0.5	1.2	0.6

the measured interval the plasma concentration changes rapidly and the difference in ratios calculated for different times indicates that plasma–CSF equilibrium has not been attained. Nevertheless the ratios are highly in favour of plasma and in all cases the CSF concentration is less than 3% of the corresponding plasma concentration.

Table 5 presents the control CBF values of nine patients and the CBF values measured at three different times after the start of the vinpocetine infusion. Maximum increase of CBF (25%) was measured at 32 min. This time agrees quite well with the time of maximum vinpocetine concentration in CSF in patients Nos 10 and 11.

Table 5
Cerebral blood flow* (average value for the four regions) after 1 mg/kg infusion of vinpocetin

	Time†			
Subject	Control	10 ± 0.64	32 ± 1.3	62 ± 4.4
1‡	33.9	32.1	42.2	44.0
2‡	33.8	33.8	38.3	37.1
3‡	51.1	47.0	60.0	47.9
4‡	32.3	41.8	42.8	37.0
5‡	48.5	52.1	79.1	—
6‡	41.3	35.2	42.4	42.6
7	30.4	—	43.1	36.7
8	39.9	42.0	43.1	47.1
9	34.4	42.4	49.9	41.1
Mean ± S.D.	38 ± 7.3	40.8 ± 6.8	49.0 ± 12.9	41.7 ± 4.51
P	—	NS	<.005	<0.02

* Units: CBF, ml min^{-1} g^{-1} 100; time, min.
† Time between the onset of the infusion and the start of Xe inhalation.
‡ Patients participating in the pharmacokinetic study.

Discussion

The triphasic decline of the post-infusion part of the pharmacokinetic curve of vinpocetine suggests three distribution phases. The first distribution phase is characterized by a very short half-life (0.044±0.004 h), which is commensurate with the duration of blood sampling. This serves as an explanation for the apparent fall in plasma concentration measured at 25 min.

The elimination half-life was found to be 4.7±2.13 h compared with 3.9±1.6 h and 2.5±0.5 h in previous reports [3, 4].

The CL value of vinpocetine (0.79±0.1 l h^{-1} kg^{-1}) is higher than that (0.366±0.24 l h^{-1} kg^{-1}) found by Vereczkey *et al.* [3], but it is similar to that (0.9±0.2 l h^{-1} kg^{-1}) reported by Polgár and Vereczkey [4]. These high CL values, which exceed several times the normal value of endogenous creatinine clearance (0.1 l h^{-1} kg^{-1} if a body weight of 70 kg is assumed), considered with the amount of AVA detected in plasma and the low amount of drug excreted in unchanged form [4, 12] show that metabolic clearance plays a dominant role. The high V_d value suggests significant binding of vinpocetine to tissues.

Both vinpocetine and AVA can be detected in the CSF. As mentioned by Bonati *et al.* [13] the factors that determine the distribution of a drug in the CNS are: CBF; physicochemical properties of the drug; plasma–protein binding; and modifications of the blood–brain barrier. These criteria were taken into consideration in evaluating the results of the present work.

Vinpocetine is highly lipid soluble. Its partition coefficient (log *P*) is 3.02 in *o*-xylene and water and 3.14 in benzene and water. The pK_a value of the drug is 7.31. The lipophilic character of a molecule allows its penetration through the blood–brain barrier but also promotes its redistribution to fatty tissues [13]. If it is considered that within the CNS a drug is redistributed between the CSF and brain tissue [13], the concentration of vinpocetine in CSF does not give information on the absolute amount of drug found in brain tissue. The only conclusion that can be drawn from this part of the experimental data is that vinpocetine passes through the blood–brain barrier and reaches the CNS.

The pK_a values of AVA are 2.4 and 8.3; hence AVA is ionized over the entire pH range and cannot pass through the biological membranes by passive transport. Yet absorption of AVA from the gastro-intestinal tract of the rat and the dog [14] is evidence for the ability of this substance to pass through the lipid membranes. This phenomenon can be explained if formation of a complex between AVA and a carrier molecule is postulated. On the basis of the present experimental data it is uncertain whether AVA is formed from vinpocetine in the CNS or whether it is transported through the blood–brain barrier.

The high degree of protein binding of vinpocetine can serve as an explanation for the low CSF:plasma concentration ratios. The binding *in vitro* of vinpocetine to human plasma proteins was measured at the authors' request by A. Benakis and his co-workers in the Laboratory of Drug Metabolism, University of Geneva. Protein binding was found to be concentration-dependent and varied from 99.9% at 10 ng/ml to 97.8% at 100 ng/ml and 86.6% at 500 ng/ml.

Since at pH 7.4 about 50% of the drug is in ionized form, the theoretical ratios for CSF:plasma partition are 6.7, 1.1 and 0.5% for plasma concentrations of 500, 100 and 10 mg/ml respectively, provided that the passage of vinpocetine through the biological membranes occurs only by passive transport. The experimental values are in the same range, although these differ from the theoretical values, probably because equilibrium was not attained.

The CSF:plasma ratio of vincamine (5–20%) is higher than that of vinpocetine [15]; this might be due at least in part to differences in the physicochemical properties of the two drugs.

If in patients Nos 10 and 11 CBF results are assumed to be similar to those found in patients Nos 1–9, it can be concluded that there is a good correlation between the amount of drug in the CSF and its effect on the CBF. Although vinpocetine causes a significant increase in CBF the duration of its effect is relatively short. Since clinical experience shows that vinpocetine has a long-term beneficial effect on patients with cerebrovascular disorders [16], it is likely that the influence of the drug on the CBF is only partly responsible for its action and that other mechanisms may be also involved.

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