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Short communication

Omeprazole does not change the oral bioavailability or pharmacokinetics of vinpocetine in rats

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Abstract:
Previous studies proved that food strongly enhanced the bioavailability of vinpocetine. Food may change the pharmacokinetics of a drug by affecting various factors, including gastrointestinal pH. However, the influence of proton pump inhibitor-induced pH alterations on vinpocetine pharmacokinetics is not known.
The aim was to evaluate the influence of omeprazole on the pharmacokinetics of oral vinpocetine.
One group of male Wistar rats received single oral doses of vinpocetine (2 mg/kg – regimen V). In the second group, omeprazole (10 mg/kg) was administered intraperitoneally for 5 days before vinpocetine administration (regimen OV). For analysis of vinpocetine pharmacokinetics, blood samples were obtained before and 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 h after vinpocetine administration. Vinpocetine concentrations were measured by high performance liquid chromatography (HPLC).
The mean values of AUC_{0-t}, AUC_{0-inf} and C_{max} in regimen V were very similar to respective values in regimen OV. The mean T_{max} in both regimens was estimated for 1.5 h. There were no statistically significant differences between both regimens. In conclusion, omeprazole did not affect the pharmacokinetic profile of vinpocetine.

Key words:
vinpocetine, omeprazole, oral bioavailability, rats

Introduction

Vinpocetine is a synthetic derivative of a vincamine alkaloid isolated from Lesser Periwinkle (*Vinca minor*). The mechanism of vinpocetine action is mainly associated with the inhibition of phosphodiesterase 1 (PDE1) and vasodilation. In various types of vascular or degenerative cerebral disorders in humans, vinpocetine acts selectively on tissues of the central nervous system, increasing cerebral metabolism and circulation [10, 14, 15]. However, there is no clear evidence for any beneficial effect of vinpocetine on such

diseases as cerebral stroke, hemorrhage or dementia in Alzheimer's disease.

In humans, vinpocetine is characterized by low bioavailability (7%) following oral administration resulting from poor solubility in aqueous solutions and a significant first-pass effect [21]. Food markedly increases its bioavailability to approximately 60 to 100% [8].

The high prevalence of vascular or degenerative cerebral disorders and common polypharmacotherapy in elderly patients increases the risk of interactions between oral vinpocetine and other drugs. Concomitant medications may alter the rate and extent of vinpocetine absorption, which depends on numerous factors, including pH in the stomach and small intestine. Therefore, pH modifications through ionization of molecules may result in significant changes in absorption of orally administrated substances. Drugs reducing gastric pH may also change the absorption of co-administrated medications, affecting the chelation of drugs or causing changes in gastrointestinal motility, among other effects [19]. The clinical significance of altered drug absorption is ambiguous and may be potentially dangerous [13].

Proton pump inhibitors (PPIs) are currently the most potent agents for reducing gastric acid secretions. They inhibit hydrochloric acid production by proton pumps located in parietal cells of the gastric mucosa [18]. PPIs are widely prescribed as first-line treatment in the prevention and therapy of peptic ulcer and in gastroesophageal reflux disease (GERD). Currently, they are registered in many European countries as over-the-counter (OTC) products and may be used by many patients without the supervision of a physician.

The aim of this study was to evaluate the effect of gastric pH increase caused by a popular PPI, omeprazole, on the absorption and bioavailability of oral vinpocetine in rats.

Materials and Methods

Chemicals, animals and drug administration

Vinpocetine and omeprazole were kindly provided by Biofarm Sp. z o.o., Poland, and Polpharma SA, Poland, respectively. Vinpocetine was dissolved in 5% ascorbic acid solution before administration.

Animals were obtained from the Animal Laboratory of the Department of Pathological Anatomy, Wroclaw Medical University. Twelve male Wistar rats were divided into 2 groups of 6 animals each. Rats were housed individually in chambers with a 12:12 h light-dark cycle and a temperature maintained at 21–23°C with free access to water. Animals were fasted overnight for at least 10 h before vinpocetine administration. The first group received a single oral dose of vinpocetine at 2 mg/kg b.w. (regimen V). In the second group, omeprazole was administered intraperitoneally at a dose of 10 mg/kg b.w. once daily for 5 days prior to vinpocetine administration (regimen OV). Vinpocetine in both groups was administered *via* gastric gavage using a ball-tipped needle. Blood samples (0.2 ml) were collected from the tail or saphenous veins before and 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 h after vinpocetine administration. Samples were centrifuged, and harvested plasma was frozen at –20°C until analysis.

This experiment was approved by the Local Ethics Commission for Experiments on Animals in Wroclaw.

Determination of vinpocetine by HPLC

HPLC analysis was performed on a Dionex UltiMate 3000 instrument with an autosampler (WPS-3000TSL) and a pump (DGP-3600A). Detection was made by a UV-Vis detector (Ultimate 3000). The column was an Acclaim® Mixed-Mode HILIC-1 Column (4.6 × 150 mm, 5 μm analytical column). The gradient had a constant flow rate of 1.0 ml/min with a mobile phase of methanol/0.1 M NH_4OAc (83/17, v/v). The UV wavelength monitored was 274 nm.

Extraction procedure

Vinpocetine from plasma samples was extracted by vortex with cyclohexane (1 ml). The extraction procedure was performed in triplicate. Collected organic solvent (3 ml) was evaporated under nitrogen, and 0.1 ml of methanol (HPLC grade) was added. This sample was submitted to HPLC analysis. For calibration, 20 μl of vinpocetine solution was injected into the HPLC column.

A calibration curve for the investigated compound was calculated from the area values obtained by injecting 20-μl methanol solutions of vinpocetine (0.015–0.39 μg). Seven different concentrations were prepared as standards. Injection was performed in

triplicate for every standard mixture. The relationship of peak area to concentration of the analyte resulted in an excellent linearity with a high correlation coefficient (R^2 = 0.9998) in the concentration range under investigation.

The precision of the determination was tested by repetitive injection (n = 6) of a mixture of vinpocetine at the concentrations listed above. The results indicated relative standard deviations (RSD) between 0.6 and 1.7%.

Pharmacokinetic parameters

Pharmacokinetic parameters of vinpocetine were calculated based on non-compartmental analysis using the Topfit software package (Gustaw Fisher, Stuttgart, Germany, 1993). C_{max} and T_{max} were directly derived from the observed plasma concentrations. The total area under the curve (AUC_{0-inf}) was estimated by the trapezoidal rule with extrapolation to infinity using C_n/k_e, where C_n is the last measurable concentration and k_e is the elimination rate constant calculated by the terminal linear segment of the log of plasma concentration-time data. The elimination half-life ($T_{0.5}$) was calculated from ln $2/k_e$. Plasma drug clearance (Cl) was estimated by dividing the dose (D) of vinpocetine by AUC_{0-inf}, and the volume of distribution (V) was calculated from D/k_e AUC_{0-inf}. The mean residence time (MRT) was obtained from the formula AUMC/AUC (AUMC – area under the concentration × time curve).

Statistical analysis

Data were expressed as the mean ± standard deviation (SD). The statistical analysis was done using Student's *t*-test. Hypotheses were considered positively verified if $p < 0.05$. Statistica 8.0 software was used for this study.

Results

The pharmacokinetic parameters of vinpocetine in both investigated regimens are presented in Table 1. The mean plasma concentration-time profiles following the single administration of vinpocetine alone (regimen V) and after pre-treatment with omeprazole (regimen OV) were similar in both groups (Fig. 1). Based on non-compartmental analysis, the AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} showed no statistically significant differences (p = NS in all cases), demonstrating no influence of omeprazole and subsequent change in gastric pH on the bioavailability of vinpocetine. T_{max} after oral vinpocetine dosing was also not significantly changed when omeprazole was pre-administered, indicating no difference in the rate of vinpocetine absorption.

Discussion

Vinpocetine influences brain circulation and oxygen utilization without changing systemic circulation, increases the tolerance of the brain to vascular hypoxia and ischemia, has an anticonvulsant effect, inhibits phosphodiesterase-1 and decreases platelet aggregation and blood viscosity. However, despite its numerous *in vitro* and *in vivo* activities, vinpocetine, in general, is best known in clinical practice for its neuroprotective effects.

Vinpocetine appears to follow linear pharmacokinetics [11, 16]. After oral administration, it is readily absorbed from the gastrointestinal tract and reaches maximal concentration after 1–1.5 h [22]. However, one of the main disadvantages of this poorly water-soluble drug is its low bioavailability, not exceeding 7% in humans [5, 16]. This is significantly lower than the 50% bioavailability seen in rats [23, 27].

Low intestinal absorption of vinpocetine prompted research [1, 26] into modified oral pharmaceutical preparations and delivery systems of vinpocetine that would increase its bioavailability. These formulations remarkably improved oral bioavailability of vinpocetine, from 1.72 [1] to 3.5 times [26] higher than a crude powder suspension.

The effects of food and alimentary tract pH-altering substances on the bioavailability of vinpocetine is reported in non-clinical and clinical studies on small groups of subjects. In a pilot study, Lohmann et al. investigated the relative oral bioavailability of 10 mg tablets of vinpocetine in 8 healthy volunteers in relation to food intake and found that the drug bioavailability under non-fasting conditions was approximately 60 to 100% higher than when it was given on an empty stomach. Food had no effect on the absorption rate of vinpocetine, however, and the maximum serum concentration was observed 60 min after oral

Tab. 1. The mean ± SD pharmacokinetic parameters of vinpocetine

Pharmacokinetic parameters	Regimen	
	V (vinpocetine alone)	OV (vinpocetine + omeprazole)
C_{max} (ng/ml)	135.33 ± 11.71	149.0 ± 13.87
T_{max} (h)	1.50 ± 0.0	1.50 ± 0.0
$T_{0.5}$ (h)	1.73 ± 0.5	1.78 ± 0.27
MRT (h)	3.62 ± 0.21	3.35 ± 0.2*
AUC_{0-t} (ng h/ml)	504.03 ± 57.28	483.47 ± 42.40
AUC_{0-inf} (ng h/ml)	524.60 ± 56.67	499.52 ± 43.64
AUC_r (% AUC_{0-inf})	3.95 ± 2.45	3.20 ± 1.73
Cl (ml/min)	37.03 ± 4.73	39.07 ± 5.09
Cl (ml/min/kg)	80.43 ± 8.92	84.05 ± 6.67
V (l)	5.60 ± 1.55	6.02 ± 1.14
V (l/kg)	12.25 ± 3.53	12.97 ± 2.11

* $p < 0.05$ comparing regimen V with regimen OV (n = 6)

administration, regardless of the food and the medication dose [8]. Thus, it has been recommended that vinpocetine be taken with or after meals.

Food may affect drug pharmacokinetics by altering bile flow, splanchnic blood flow, gastrointestinal pH and gastric emptying and through physical/chemical interactions with the drugs [2, 4, 6]. The pH value in the alimentary tract is one of the crucial factors for drug absorption and can vary significantly with the use of antacids, H_2-receptor blockers or PPIs. Alterations in solubility and ionization of active compounds caused by pH changes play a large role in the absorption of orally administered drugs. In the case of weak bases, such as vinpocetine, enhanced gastric pH increases the volume of the unionized form of the drug and theoretically should increase its absorption. Thus, medications increasing gastric pH may also be of significance for absorption of co-administered drugs [19].

The results of another study by Lohmann et al. [9] showed that magnesium-aluminum hydroxides gel had no influence on the intestinal absorption of vinpocetine in 18 healthy subjects. No differences in AUC, C_{max}, T_{max}, and MRT of vinpocetine were demonstrated. This was surprising, as magnesium hydroxide

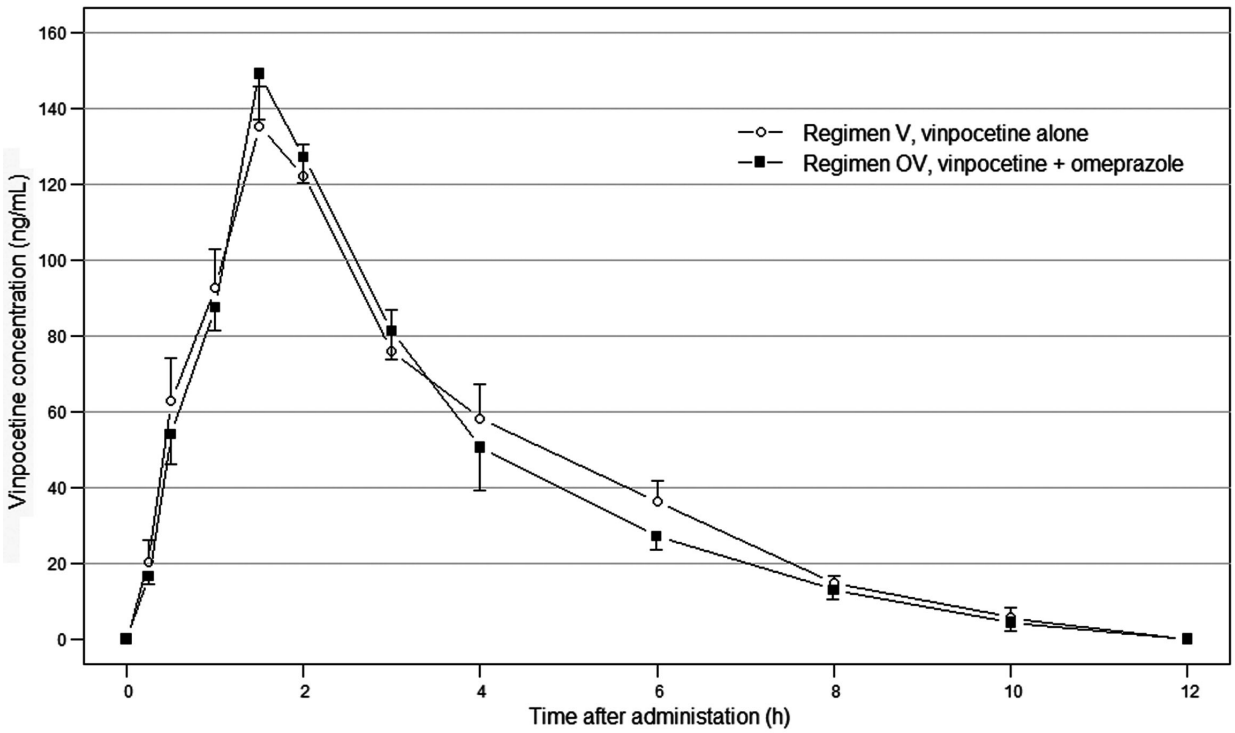

Fig. 1. The mean ± SD plasma vinpocetine concentration following single oral administration at a dose of 2 mg/kg b.w. alone (Regimen V) or with pre-treatment with omeprazole administered intraperitoneally at a dose of 10 mg/kg b.w. once daily for five days (Regimen OV)

and aluminum hydroxide may alter the rate and even the extent of drug absorption by increasing gastrointestinal pH [17]. However, it must be considered that antacids act directly within the gastric lumen, and their interactions with other concomitantly ingested drugs may also involve physicochemical interactions, alterations in gastrointestinal motility or effects on carriers and membrane bound enzymes [13, 19]. Furthermore, chelate formations may be involved in the increased absorption of some drugs in the presence of magnesium hydroxide [19].

Omeprazole belongs to the PPI family of drugs and strongly suppresses gastric acid secretion by specific inhibition of the H^+/K^+ ATPase enzyme system at the secretory surface of the gastric parietal cells [3]. Previous studies demonstrated that increases in gastric pH have been shown to affect the absorption of other concomitantly administered drugs following the initiation of omeprazole therapy, especially the absorption of poorly soluble substances and medicines characterized by pH-sensitive solubility [20]. In our experiment, omeprazole was administered for five consecutive days because maximum gastric acid suppression is reliably achieved only after multiple doses [25].

Earlier results [8] lead to a hypothesis that omeprazole, like food intake, may change vinpocetine bioavailability. However, the results of pharmacokinetic parameters assessed in our study clearly showed that the rate and extent of absorption of orally administrated vinpocetine were not significantly influenced by co-administration of omeprazole in rats. For example, plasma vinpocetine concentrations were very similar for the two investigated regimens. In addition, T_{max} in both groups was observed 1.5 h after the drug administration. The mean AUC $_{0-t}$ and AUC $_{0-inf}$ values were not significantly different, which reflected the similar bioavailability of vinpocetine administered orally with or without omeprazole. Moreover, no significant difference was observed in C_{max} values in both groups. Analyzing our results and the results of Lohmann, it is clear that the increase in vinpocetine bioavailability following food intake observed by Lohmann was associated with changes other than a direct increase in gastric pH [2, 4, 6, 8].

Limitations of this study were a low population of animals and some interspecies differences in vinpocetine pharmacokinetics between humans and rats, preventing us from simple extrapolation of the obtained results into a clinical setting. Important species differences in the bioavailability of numerous substances between humans and rats are a result of differences in metabolism [7].

In rats, unlike in humans, vinpocetine undergoes significant extrahepatic metabolism involving plasma esterases [24]. Conversely, it has been demonstrated that hepatic enzymes are primarily responsible for the first-pass effect of vinpocetine and that the liver metabolism of both omeprazole and vinpocetine depends on cytochrome P450 isoenzymatic activity [12]. This activity varies between humans and rodents for specific drugs because of species differences in the amino acid sequences of enzyme isoforms. Unfortunately, differences in CYP enzymes involved directly in vinpocetine metabolism between human and rats are unknown. Generally, CYP3A4 is the most abundant isoform for the metabolism of various drugs in humans. In rats, CYP2C11 represents 54%, CYP3A2 17% and CYP1A2 2% of the total hepatic cytochrome P450s [12].

To the best of our knowledge, this is the first study evaluating the influence of pH alterations in the gastrointestinal tract on vinpocetine pharmacokinetics during PPI treatment in rats. Similar values of AUC, C_{max}, and T_{max} found in vinpocetine and vinpocetine/omeprazole regimens showed no apparent effect for omeprazole on the rate and extent of vinpocetine absorption. This indicates that pH changes in the gastrointestinal tract did not influence the bioavailability of orally administrated vinpocetine.

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