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Investigation of low levels of plasma valproic acid concentration following simultaneous administration of sodium valproate and rizatriptan benzoate

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Abstract

Drug interaction between rizatriptan benzoate, an anti-migraine agent, and sodium valproate (VPA-Na), an anticonvulsant, was studied in rats. When rizatriptan benzoate was administered orally immediately after VPA-Na oral administration, the pharmacokinetic parameters, such as plasma valproic acid (VPA) and area under the plasma concentration–time curve up to 3 h (AUC_{0-3}), were significantly decreased compared with those in the control group. However, when rizatriptan benzoate was administered intraperitoneally immediately after VPA-Na orally, these parameters were not changed. In addition, when benzoic acid was administered orally immediately after VPA-Na orally, these were significantly lower compared with the control values. Therefore, it might be possible that VPA transport by monocarboxylate transporter was competitively inhibited by rizatriptan benzoate and thus absorption of VPA was decreased.

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Introduction

Sodium valproate (VPA-Na) is a branched-chain fatty acid that is used in the treatment of absence seizures, myoclonus and, usually in combination with other traditional anticonvulsants, in generalized epilepsy (Meunier et al 1963). We have reported the effect of salicylate on the pharmacokinetics of valproic acid (VPA) after oral administration of VPA-Na in rats (Ohshiro et al 2003). In that paper, the plasma VPA concentrations, including maximum plasma concentration (C_{max}) and area under the plasma concentration–time curve up to 3 h (AUC_{0-3}), were significantly decreased compared with those in the control group, and these results suggest that they may be related to reduction of VPA absorption.

Rizatriptan benzoate is a serotonin 5-$HT_{1B/1D}$ receptor agonist for acute treatment of migraine (Shadle et al 2000). Migraine headache is a common disorder with the greatest prevalence in women aged 35–45 years. Some epileptic patients receiving long-term anticonvulsant therapy occasionally require co-administration with other medicines, such as an anti-migraine agent. A pharmacokinetic interaction between VPA and rizatriptan benzoate has not been reported and so, in this study, we investigated a possible drug interaction between rizatriptan benzoate and VPA.

Material and Methods

Chemicals

VPA-Na (Depaken syrup (5%VPA-Na); Kyowa Hakko Kogyo, Tokyo, Japan), rizatriptan benzoate (Maxalt 10 mg tablets; Eisai Co. Ltd, Tokyo, Japan) and benzoic acid (Nacalai tesque, Inc., Kyoto, Japan) were purchased for the preparations. Distilled water and other reagents were of analytical grade.

Animals

Twenty-five male Sprague-Dawley rats, 230–300 g, were housed in groups of four or five to a plastic-walled cage (26×36×25 cm), and had free access to food and water, except for the 12 h before the experiment. The rats were maintained on a 12-h light–dark cycle (light on 0800–2000 h). The ambient temperature and humidity were kept at 22–24°C and ca. 60%, respectively. A single dose of VPA-Na was given intragastrically through a catheter to overnight-fasted rats (n=15; body weight, 249.1±3.5 g) at a dose of 100 mg/kg/5 mL as a 2% distilled water solution of Depaken syrup. Immediately after the administration of VPA-Na, rizatriptan benzoate was administered orally (n=5) or intraperitoneally (n=5) to rats at a dose of 20 mg/kg/5 mL or 10 mg/kg/5 mL as a suspension in distilled water, respectively. As a control (n=5), distilled water was similarly given to VPA-Na treated rats at a volume of 5 mL kg^{-1}. In the two weeks after, the same dose of VPA-Na was given intragastrically to rats (n=10; body weight, 304±6.7 g). Immediately after that, benzoic acid was administered orally (n=5) at a dose of 10 mg kg^{-1} as a distilled water suspension or the same dose of distilled water (n=5) was given to VPA-Na treated rats. The rats were anaesthetized with diethyl ether before oral administration. The blood samples were collected by tail-nick method. Small quantities of blood were drawn at 0.25, 0.5, 1, 2 and 3 h following treatment with VPA-Na. Blood samples were centrifuged (model CT 12; Hitachi, Tokyo, Japan) at 12 000 rev min^{-1} for 5 min to separate the plasma. The quantitative analysis of VPA in plasma samples was conducted using an automated Abbott TDXFLX fluorescence polarization analyzer (Abbott Laboratories, Abbott Park, USA).

The rats used in this study were handled in accordance with the Guidelines for Animal Experimentation of the University of the Ryukyus, and the experimental protocol was approved by the Animal Care and Use Committee of this institution.

Analysis of data

The pharmacokinetic parameters were obtained from VPA concentrations. Maximum plasma concentration (C_{max}) of VPA and time to reach C_{max} (T_{max}) were estimated from the actual measurement. Elimination rate constant (Kel) was determined by a linear least-square regression analysis using the natural logarithm (ln) of the VPA plasma concentrations measured at 1, 2 and 3 h after oral administration. Plasma half-life (t½) of VPA was calculated from 0.693/Kel. AUC_{0-3} values were calculated using the linear trapezoidal rule. Results were expressed as mean ± s.e.m. In Table 1, the effect of the various treatments on the pharmacokinetic parameters was analysed using a one-way analysis of variance, and individual differences between the treatments was evaluated using Dunnett's test. The statistical significance in Table 2 was analysed using Student's *t*-test. In Figures 1 and 2, the results were analysed using a repeated measures analysis of variance followed by Dunnett's test.

Results

The time courses of mean plasma VPA concentrations after oral administration of VPA-Na followed by oral and intraperitoneal administration of rizatriptan benzoate are shown in Figure 1. The plasma VPA concentrations were significantly lower than the control levels after simultaneous oral administration of VPA-Na with rizatriptan benzoate. The mean pharmacokinetic parameters, T_{max}, C_{max}, t½ and AUC_{0-3} are given in Table 1. When VPA-Na was given in combination with rizatriptan benzoate orally, AUC_{0-3} significantly decreased compared with VPA-Na alone. No significant difference in T_{max} was detected. However, when rizatriptan benzoate was administered intraperioneally immediately after VPA-Na

Table 1 Pharmacokinetic parameters of plasma VPA following oral administration (p.o.) of 100 mg kg^{-1} VPA-Na alone (control) and with 20 mg kg^{-1} rizatriptan benzoate administered orally (p.o.) or with 10 mg kg^{-1} intraperitoneally (i.p.) in rats

Treatment	n	T_{max} (h)	C_{max} ($\mu g mL^{-1}$)	t½ (h)	AUC_{0-3} ($\mu g h mL^{-1}$)
Sodium valproate alone p.o. (control)	5	0.50 ± 0.01	163.21 ± 18.84	0.44 ± 0.05	217.62 ± 15.05
Sodium valproate p.o. with rizatriptan benzoate p.o.	5	0.44 ± 0.06	103.25 ± 1.92	0.60 ± 0.03*	130.26 ± 11.89*
Sodium valproate p.o. with rizatriptan benzoate i.p.	5	0.50 ± 0.01	176.51 ± 18.46	0.47 ± 0.03	230.87 ± 22.54

Each value is mean ± s.e.m. T_{max}, time to reach C_{max}; C_{max}, maximum plasma concentration; t½, apparent elimination half-life; AUC, area under the plasma concentration–time curve. *$P < 0.05$, compared with the control groups.

Table 2 Pharmacokinetic parameters of plasma VPA following oral administration (p.o.) of 100 mg kg^{-1} VPA-Na alone (control) or with 10 mg kg^{-1} benzoic acid administered orally (p.o.) in rats

Treatment	n	T_{max} (h)	C_{max} ($\mu g mL^{-1}$)	t½ (h)	AUC_{0-3} ($\mu g h mL^{-1}$)
Sodium valproate alone p.o. (control)	5	0.50 ± 0.01	214.86 ± 7.91	0.49 ± 0.02	234.49 ± 16.67
Sodium valproate p.o. with benzoic acid p.o.	5	0.40 ± 0.06	145.97 ± 17.63**	0.57 ± 0.12	148.78 ± 17.80**

Each value is mean ± s.e.m. T_{max}, time to reach C_{max}; C_{max}, maximum plasma concentration; t½, apparent elimination half-life; AUC, area under the plasma concentration–time curve. **$P < 0.01$, compared with the control groups.

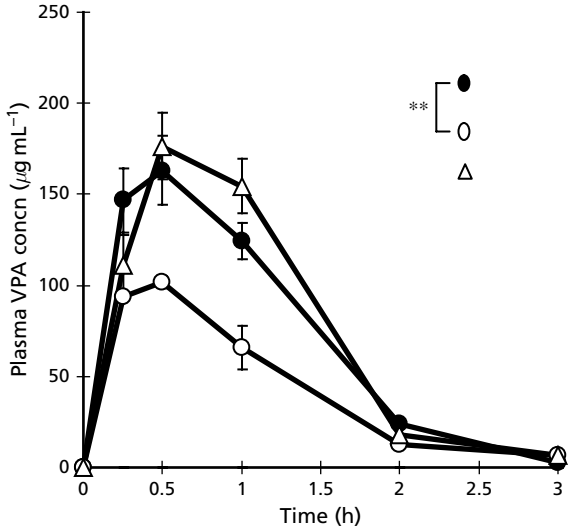

Figure 1 Time course of plasma VPA concentrations following oral administration (p.o.) of 100 mg kg^{-1} VPA-Na plus oral administration of distilled water or rizatriptan benzoate 20 mg kg^{-1} or intraperitoneal (i.p.) administration of rizatriptan benzoate 10 mg kg^{-1} in rats. Results are expressed as mean ± s.e.m. for 5 rats. $^{**}P < 0.01$, compared with the control groups. ●, control with distilled water p.o.; ○, with rizatriptan benzoate p.o.; △, with rizatriptan benzoate i.p.

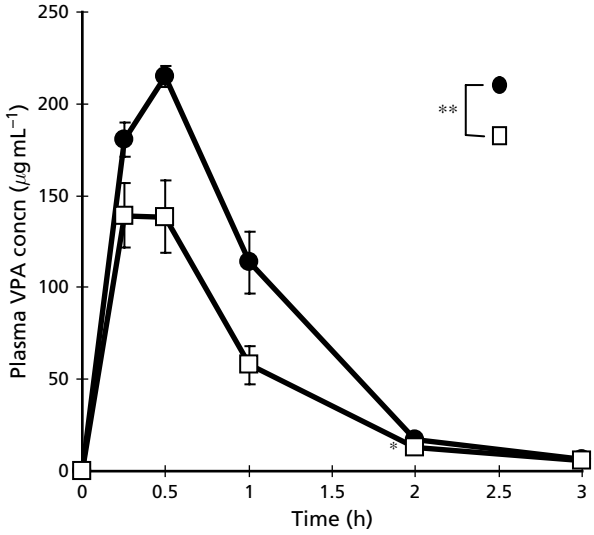

Figure 2 Time course of plasma VPA concentrations following oral administration (p.o.) of 100 mg kg^{-1} VPA-Na plus oral administration of distilled water or benzoic acid 10 mg kg^{-1} in rats. Results are expressed as mean ± s.e.m. for 5 rats. $^{**}P < 0.01$, compared with the control groups. ●, control with distilled water p.o.; □, with benzoic acid p.o.

orally, VPA concentrations and pharmacokinetic parameters, such as AUC_{0-3}, were not changed.

Figure 2 shows the mean plasma concentrations of VPA when given alone and in combination with benzoic acid in the rats. The plasma VPA concentrations were significantly lower than the control levels after simultaneous oral administration of VPA-Na with benzoic acid. The values of T_{max}, C_{max}, t½ and AUC_{0-3} are shown in Table 2. The C_{max} and AUC_{0-3} of VPA decreased when benzoic acid was co-administered. There was no significant change in T_{max} and t½.

Discussion

It was reported that the therapeutic range of VPA in plasma was 50–100 μg mL^{-1} (Gugler & Von Unruh 1980; Klotz & Antonin 1997), and the mean C_{max} of rizatriptan benzoate in healthy males receiving a single 10-mg tablet oral dose was 25.6 ng mL^{-1} (Musson et al 2001). The absorption of rizatriptan after oral administration was approximately 90%, but it experienced a moderate first-pass effect, resulting in a bioavailability estimate of 47% (Vyas et al 2000). The dose of each therapeutic agent employed in this study was set in consideration of the dosage used in animal experiments when each therapeutic agent was being developed as a medicine, and the doses for intraperitoneal administration was set in consideration of the first-pass effect and the bioavailability. In this study, therefore, 100 mg kg^{-1} VPA-Na and 20 and 10 mg kg^{-1} rizatriptan benzoate was used, respectively.

As shown in Figure 1 and Table 1, the plasma VPA concentrations and AUC_{0-3} for VPA were significantly decreased after simultaneous oral administration of 100 mg kg^{-1} VPA-Na with 20 mg kg^{-1} rizatriptan benzoate. In this experiment, the degree of mean AUC of VPA-Na decrease was about 40% in co-administered rats. VPA is used in the treatment of epileptic seizures and it has been reported that the therapeutic range of VPA in plasma is 50–100 μg mL^{-1}. If this interaction was taking place in a patient whose epileptic seizures were well-controlled, the predicted concentration of VPA-Na would be lower than the therapeutic range and seizures may occur (Fudio et al 2006). As mentioned above, we have reported a similar effect of salicylate on the pharmacokinetics of VPA after oral administration of VPA-Na in rats (Ohshiro et al 2003). In this paper, salicylic acid was administered orally after oral VPA-Na; the plasmaVPA concentrations, including C_{max} and AUC_{0-3}, were significantly decreased compared with those in the control group. We have also reported that plasma concentration levels of carvedilol following the simultaneous administration of carvedilol and meropenem (Hobara et al 1998a) or cefozopran (Hobara et al 1998b) were significantly lower compared with those in the control group.

Furthermore, to remove the influence of rizatriptan benzoate on VPA-Na absorption, rizatriptan benzoate was administered intraperitoneally. The results showed the VPA concentrations and pharmacokinetic parameters such as C_{max} and AUC_{0-3} were not changed. On the other hand, after simultaneous oral administration of VPA-Na with benzoic acid, as shown in Figure 2 and Table 2 the plasma VPA concentrations, C_{max} and AUC_{0-3} were significantly decreased compared with the control levels. These results suggested an inhibition of VPA absorption by benzoic acid. Intestinal absorption of VPA and benzoic acid has been proposed to occur not only through passive diffusion according to the pH-partition theory (Brodie & Hogben 1957), but also through carrier-mediated mechanisms. Regarding the latter, an in-vitro experiment showed that VPA was a substrate for monocarboxylic acid transporters (MCTs) in the gastrointestinal

epithelium (Tsuji et al 1994; Tamai et al 1997) and, specifically, by the MCT1 isoform (Tamai et al 1995). Moreover, selected monocarboxylic acids inhibited the uptake of [^{14}C]VPA by BeWo cells, whereas dicarboxylic acids did not alter the uptake process. Analysis of Lineweaver–Burk plots of VPA uptake in the presence of benzoic acid, a marker for the monocarboxylic acid transporter, revealed a competitive process for uptake (Utoguchi & Audus 2000). Although there is no direct evidence for VPA-Na transport activity by MCTs, transport activity of VPA-Na by MCTs was strongly suggested by those articles.

Conclusion

In conclusion, this study demonstrated that simultaneous oral administration of VPA-Na and rizatriptan benzoate decreased the concentration of VPA in plasma, including AUC_{0-3} of VPA. Therefore, it might be possible that VPA transport by MCTs was competitively inhibited by rizatriptan benzoate, and thus absorption of VPA was decreased. However, to clarify these discrepancies of drug interactions, further detailed studies will be needed.

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