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Pharmacokinetic Comparison of Two Valproic Acid Formulations

— A Plain and a Controlled Release Enteric-Coated Tablets —

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We investigated the single- and multiple dose pharmacokinetics of a new controlled-release formulation (Orfil® retard enteric coated tablet) of valproic acid in comparison with those of the plain tablet as a reference. Twelve healthy volunteers were given each formulation of 300 mg in the single-dose study. In the steady-state multiple-dose study, twelve epileptic patients received 1200 mg/day of the reference drug (300mg 9AM, 300mg 3PM, 600mg 9PM) and the test formulation (600 mg 9 AM, 600 mg 9 PM) with at least one week interval in cross-over manner. The AUC values of the test controlled release formulation were 91.7% (95% confidence interval: 78.4-100.4%) of the reference drug in the single-dose study and 98.2% (95% confidence interval: 86.2%-109.9%) in the steady-state study. The AUC's of the two formulations were not significantly different by ANOVA test. The C_{max} and T_{max} values of the test formulation were significantly different from the values of the reference in single-(T_{max}: 158.4%, C_{max}: 52.5% of the reference) and multiple-dose study (T_{max}: 153.5% of the reference). The MRT values of the test formulation were also significantly greater (129.4% of the reference) in the single-dose study. Regarding the controlled-release characteristics of the test formulation, fluctuation index and percentage fluctuation of the twice a day dosage regimen of the test formulation were comparable with those of the thrice a day dosage regimen of the conventional tablet. Area deviation was even smaller in the test regimen of the controlled release formulation. From these results, we concluded that the twice a day dosage regimen of controlled-release valproic acid was preferable or comparable to the thrice a day dosage reqinen of conventional valproic acid formulation.

Key Words: *Valproic acid, Controlled release, Bioavailability, Fluctuation*

INTRODUCTION

Epilepsy is a chronic disease that requires long-term therapy. At present, the following 4 major antiepileptic drugs are in use: phenobarbital, phenytoin, carbamazepine and valproic acid. Antiepileptic activities of these drugs correlate better with the concentrations of the drugs in blood than with the administered doses. This phenomenon is due to inter-and intra-individual variability in drug absorption and disposition. Moreover, all the antiepiletics are showing a narrow therapeutic index. Therefore, plasma drug concentration monitoring is required to achieve and maintain the therapeutic drug concentration range.

Among the major antiepileptic drugs, valproic acid has the shortest half-life (6 to 17 hours in adults and 4 to 14 hours in children in monotherapy) (Levy, 1983a; Levy and Shen, 1989; Zaccara et al., 1988) and must be administered several times a day (Porter, 1986;

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1989). This results in the problems of compliance and the fluctuations of plasma concentrations. Because of the narrow therapeutic range (50-150 μg/ml) of valproic acid plasma level and its short half-life, the fluctuation of its plasma concentration can often result in subtherapeutic trough even in thrice a day dosage regimen and high peak. On the contrary fluctuations in plasma concentrations of plain valproic acid formulation frequently result in high peak level, which may be concerned with the potential embryotoxicity in pregnant patients (Nau, 1990). These problems can be overcome by a controlled release formulation which enables reduced dose frequency and maintenance of constant drug concentration by prolonged absorption in the gastrointestinal tract.

However, many controlled release drug formulations have unreliable gastrointestinal absorption from decreased bioavailability or instantaneous release of the whole preparation. Therefore, we tried to evaluate the bioavailability and controlled release characteristics of Orfil® retard enteric coated tablet, a controlled release formulation of valproic acid developed by Desitin Arzneimittel GmbH, in comparison with Orfi® tablet, a plain formulation. The relative bioavailability and pharmacokinetic profiles of the new controlled release formulation were assessed by single and multiple oral administration of Orfil® retard and Orfil® to healthy volunteers and epileptic patients.

MATERIALS AND METHODS

Study Subjects

Twelve healthy volunteers (male, average age 27.8 years) participated in the single dose study. In the multiple dose study, twelve stable epileptic patients (19-38 years of age, average 25.4) were recruited, who were already taking valproic acid (900-1200 mg per day) continuously. All the study subjects had normal cardiac, hepatic and renal functions. Any subjects with abnormal hematologic and blood chemistry findings were excluded. No normal volunteers had had any medication for at least 2 weeks prior to the study. The subjects were fully informed of the objective and the procedure of the study, possible risk, confindentiality and their rights. The study protocol was approved by the Committee on Clinical Research of Seoul National University Hospital. The reference drug was Orfil® 300mg tablet (conventional valproic acid) and the test drug was Orfil® retard 300 mg tablet of controlled release formulation.

Study Design

In single dose study, twelve subjects were randomly assigned to receive the reference drug (300 mg) or test drug (300 mg) in a cross-over manner. There was a seven day washout period between medications. Serial blood samplings were obtained frequently from zero time up to specified timing (0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 24, 30, 36, 48, and 72 hour post dose) through intravenous heparin-locked catheter. The plasma of the collected blood was separated in refrigerated centrifuge at 3,000 rpm for 10 minutes and stored at −20°C until drug assay. Urine samples were collected up to 24 hours after dose to calculate renal clearance of the formulations. Urine sample were stored at −20°C until the assay of the drug level.

In the multiple dose study, twelve epileptic patients who met the selection criteria were randomly assigned for a balanced randomized crossover steady-state evaluation. The subjects received reference drug three times a day (1200 .mg/day, 300mg 9 AM, 300 mg 3 PM, 600 mg 9 PM) and test twice a day (1200 mg/day, 600 mg 9 AM, 600 mg 9 PM) in crossover manner at least for more than 1 week prior to the kinetic evaluation. Serial blood samples were obtained up to 12 hours after the morning dose (0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 6.5, 7, 8, 9, 10, 11, 12 hours) and at the time of the next morning dose. Twenty four hour urine samples were collected during the kinetic evaluation. The subjective adverse effects were recorded according to their duration, intensity, and possible relation to the drug throughout the study period.

Measurement of Valproic Acid Concentration in Biological Fluid

Determination of valproic acid level was performed by fluorescence polarization immunoassay (TDx®, Abbott). The detection limit and inter-assay variation of the method were less than 0.7 μg/ml and 5%, respectively. Each sample was analyzed in duplicate. The average of the two determinations was reported.

Analytical Biometrics

AUC's (area under the concentration-time curve) were calculated to evaluate the relative bioavailability of the controlled release formulation in single and steady-state multiple dose studies. Other pharmacokinetic parameters estimated were as follows, C_{max} (maximal concentration), C_{min} (minimal concentration), T_{max} (time to reach maximal concentration), $T_{1/2}$ (half-life), CL (clearance), MRT (mean residence time: average existing duration of a drug molecule in the

body after dosing).

To compare the daily fluctuation of plasma drug concentration after drug administration, the following three parameters were evaluated. The higher values represent greater fluctuations in steady-state plasma valproic acid concentrations.

1) % fluctuation = $\frac{C_{max} \times C_{min}}{C_{min}} \times 100$

(Gibaldi, 1984)

2) Fluctuation Index = $\frac{C_{max} - C_{min}}{(C_{max} + C_{min}) \div 2}$

(Caldwell et al., 1981)

3) Area Deviation = sum of areas made between average concentration line and concentration-time curve of steady-state (Boxenbaum, 1984).

Bioequivalence between regular and controlled release formulations was tested by ANOVA, paired t-test, and confidence limit analysis.

RESULTS

The concentration-time curves of plasma valproic acid after single oral dose of reference and test drugs are presented in Fig. 1. The test drug showed lower C_{max} and slower time to peak compared with the reference drug. The mean values of pharmacokinetic parameters in the single dose study are summarized in Table 1. The AUC which represents the extent of bioavailability was not significantly different between the reference (plain formulation) and test (controlled release formulation) drugs, although the mean value of the test drug was slightly lower than that of the reference drug. T_{max} and MRT of the test drug were sig-

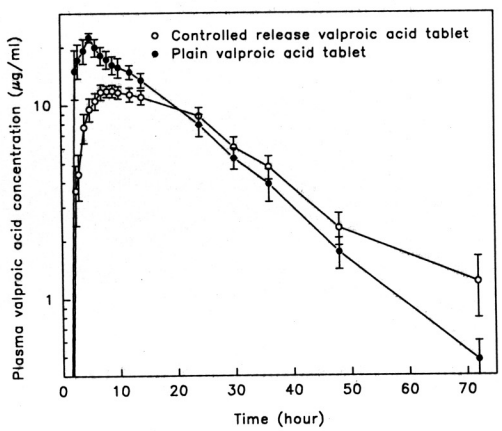

Fig. 1. Averaged log concentration-time curve of valproic acid controlled release formulation 300mg (O) and plain 300mg (●) in 12 healthy volunteers after oral administration. Data are presented as mean±standard error.

Table 1. Pharmacokinetic parameters obtained from single oral dose studies of test and reference valproic acid formulations (300 mg) in 12 healthy volunteers

	Reference (n=12)	Test (n=12)	Significance	Confidence Interval
AUC ($\mu g \cdot h/ml$)	430.63±134.07	395.10±185.01 (91.74%)	NS	78.3-100.4% (95%) (±19.23)%
C_{max} ($\mu g/ml$)	25.33±3.97	13.24±3.49 (52.48%)	$p<0.01$	
T_{max} (h)	5.21±2.61	8.25±2.53 (158.35%)	$p<0.01$	
MRT (h)	19.56±4.20	25.31±7.10 (129.40%)	$p<0.01$	
$T_{1/2}$ (h)	11.08±2.67	12.47±5.83 (112.55%)	NS	
CL_{Tot} (L/h)	750.09±205.41	865.17±270.56 (115.34%)	NS	
CL_{Ren} (L/h)	57.35±119.98	40.35±48.96 (70.36%)	NS	

AUC: area under the concentration-time curve, MRT: mean residence time, CL_{Tot} and CL_{Ren}: total and renal clearance

*: 80.76-102.74% (90% confidence limit) **: Symmetrical confidence interval

Table 2. Pharmacokinetic parameters obtained from multiple oral dose steady-state studies of test and reference valproic acid formulations (300 mg) in 12 healthy volunteers

	Reference (n=12)	Test (n=12)	Significance	Confidence Interval
$AUC_{0\text{-}12h}$ ($\mu g \cdot h/ml$)	944.00±247.84	925.30±283.67 (98.02%)	NS	86.2-109.9%(95%) (±12.43%)
C_{max} ($\mu g/ml$)	88.77±22.88	86.51±23.46 (97.45%)	NS	86.2-108.7%(95%) (±12.24%)
T_{max} (h)	3.85±1.14	5.92±1.82 (153.77%)	p<0.01	
CL_{Tot} (L/h)	336.76±83.36	350.94±95.53 (104.21%)	NS	
CL_{Ren} (L/h)	12.06±4.04	10.46±5.22 (86.73%)	NS	

AUC: area under the concentration-time curve, MRT: mean residence time, CL_{Tot} and CL_{Ren}: total and renal clearance *: Symmetrical confidence interval

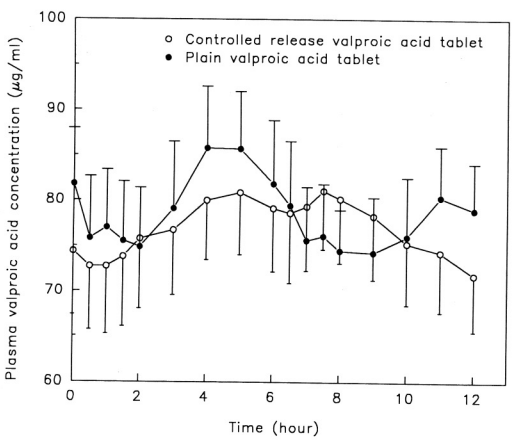

Fig. 2. Plasma concentration-time curves of controlled release formulation (O) and plain formulation (●) of valproic acid in 12 epileptic patients at multiple dose at steady-state. Controlled release formulation (600 mg: two Orfil® retard 300 mg tablets) was administered at time 0 and plain formulation (one 300 mg tablet) was administered twice at time 0 and 6, respectively.

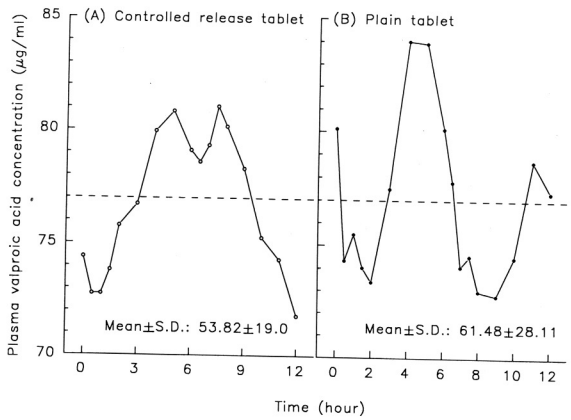

Fig. 3. Area deviations of controlled release formulation (A) and plain formulation (B) of valproic acid. Average concentrations of the two were adjusted to 77.1 $\mu g/ml$.

nificantly greater than those of the reference drug. Peak valproic acid concentrations after test drug administration were about half of the reference drug's. Other parameters such as half-life, total and renal clearance showed no statistical differences.

In the multiple dose study, the average plasma concentration-time curve of the test valproic acid formulation showed a lower peak level and delayed time to peak. T_{max} was the only significantly different parameter between the two formulations (Table 2), which has little clinical meaning in this steady-state. Other parameters, including the AUC were not significantly different between reference and test drugs. The results showed that the two formulations of valproic acid were equivalent in bioavailability.

Three parameters for the daily fluctuation of the plasma valproic acid level were all comparable between dosing schedules of reference and test drugs (Table 3). The mean values of % fluctuation and fluctuation index were slightly higher in the reference drug regimen. However, the area deviation, which is the most reliable parameter, was lower in the test drug regimen despite the drug being given twice a day. There were no statistically significant differences in all three parameters (Table 3). The averaged area deviations of the test and reference drug were illustrated in Fig. 3. The results suggested that a three times a day regimen of conventional valproic acid formulation could be replaced by a twice a day regimen of the same

Table 3. Fluctuations of plasma valproic acid concentrations in multiple dose steady-state of test and reference formulations

	% Fluctuation	Fluctuation index	Area deviation
Test (n=12)	33.85±14.26	0.38±0.11	53.82±19.0
Reference (n=12)	28.93±9.50	0.25±0.07	61.48±28.11

Data are presented as mean±standard deviation $p<0.05$ by paired t-test

daily dose of controlled release valproic acid. There were no significant study drug related adverse effects during the study period of single and multiple dose study.

DISCUSSION

Valproic acid was first clinically applied as an anticonvulsant in 1964 by Carraz et al. Since its approval for marketing by the FDA in 1978, it has been widespread throughout the world. The action mechanism of the drug has not been settled, though current hypotheses have centered on potential interactions with voltage-sensitive sodium channels (MacDonald, 1988) and on the possible enhancement of GABA accumulation (Loscher, 1985). Whatever the mechanism is, valproic acid is rated to be a highly effective anticonvulsant, especially in generalized seizures including absence seizure.

Despite its extensive clinical use, literature data on the pharmacokinetics of valproic acid in humans are scanty (Loiseau et al., 1975; Schobben and van der Kleijn, 1975; Klotz and Antonin, 1977). Given on an empty stomach, valproic acid is rapidly and nearly completely absorbed and the bioavailability reaches approximately 100% (Wilder et al., 1983). Until now, several various formulations of the syrup, capsule, tablet and enteric coated tablet have been introduced, which showed peak times of one to four hours depending on the type of formulation. Ingested with meals, the absorption rate is slightly delayed but the amount of absorption is not disturbed (Meinardi et al., 1975). Early studies involving adult human volunteers indicated an elimination half-life of approximately 15 to 17 hours (Chapman et al., 1982). The elimination halfe-life is widely variable among individuals receiving the drug (Levy, 1983b). However, coadministration of enzyme inducing antiepileptic drugs such as phenytoin or carbamazepine decrease the half-life into the range of 6 to 12 hours (Schappel et al., 1982; Perruca et al., 1978). With such a short half-life in combination therapy, valproic acid is generally given 3 times a day to maintain the effective plasma concentration. Furthermore, due to wide individual variations in the absorption rate, biotransformation, and excretion rate, great fluctuation of plasma level out of therapeutic range can usually be anticipated in many patients (Meijer and Hessing-Brand, 1973; Schobben and van der Kleijn, 1974; Baruzzi et al., 1977; Wulff et al., 1977; Bruni et al., 1976; Hendriksen and Johannessen, 1982). In this regard, development of a controlled release formulation is an important approach to improve patient compliance and to maintain plasma levels in the narrow therapeutic range of 50 to 100 μg/ml over a prologed period, which minimizes the occurrence of adverse effects and increases the overall antiepileptic efficacy of the drug.

The tested drug is a controlled release formulation of valproic acid, recently developed by Desitin Arzneimittel GmbH. It was tested in human volunteers as a single dose in Germany and the report showed favorable results about absorption rate and relative bioavailability compared to the existing enteric coated valproate tablet (Schulz, 1990). However, the data from a single dose study were not sufficient for the claim of controlled release pharmacokinetic characteristics. To be a successful controlled release formulation, it is required that the drug must be absorbed consistently and completely throughout the gastrointestinal tract and first-pass metabolism is not saturable. In fact, many controlled release formulations show decreased bioavailability compared with the plain formulations and variable absorption. As the controlled release formulations are usually administered less frequently, the single administered dose of the formulation is greater than that of plain formulations. If the whole dose is released at once through some physicochemical mechanisms in the gastrointestinal tract, there is increased risk of toxicity. Therefore, the controlled release formulations must be evaluated in view of their bioavailability and controlled release characteristics before their clinical applications.

In this study, the test drug was evaluated by the extent of bioavailability by AUC and controlled characteristics by three parameters: percent fluctuation (Gibaldi, 1984), fluctuation index (Caldwell et al., 1981) and area deviation (Boxenbaum, 1984). Both the fluctuation index and percent fluctuation are very sensitive to aberrantly high or low values of C_{max} or C_{min}, showing their limitations to the studies of valproic acid

and other drugs with less predictability of dose-concentration relationship. Therefore the area deviation seems to be most important parameter among the three parameters for the evaluation of controlled release valproic acid formulations. The twice a day dose regimen of the test controlled release formulation showed similar bioavailability and steady-state fluctuation of plasma drug concentration compared to those of thrice a day dose regimen of the reference enteric coated tablet.

These results demonstrate that the thrice a day dose regimen of Orfil® retard tablet might reduce concentration-related adverse effects, make the therapeutic drug monitoring easier, and increase the compliance of the anti-epileptic therapy with valproic acid, comparing to the thrice a day dose regimen of Orfil® tablet.

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