Available online at www.ijpsdronline.com
International Journal of Pharmaceutical Sciences and Drug Research 2011; 3(2): 101-103

Research Article ISSN 0975-248X

Comparative Bioavailability Study with Two Sodium Valproate Tablet Formulations in Healthy Subjects

Dhaneshwar Shep[1], Asmita Nimkar[2], Rajen Shah[2], Vijaya Jaiswal[1*]

[1]*Troikaa Pharmaceuticals Ltd., Commerce House-1, Satya Marg, Bodakdev, Ahmedabad, Gujarat, India*
[2]*Raptim Research Ltd, Navi Mumbai, Maharashtra, India*

ABSTRACT

The aim was to assess the comparative bioavailability of two formulations (200 mg tablet) of sodium valproate in healthy subjects. This open label randomized, two periods, two treatments, two sequence, 2-way crossover design study was conducted in 18 healthy Indian adult subjects. Subjects received sodium valproate 200 mg of either test or reference formulation with a washout period of 7 days. After study drug administration, serial blood samples were collected over a period of 60 hours. Plasma concentrations of Valproic acid were measured by pre-validated LC-MS-MS method. Pharmacokinetic (PK) parameters C_{max}, T_{max}, $t_{1/2}$, AUC_{0-t}, $AUC_{0-\infty}$, and k_{el} were determined for the 2 sodium valproate formulations. C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were used to test for bioequivalence after log-transformation of plasma data. The formulations were to be considered bioequivalent if the log-transformed ratios of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were within the predetermined bioequivalence range of 80% to 125%. A total of 18 healthy subjects were enrolled. No significant differences were found based on analysis of variance, with mean values and 90% confidence intervals of test/reference ratios for these parameters as follows: C_{max}, 15.64 versus 15.20µg/ml (90.79 to 115.45); AUC_{0-t}, 72.71 versus 66.95µg.h/ml (96.03 to 124.87); and $AUC_{0-\infty}$, 105.65 versus 98.11µg.h/ml (94.61 to 124.75). In these healthy Indian subjects, results from the PK analysis suggested that the test and reference formulations of sodium valproate 200 mg tablets were bioequivalent. Both the formulations were well tolerated.

Keywords: Bioavailability, Bioequivalence, Pharmacokinetics, Sodium Valproate.

INTRODUCTION

Valproic acid has been approved by the US Food and Drug Administration for treatment of absence, myoclonic, and tonic-clonic seizures, as well as for prophylaxis of migraine headache and as an adjuvant in the treatment of mania associated with bipolar disorder. [1-2] Valproic acid is available in different dosage forms for parenteral and oral use. All available oral formulations are almost completely bioavailable, but they differ in dissolution characteristics and absorption rates. [3] Once absorbed, valproic acid is largely bound to plasma proteins and has a relatively small volume of distribution. Valproic acid undergoes extensive hepatic metabolism and its elimination $t_{1/2}$ ranges between 10 and 20 hours. [4-5]

Valproic acid has been associated with a highly variable intersubject absorptive phase [1]; therefore, some salts, the most common of which are sodium, calcium, and magnesium have been developed to design and produce forms that diminish variation during enteric absorption.

Differences in the bioavailability of different brands of the same anticonvulsant have also been reported. [6-8] The bioavailability of a drug is the quantum of the drug available in the systemic circulation for its action after absorption. [6, 9] In the management of epilepsy which requires a long-term treatment for years, the bioavailability of the anti-convulsant drug should not fluctuate from time to time. If the level goes up, it may lead to intoxication and if it lowers down, seizure may relapse. Recently, non-equivalence in the bioavailability of two different brands of another anti-convulsant drug - carbamazepine has also been reported. [6-7] This is important to consider while changing prescription from innovator to generic brand as non-bioequivalence between two brands may result in fluctuation in plasma concentration of the drug. The objective of this study was to compare the bioavailability of the Test Formulation of sodium valproate 200 mg (Troikaa Pharmaceuticals Ltd, India) with the Innovator Product (Sanofi-Synethelabo).

SUBJECTS AND METHODS

***Corresponding author: Dr. Vijaya Jaiswal,**
Troikaa Pharmaceuticals Ltd., Commerce House-1, Satya Marg, Bodakdev, Ahmedabad, Gujarat, India;
Tel.: +91-79-26856242-45; **Fax:** +91-79-26856246;
E-mail: medicalservices@troikaapharma.com

The study was carried out at Raptim Research Ltd, Navi Mumbai, India. All the subjects provided written informed consent to participate in the study prior to enrolment and were free to withdraw at any time during the study. The study was approved by the institutional ethics committee and was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki.

Study population and design

A total of 18 healthy Subjects were enrolled in the study with a mean age, weight and height of 28.06 years, 58.61 kg and 166.83 cm respectively. Subjects were deemed healthy on the basis of their medical history, physical examination and pathological investigation results including hematology & biochemical tests, serology, routine urine testing, urine drug screen and ECG before they were enrolled in the study. All participants provided written informed consent before inclusion in the study. Study was initiated only after approval from Ethics Committee.

Open label, randomized, two period, two treatment, two sequence, 2-way crossover design study was conducted in 18 healthy Indian adult subjects under fasting conditions. There was a 7 days washout period between the doses. The dose administration was performed as per the randomization generated at Raptim Research Ltd, Navi Mumbai. Subjects received a single oral dose of test formulation of sodium valproate 200 mg (Troikaa Pharmaceuticals Ltd, India) or reference formulation (Sanofi-Synethelabo) with 240 mL of water after an overnight fast.

Blood sampling

Following administration of the Test/ Reference products, a total of 21 blood samples of 6 ml each were collected at 0.00 hrs (pre dose), 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 14, 16, 18, 24, 36, 48 and 60 hours following drug administration. Prior to dosing, on the scheduled day of the study, the IV cannula was inserted in the forearm vein of the subject. The blood samples were collected in pre-labeled centrifuge tubes containing EDTA as an anticoagulant. The plasma from blood sample was separated by centrifugation at 2,500 to 3,000 rpm for 5 minutes. The plasma from each centrifuge tube was transferred to pre labeled screw cap vials, in replicates (one set was used for analysis and the other set was kept as replicate samples, to be used for repeat analysis if required). Each vial contained approximately 1 ml plasma. Both the sets were stored at -20^{o}C ± 5^{o}C.

Method of analysis

Pharmacokinetic analysis

The plasma pharmacokinetic parameters were estimated include the observed maximum plasma concentration C_{max}, the time to reach C_{max}, (T_{max}) and the area under the plasma concentration-time curve from 0 hour to last measurable concentration (AUC_{0-t}) and 0 hour to infinity ($AUC_{0-\infty}$). The maximum plasma concentration (C_{max}) and the time to reach maximum concentration (T_{max}) were directly determined from the plasma concentration versus time curves. The Area under the curve from 0 hour to t (AUC_{0-t}) was calculated by the linear trapezoidal rule. The area under the curve from 0 hour to infinity ($AUC_{0-\infty}$) was estimated by summing the area from AUC_{0-t} and $AUC_{0-\infty}$, where $AUC_{0-\infty} = AUC_{0-t} + C_t / k_{el}$, with '$C_t$' defined as the last measured plasma concentration at time t, and 'k_{el}' the slope of the terminal portion of the plasma concentration versus time curve, obtained by linear regression. Logarithmic transformation was done before data analysis for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. Analysis of variance (ANOVA) was used to assess effects. Intra-subject variability in terms of the overall percentage coefficient of variation (%CV), were evaluated from the ANOVA results for log transformed data. For the pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ 90% confidence intervals for the ratios of Test and Reference product averages were calculated using the ANOVA of the ln-transformed data. The product was tested for bioequivalence using ratios of the Log transformed pharmacokinetic parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ and its 90% confidence interval. The formulations were to be considered bioequivalent if the log transformed ratios (test/reference) of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were within the predetermined bioequivalence range of 80% to 125%. Pharmacokinetic output from statistical software WinNonlin-Professional version 5.0.1 was used for analysis.

Safety and tolerability

General clinical safety was assessed via physical examinations and vital signs conducted at screening, during study and at the end of the study. Clinical laboratory tests and ECGs were also conducted at screening, before dosing within each treatment period, and at the end of the study. Adverse events were assessed for severity and relationship to treatment throughout the study.

RESULTS

The sodium valproate plasma concentration-time profiles of the test and reference formulations were comparable. The mean serum concentration–time curves of 2 formulations of sodium valproate products each administered as a single 200 mg oral dose to healthy Indian male volunteers are shown in the Fig. 1. The primary PK parameters for both drugs are listed in Table 1. The mean C_{max} values of the test and reference formulations were 15.64 and 15.20 µg/ml, respectively. The mean T_{max} values were 3.69 and 3.61 hours. Results for the extent of absorption, as determined from mean AUC_{0-t} and $AUC_{0-\infty}$ values, were 72.71 and 105.65 µg.h/ml respectively after administration of the test formulation and 66.95 and 98.11 µg.h/ml respectively after administration of the reference formulation. The mean $t_{1/2}$ was 5.39 hours for the test formulation and 4.24 hours for the reference formulation. On ANOVA, no period, formulation or sequence effects were observed for any PK property. The 90% confidence intervals of the ratios (test vs reference) for the natural log (ln)-transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ are shown in Table 2. The 90% confidence intervals for the ratios of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 90.79 to 115.45, 96.03 to 124.87 and 94.61 to 124.75 respectively, meeting the predetermined criteria for bioequivalence.

Safety and tolerability

All 18 subjects were completed the study and there were no premature withdrawals, replacements or death during the study. None of the subjects experienced or reported any adverse event, during the entire course of the study. No clinically significant abnormalities were reported in the physical examination, vital signs, ECGs and post-laboratory results. Post study physical examinations, vital signs, ECGs, and laboratory results were found to be within the normal range and not indicative of any clinical abnormality.

DISCUSSION

This study examined the pharmacokinetic properties and bioequivalence of 2 formulations of sodium valproate 200 mg tablet in healthy Indian adult male subjects. The most important objective of bioequivalence testing is to assure the safety and efficacy of generic formulations. When two

Table 1: Summary of pharmacokinetic parameters of Sodium Valproate, following administration of the reference and test formulations

Products	Test						Reference					
Parameter	C_{max} (µg/ml)	T_{max} (h)	AUC_{0-t} (µg.h/mL)	$AUC_{0-\infty}$ (µg.h/mL)	$t_{1/2}$ (h)	K_{el} (h^{-1})	C_{max} (µg/ml)	T_{max} (h)	AUC_{0-t} (µg.h/mL)	$AUC_{0-\infty}$ (µg.h/mL)	$t_{1/2}$ (h)	K_{el} (h^{-1})
Mean	15.64	3.69	72.71	105.65	5.39	0.16	15.20	3.61	66.95	98.11	4.24	0.21
SD	3.76	0.91	20.67	34.39	2.59	0.07	3.20	0.98	23.74	34.66	1.92	0.13
% CV	24.00	24.60	28.40	32.60	48.20	46.30	21.00	27.10	35.50	35.30	45.40	61.70

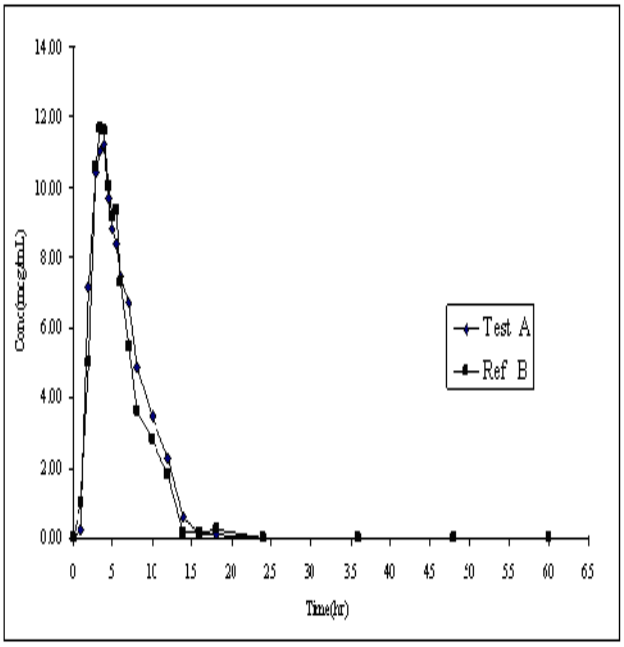

Fig. 1: The mean plasma concentration time – profile for Sodium Valproate Test and Reference formulation

Table 2: 90 % Confidence Interval for the ratio of log - transformed data comparing Test product (A) and Reference product (B)

Parameter	Lower Confidence Limit	Upper Confidence Limit
C_{max}	90.79 to 115.45	90.79 to 115.45
AUC_{0-t}	96.03 to 124.87	96.03 to 124.87
$AUC_{0-\infty}$	94.61 to 124.75	94.61 to 124.75

formulations of the same drug are equivalent in the rate and extent to which the active drug ingredient is absorbed, and becomes equally available at the site of drug action, they are bioequivalent and thus are assumed to be therapeutically equivalent. [10] To demonstrate bioequivalence, certain limits should be set, depending on the nature of the drug, patient population and clinical end-points. [10-11] It is generally accepted that the 90% confidence interval for the ratio of averages of logarithmically transformed AUC and C_{max} should lie within the range of 80 to 125 %. [10, 12-13]

Our study data show that both sodium valproate formulations are bioequivalent for the rate and extent of absorption. The 90% confidence intervals were completely contained within the predefined bioequivalence criteria of 80% to 125% for the primary end point of C_{max} and AUC. The study results revealed that the 2 formulations of sodium valproate were similar in PK characteristics among these healthy Indian male subjects. The 90% confidence intervals for the ratios of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 90.79 to 115.45, 96.03 to 124.87 and 94.61 to 124.75 respectively, meeting the predetermined criteria for bioequivalence. The AUC_{0-t} and $AUC_{0-\infty}$ values of test formulation were comparable to that of reference formulation. The mean C_{max} of the test was 15.64µg/ml, which was comparable to that of the reference formulation 15.20µg/ml. J H Rha *et al* reported C_{max} 13.24 and 25.33µg/ml for two different formulations of valproic acid 300 mg. [14] The mean T_{max} of the test was 3.69 hours which was comparable to that of the reference formulation (3.61 hours). T_{max} was earlier for both the formulations in comparison to T_{max} reported by J H Rha *et al* for two different formulations of valproic acid 300 mg (5.21 and 8.25 hours) in healthy subjects. [14] In the present study both formulations were well tolerated and no adverse events were reported during the study.

In these healthy Indian subjects, results from the pharmacokinetic analysis suggested that the test and reference formulations of sodium valproate 200 mg tablets were bioequivalent. Both formulations were well tolerated.

ACKNOWLEDGEMENTS

The authors wish to thank to Troikaa Pharmaceuticals Ltd., Ahmedabad for providing the drug samples and the staff of Raptim Research Ltd, Navi Mumbai for conducting this pharmacokinetic study.

REFERENCES

1. Marcelín-Jiménez G, Angeles-Moreno AP, Contreras-Zavala L, Morales-Martínez M, Rivera-Espinosa L. A single-dose, three-period, six-sequence crossover study comparing the bioavailability of solution, suspension, and enteric-coated tablets of magnesium valproate in healthy Mexican volunteers under fasting conditions. Clin Ther. 2009; 31:2002-2011.
2. Food and Drug Administration (FDA). Valproate. Major Drug Information Pages. http://www.fda.gov/cder/indexhtml. Accessed January 18, 2009.
3. Akira Fujii, Norio Yasui-Furukori, Taku Nakagami, Takenori Niioka, Manabu Saito, Yasushi Sato and Sunao Kaneko. Comparative in vivo bioequivalence and in vitro dissolution of two valproic acid sustained-release formulations. Drug Des Devel Ther. 2008; 2:139-144.
4. Zaccara G, Messori A, Moroni F. Clinical pharmacokinetics of valproic acid-1988. Clin Pharmacokinet. 1988; 15:367-389.
5. Pollack GM, McHugh WB, Gengo FM. Accumulation and washout kinetics of valproic acid and its active metabolites. J Clin Pharmacol. 1986; 26:668-676.
6. Dhanaraj M, Jayavelu A. Non-equivalence of bioavailability between generic and branded form of sodium valproate. Neurol India. 2004; 52:398.
7. Tyre JH, Eadie MJ, Sutherland JM, Hooper WO. Outbreak of anticonvulsant intoxication in an Australia city. Br Med J. 1970; 4:271-273.
8. Revankar SN, Desai ND, Bhat AD, Bolar HV, Sane SP, Gupta C. Comparison of absorption rate and bioavailability of two brands of carbamazepine. J Assoc Physic Ind. 1999; 47:699-702.
9. Editorial. Biological availability of drugs. Lancet 1972; 1:83.
10. Hassan Y, Alfadly SO, Azmin MN, Peh KK, Tan TF, Noorizan AA, Ismail O. Bioequivalence evaluation of two different formulations of ciprofloxacin tablets in healthy volunteers. Singapore Med J. 2007; 48:819-823.
11. Abdallah RM, Alam SM, Awaad FM. Bioequivalence of two brands of ciprofloxacin 750 mg tablets (Sarf and Ciprobay) in healthy human volunteers. Drug Dev Ind Pharm. 2002; 28:423-429.
12. Westlake WJ. Use of confidence intervals in analysis of comparative bioavailability trials. J Pharm Sci. 1972; 61:1340-1341.
13. Dhaneshwar Shep, Ankit Shah, Asmita Nimkar, Rajen Shah, Vijaya Jaiswal. Comparative bioavailability study with two amiodarone tablet formulations in healthy subjects. Int J Res Pharm Sci. 2010; 1:481-485.
14. Rha JH, Jang IJ, Lee KH, Chong WS, Shin SG, Lee N, Myung HJ. Pharmacokinetic comparison of two valproic acid formulations. J Korean Med Sci. 1993; 8:251-256.