ORIGINAL ARTICLE

Comparative Bioavailability Study of a Generic Sustained Release Diclofenac Sodium Tablet

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Summary

The bioavailability of a generic diclofenac sodium sustained release tablet preparation (Zolterol®, SR) was compared with the innovator product, Voltaren®, SR. Twelve healthy adult male volunteers participated in the study, which was conducted according to a randomized, two-way crossover design with a wash out period of one week. The bioavailability of diclofenac was compared using the parameters area under the plasma concentration-time curve ($AUC_{0-\infty}$), peak plasma concentration (C_{max}) and time to reach peak plasma concentration (T_{max}). No statistically significant difference was observed for both logaritmically transformed $AUC_{0-\infty}$, C_{max} values and T_{max} value of the two preparations.

Key Words: Diclofenac, Bioequivalence, Sustained Release, Bioavailability

Introduction

Diclofenac sodium is a well known non-steroidal anti-inflammatory drug (NSAID) that has been shown to be active in suppressing inflammation and has antipyretic as well as analgesic activities. It has been confirmed to be effective in the treatment of rheumatoid arthritis and degenerative bone disease[1,2].

Although the absorption of diclofenac following oral dosing is extremely rapid, only about 60% of the parent drug reaches the systemic circulation due to extensive first-pass metabolism[3]. Rapid systemic clearance of diclofenac necessitates repeated dosing. Therefore, sustained release formulations of diclofenac offer the advantage of once daily dosage regimen. The present study was conducted to evaluate the bioavailability of a locally produced enteric-coated tablet formulation of diclofenac (Zolterol®, SR) with that of the innovator product, Voltaren®, SR.

Materials and Methods

Products Studied

Zolterol® SR tablets (100 mg diclofenac sodium), were manufactured by CCM Pharma Pte. Ltd., Malaysia and Voltaren® SR tablets (100 mg diclofenac sodium) were manufactured by Novartis, Switzerland. Mefenamic acid and diclofenac sodium were obtained from National Pharmaceutical Control Bureau of Malaysia. All other reagents used were of AR (analytical reagent) or HPLC (high-performance liquid chromatography) grade.

Study Design

The study protocol was approved by School of Pharmaceutical Sciences, USM–General Hospital Penang Joint Committee on Bioavailability Studies. Twelve (12) healthy male volunteers between 32 and 46 years old (39 ± 4) and weighing from 57 to 78 kg (70 ± 6) participated in the study after providing written informed consent. All were judged to be healthy and

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were not receiving any medication during the study period. The protocol used was a conventional, two-way, split group, crossover study with 6 subjects in each of the two treatment groups. In the first trial period, each volunteer of group 1 was given one tablet of Voltaren® SR while those of group 2, one tablet of Zolterol® SR. After a washout period of one week, each volunteer then received the alternate product. Both products were administered in the morning (10.00 am) with 150 ml of water after an overnight fast. Food and drinks were withheld for at least 2 hours after dosing. Lunch and dinner comprising chicken and rice, were served at 4 hours and 10 hours after dosing. Blood samples of 5 ml volume were collected in Vacutainer® tubes (containing sodium heparin as anticoagulant) at 0 (predose), 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 14, 18 and 24 hours after dosing via an in-dwelling cannula placed in the forearm. Two more blood samples were taken at 30 and 36 hours via direct veinpuncture. The blood samples were centrifuged for 15 min at 2000 G and the plasma was then transferred to a new tube to be kept frozen until analysis.

Analysis of Diclofenac Plasma Concentration

Instrumentation

The plasma samples were analyzed using a reversed-phase high-performance liquid chromatographic (HPLC) method. The HPLC system comprised of a Gilson 305 pump, a Gilson 119 UV/VIS detector (Gilson Medical Electronics, Villiers-le-Belle, France) connected to a Hitachi D-2500 integrator (Hitachi, Tokyo, Japan) and a Rheodyne 7125 (Rheodyne, Cotati, CA, USA) sample injector fitted with a 50 µl sample loop. The detector was operated using a sensitivity range of 0.005 AUFS and wavelength of 280 nm. A YMC-Pack ODS-A column (5 µm, 150 x 4.6 mm ID) from YMC Co. Ltd. (Kyoto, Japan) fitted with a refillable guard column (Upchurch Scientific, Oak Harbour, USA) packed with Perisorb RP-18, 30-40 µm pellicular stationary phase (Upchurch Scientific, Oak Harbour, USA) was used for separation.

Extraction and Analysis

The mobile phase comprised 0.01 M ammonium formate and acetonitrile (50:50, v/v) adjusted to pH 3.5 with concentrated hydrochloric acid. Analysis was run at a flow rate of 1.5 ml/min and quantification was by peak height.

Diclofenac was extracted from the plasma samples according to the following procedure: 500 µl aliquot of plasma sample was accurately measured into a 2.0 ml Eppendorf® microcentrifuge tube, followed by the addition of 50 µl of 4 M HCl and of 50 µl of mefenamic acid (20 µg/ml in 60% methanol) as internal standard. 1.5 ml of dichloromethane was then added as extracting solvent. The mixture was vortexed for 1 min using a vortex mixer and then centrifuged at 12800 G for 15 min. The organic layer was transferred into a new Eppendorf®, tube and then evaporated to dryness at 45°C under a gentle stream of nitrogen gas. The extraction process was repeated with 1 ml of fresh dichloromethane and the supernatant added to the dried residue of the first extraction. After evaporation to dryness, the residue was reconstituted with 80 µl of mobile phase and 50 µl injected into the column.

Validation

The *intra*-day and *inter*-day accuracy and precision of the assay method at various concentration levels, together with the recovery values of the extraction procedure are given in Table I. The accuracy was expressed as the percentage of the measured concentration over that of the spiked value whereas the precision was denoted using the coefficient of variation. Both the *intra-day* and *inter*-day accuracy values were all within 94-106% range at the concentrations determined, while all the coefficient of variation values were less than 10% at the same concentrations. In addition, the recovery values were all more than 85% for diclofenac and 86.9% for mefenamic acid. The response of the detector was linear over a concentration range of 62.5-2000.0 ng/ml. The detection limit was approximately 30 ng/ml at a signal to noise ratio of 3:1, while the limit of quantification was set at 62.5 ng/ml, being the lowest concentration value used in constructing the standard curve.

Data Analysis

The two preparations were compared using the parameters total area under the plasma concentration-time curve ($AUC_{0-\infty}$), peak plasma concentration (C_{max}) and time to reach maximum plasma concentration (T_{max}). The C_{max} and T_{max} values were obtained directly from the plasma-concentration data[4], while $AUC_{0-\infty}$ was obtained by adding the area from time zero to the last sampling time (AUC_{0-t}) and the area from the last sampling time to infinity ($AUC_{t-\infty}$). In all cases, the $AUC_{t-\infty}$ was found to be less than 20% of the $AUC_{0-\infty}$. The values of C_{max} and $AUC_{0-\infty}$ obtained with the two preparations were analyzed using analysis of variance (ANOVA) procedure[5] for two-way crossover study. The $AUC_{0-\infty}$ and C_{max} values were logarithmically

transformed prior to the data analysis. On the other hand, the T_{max} values of the two preparations were analyzed using the Wilcoxon Signed Rank Test for paired samples.

Results

The mean plasma diclofenac concentration versus time profiles of Voltaren®, SR and Zolterol®, SR are shown in Figure 1. Both profiles showed that absorption of diclofenac from the two preparations were slow and sustained, and concentration levels were still detectable at 36 hours after dosing. Table II gives the individual values of T_{max}, C_{max}, and $AUC_{0-\infty}$ obtained with Voltaren® SR and Zolterol® SR. The parameters T_{max} and $AUC_{0-\infty}$ are related to the respective rate and extent of drug absorption, while C_{max} is related to both processes[6]. There was no statistically significant difference between the T_{max} values of Zolterol® SR and Voltaren® SR ($p>0.05$). Similarly, no statistically significant difference was observed between the values of $AUC_{0-\infty}$ ($p=0.1927$) and the values of C_{max} ($p=0.0594$) of the two preparations. In addition, the 90% confidence interval for the ratio of the $AUC_{0-\infty}$ values of Zolterol® SR over those of Voltaren® SR was estimated to be between 0.85 and 1.07, which is within the acceptable bioequivalence interval of 0.80 to 1.25. However, in the case of the parameter C_{max}, the 90% confidence interval could not be reliably estimated due to the presence of multiple peaks. Based on the higher peak values observed for each preparation, Zolterol® SR achieved a mean of 86% of that of Voltaren® SR.

Table I: Precision and Accuracy of Assay Method (N=6)

concentration	recovery		*intra*-day		*inter*-day	
(ng/ml)	mean (%)	CV(%)	Accuracy (%)	CV(%)	Accuracy (%)	CV(%)
62.5	86.9	9.8	94.2	9.8	96.4	7.2
500.0	102.0	5.1	103.9	7.9	100.2	6.0
2000.0	93.1	3.0	97.8	1.2	100.6	3.4

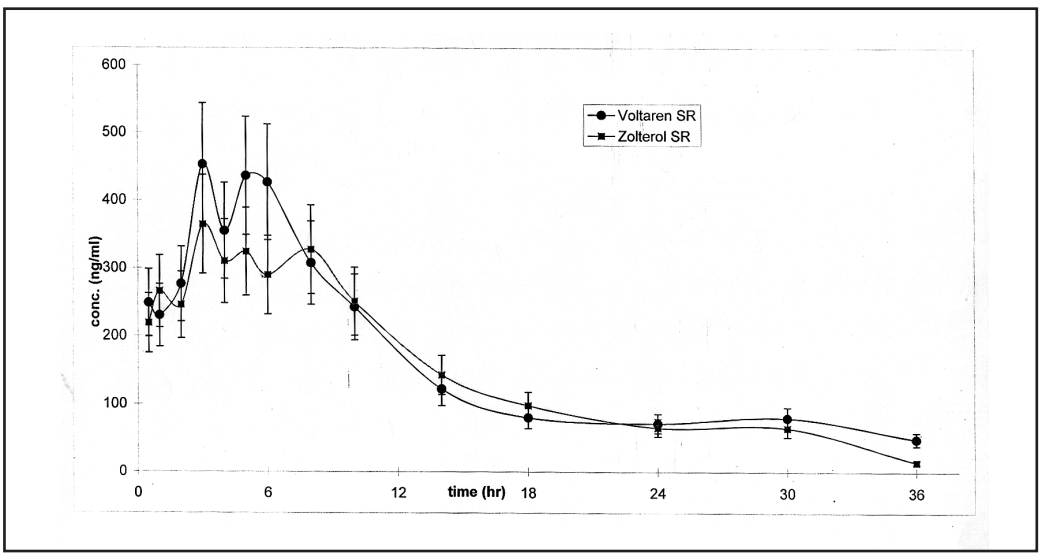

Fig. 1: Mean plasma diclofenac concentration versus time curves of Voltaren SR and Zolterol SR

Table II: Individual T_{max}, C_{max} and $AUC_{0\text{-}inf}$ Values of Volaren SR and Zolterol SR

	Voltaren SR			Zolterol SR		
Subjects	T_{max} (hr)	C_{max} (ng/ml)	$AUC_{0\rightarrow\infty}$ (hr.ng/ml)	T_{max} (hr)	C_{max} (ng/ml)	$AUC_{0\rightarrow\infty}$ (hr.ng/ml)
1	10.0	530.6	3676.9	8.0	274.9	3159.1
2	5.0	895.2	4205.0	2.0	403.3	3076.2
3	4.0	908.0	16825.4	6.0	681.4	17215.2
4	3.0	544.2	4074.6	0.5	225.4	2666.8
5	3.0	658.3	5638.6	10.0	367.1	4812.3
6	5.0	549.3	2676.5	8.0	366.9	3497.0
7	1.0	262.3	2404.6	8.0	371.6	3155.6
8	1.0	475.6	3867.2	4.0	1221.2	4026.4
9	0.5	594.7	4357.8	5.0	720.2	3928.7
10	3.0	834.0	6625.0	1.0	363.0	4899.8
11	6.0	1014.2	5441.0	5.0	593.8	5226.0
12	4.0	560.2	9286.1	1.0	547.0	7645.7
Mean	3.0	453.1	5756.6	3.0	511.3	5275.7
SD	2.6	217.6	3950.3	3.2	272.5	3996.4

Discussion

Multiple peaks were observed in both preparations but Voltaren® SR had slightly higher peak concentration values. The incidence of multiple peaks in the resulting plasma profile after administration of Voltaren® SR prior to an overnight fast has been reported by Hasan et al. [8]. This phenomenon of multiple peaks may reflect changes in the rate of drug release from the dosage form with changes in the pH of its environment within the gastrointestinal tract [9].

The T_{max} for Voltaren® SR (3.0 ± 2.5 h) reported in this study is in good agreement with the value (3.0 h) reported by Hasan et al. [10]. The T_{max} value of Zolterol® SR (3.0 ± 3.2 h) was found to be comparable to Voltaren® SR. From the plasma concentration profile obtained the elimination rate constant (k_e) could not be reliably estimated due to the sustained release nature of both products. The parameter $AUC_{0-\infty}$ showed relatively wide *inter*-subject variation, which could be attributed to differences in body weight and drug disposition among volunteers. In comparison, the *intra*-subject variation, estimated from the mean square error of the ANOVA analysis [11] appeared to be small. The *intra*-subject coefficient of variation (CV) for $AUC_{0-\infty}$ was approximately 16.0%. Considering that if the true difference between the two products is equal or smaller than 20%, the number of 12 subjects employed in the present study was found to be sufficient to provide a test power ($1-\beta$) greater than 80% to confirm that there was not a statistically significant difference between the $AUC_{0-\infty}$ values of the two products at a type 1 error rate (α) of 0.05 [12].

Conclusion

Zolterol®, SR was found to be comparable to Voltaren® SR in the extent of absorption. The mean peak concentration achieved was approximately 86% of that of Voltaren® SR. On the basis of the above results it is reasonable to conclude that Zolterol® SR can be considered to be bioequivalent to Voltaren® SR.

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