

Pharmacokinetics Study of Aceclofenac in Pakistani Population and Effects of Sucralfate Co-administration on Bioavailability of Aceclofenac

Asia Naz *¹

Anwar Ejaz Beg¹

Khwaja Zafar Ahmed¹

Huma Ali¹

Shabana Naz²

Farya Zafar¹

¹Ziauddin College of Pharmacy, Ziauddin University Karachi, Pakistan.

²Research Institute of Pharmaceutical Sciences,
Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Karachi.

KEY WORDS: : Aceclofenac, Pakistani population, pharmacokinetics, sucralfate, healthy humans and RP-HPLC

ABSTRACT

Objective: Aceclofenac is a phenylacetic acid derivative; this nonsteroidal anti-inflammatory drug is a potent anti-inflammatory analgesic and antipyretic. The objectives of this study were to conduct a pharmacokinetic study of aceclofenac in a Pakistani population, to compare the pharmacokinetic profile of the local population with the United Kingdom (UK) and to determine the effect of sucralfate co-administration on pharmacokinetics of aceclofenac in healthy volunteers.

Method: In an open-label, crossover study, 24 healthy volunteers were randomized to receive a single dose of 100 mg aceclofenac

with or without single dose of 1 g sucralfate. Plasma samples taken pre-dose and at regular intervals up to 12 hours post-dose were assayed for aceclofenac concentrations. Analysis of variance was performed on log-transformed data; for mean ratios of 0.8 to 1.25 (20%), differences were considered minimal. Bioequivalence was reached if 90% confidence intervals (CI) of treatment mean ratios were between 80% and 125%. Results: No significant differences were found based on analysis of variance. Mean values and 90% CI of aceclofenac in Pakistani/UK population ratios for these parameters were observed as follows: C_{max} 13.39 versus 13.09 µg/mL (90 % CI; 0.97-1.03); AUC_{0-t}, 28.99 versus 24.68 µg. h/mL (90 % CI ; 0.89-1.14); and AUC_{0-α} 29.82 versus 25.62 µg.h/mL (90 % CI; 0.89-1.14). The mean geometric ratios for maximum plasma

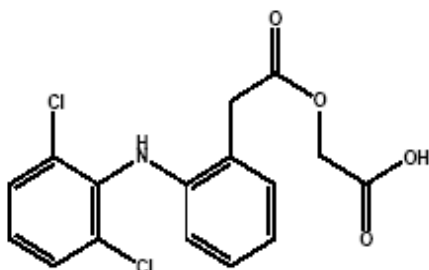
concentration (C_{max}) of the aceclofenac alone and with 1 g sucralfate treatment groups were within 20%. Confidence intervals were not within 80 to 125% for AUC_{0-t} and AUC_{0-∞}. There was on average 122% delay (90% CI; 3.13, 3.30) in time to reach maximum plasma concentration following administration with sucralfate, compared with administration of aceclofenac alone (P ≤ 0.000).

Conclusion: There was no significant difference of aceclofenac pharmacokinetic parameters between the Pakistani and UK populations. Standard bioavailability measures showed that sucralfate had a significant effect on the bioavailability of aceclofenac. Sucralfate co-administration resulted in a considerable increase in the rate of absorption and showed erratic mode.

INTRODUCTION:

For inflammatory situations, non-steroidal anti-inflammatory (NSAIDs) compounds are most frequently given to patients, but the common occurrence of gastrointestinal side effects decreases their effectiveness.¹ These side effects result in mucosal barrier breakage² that may lead to mucosal injury³ and variation in gastric mucus secretions⁴. Aceclofenac (fig. 1) has been used as an

Figure 1. Chemical structure of aceclofenac



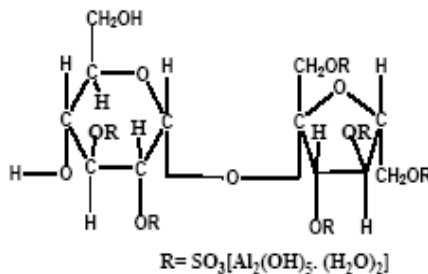
anti-inflammatory agent with analgesic and antipyretic activity.

It has enhanced gastrointestinal acceptance as compared with other NSAID compounds, like diclofenac.

Several reports indicate the use of aceclofenac for treating the signs and symptoms of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. It was found that Aceclofenac's analgesic activity is effective within 30 min of administration when taken orally. T_{max} is achieved within 1 to 3 hrs of administration. C_{max} and AUC values increase proportionally with a dose ranging from 50 to 150mg. The plasma elimination t_{1/2} is approximately 3 to 4 hrs, with elimination of parent compound through urine and to a smaller extent, through feces⁵.

Several authors have reported the clinically successful administration of sucralfate (fig. 2) in treating duodenal^{6,7} and gastric⁸ ulcer disease.

Figure 2. Chemical structure of sucralfate.



In order to inhibit NSAID-induced gastrointestinal erosions, use of sucralfate and proton pump inhibitors (PPIs) were reported to protect gastroduodenal mucosa⁹. There are several reported mechanisms of action of sucralfate, which are: (a) development of sucralfate complex with proteinaceous exudates of ulcer;¹⁰ these complexes act as a protective film, preventing additional damage induced by acid, pepsin and bile.¹¹ (b) development of sucralfate film in order to inhibit hydrogen ions; (c) decreasing pepsin activity; (d) bile salt adsorption; (e) improved mucus secretion¹⁰ and (f) improved prostaglandin synthesis^{12,13}. However sucralfate is known to adsorb bile salts, and may adsorb NSAIDs when given concomitantly. A single-dose of 2 g sucralfate given to healthy volunteers delayed the absorption

of naproxen without affecting its overall bioavailability¹⁴. It has also been demonstrated that sucralfate does not modify salicylates and aspirin blood levels.¹⁶

Pharmacokinetic parameters showed the release of the drug compound from the drug product with absorption into the circulation. Typical bioequivalence can be conducted as a crossover study, in which clearance and different physiologic factors (e.g., gastric emptying, motility, and pH) are supposed to have less variability within an individual compared with variability between individuals.¹⁵ The aims of present study were as follows: (a) to study the pharmacokinetics of aceclofenac in a previously unreported Pakistani population; (b) to compare the pharmacokinetic profile among Pakistani and UK populations; (c) to evaluate the pharmacokinetic parameters of aceclofenac, with or without sucralfate after a single oral dose.

MATERIALS AND METHOD:

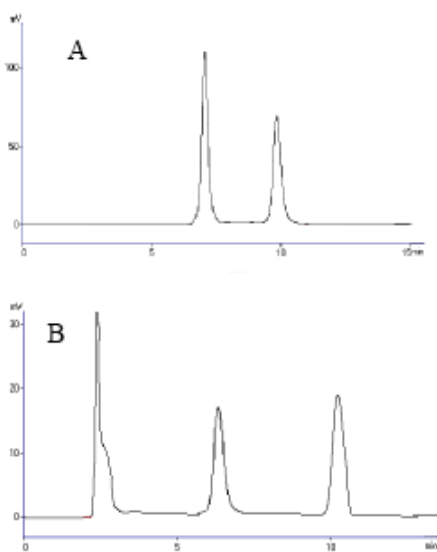
Aceclofenac (99.79 %) was gifted by Sami Pharmaceuticals (Pvt.) Ltd, Pakistan and naproxen (99.89 %) by Pharmevo Pakistan Ltd. Aceclofenac 100 mg tablet (Akeris batch No.03J, from Sami Pharmaceuticals (Pvt.) Ltd, Pakistan). Sucralfate 1g (Ulsanic, Batch No 100285, from Highnoon Laboratories Ltd, Pakistan) were obtained from retail pharmacy. Acetonitrile gradient grade (Merk, Germany) and HPLC grade water were used to prepare the mobile phase.

Apparatus and chromatographic conditions:

The apparatus was an isocratic HPLC system (LC-20AT, Shimadzu, Japan) coupled with a UV-visible detector (SPD-20A, Shimadzu, Japan) consisting of a 20 μ L injection loop. The chromatographic system was integrated via Shimadzu model CBM-102 Communication Bus Module to computer. Shimadzu CLASS-VP software (Version 5.03) was used for data acquisition and mathematical calculations. The mobile phase consisted of acetonitrile: deionized water (55:45) with final pH of 2.8 adjusted with

orthophosphoric acid. An optimum flow rate of 1 mL/min for the mobile phase resulted in retention times of 10.0 min for aceclofenac and 6.5 min for naproxen (IS), as shown in figure 3. Each analysis required less than 12 min and effluent was monitored at 286 nm.

Figure 3. Chromatograms of aceclofenac and naproxen in pharmaceutical formation (A), plasma sample obtained at 1.5 hr after a single oral dose of 100 mg aceclofenac from a healthy volunteer containing 13.4 μ g/ml of aceclofenac (B). The retention times for aceclofenac and naproxen (IS) are 10.0 and 6.0 min, respectively.



Method of Analysis

The aceclofenac concentrations in plasma were determined by the validated HPLC-method, with respect to suitable specificity, sensitivity, linearity, recovery, accuracy and precision. The stability of the plasma samples was evaluated at room temperature, under frozen conditions and during a freeze-thaw cycle.

The following data were taken from the validation report: the calibration curve for aceclofenac ranged from 0.05 to 30 μ g/mL; the linear relationship between concentration and signal intensity was obtained ($r =$

Table 1. Within and between-day variability and % accuracy or % recovery of the HPLC assay for determination of plasma aceclofenac concentrations.

Concentration ($\mu\text{g/mL}$)	Variation (%RSD)		% Accuracy/ Recovery	
	Intra-day	Inter-day	Intra-day	Inter-day
30.0	0.38	1.10	99.42	99.98
25.0	1.36	1.01	99.99	101.2
20.0	0.04	0.98	100.0	102.5
10.0	0.08	0.05	103.42	100.5
5.00	0.39	2.15	102.6	98.5
2.50	0.04	0.24	101.8	103.5
1.00	0.98	1.21	99.30	102.1
0.50	1.21	1.33	98.56	100.9
0.25	0.38	2.70	101.9	103.2
0.10	0.58	1.23	103.8	100.5
0.05	1.05	1.15	105.9	102.9

0.9991) and the value of the intercept was less than 2% of a total 100% of the test concentration in all cases. The analyte concentration that produced a signal-to-noise ratio of 3:1 was accepted as the limit of detection (LOD).

The limit of quantitation (LOQ) was identified as the lowest plasma concentration of the standard curve that could be quantified with acceptable accuracy, precision and variability. The LOD and LOQ were 6.8 and 50 ng/mL, respectively. The intra- and inter-days accuracy and precision values of the assay methods are presented in table 1. The intra-day accuracy of the method for aceclofenac ranged from 98.56 to 105.9%, while the intra-day precision ranged from 0.42 to 1.36%. The inter-day accuracy of the method ranged from 98.56 to 103.5%, while the inter-day precision ranged from 0.05 to 2.7%.

Sample Preparation

One hundred μL of internal standard (100 $\mu\text{g/mL}$) was added to 1 mL of plasma samples from the volunteers. Volume was composed of MeCN up to 2 mL. The resulting solutions were vortexed for 2 min and centrifuged at 2000 g for 3 min. The supernatant was separated, filtered and injected to

HPLC. Sample concentrations were calculated by determining the AUC of aceclofenac and comparing AUC with the standard curve, obtained after analysis of calibration samples. The presences of disturbing endogenous peaks were observed on 24 human plasma samples.

Pharmacokinetic Study of aceclofenac

The present method was applied to a comparative pharmacokinetic profile of aceclofenac alone and aceclofenac in presences of sucralfate. The ethical committee on human studies of the Ziauddin University approved this study.

Subjects

Twenty-four healthy non-smoking adult male volunteers aged between 20 to 35 years and 56 to 76 kg in weight participated in the study. On the basis of medical history, clinical examinations and laboratory tests, including hematology, blood biochemistry and urine analyses, no subject had a history or evidence of hepatic, renal, gastro-intestinal or hematological deviations, or any acute/ chronic disease or drug allergy. The subjects were instructed to abstain from taking any medication for at least two weeks prior to and during the study period. Informed consent was obtained from the subjects after

Table 2. Pharmacokinetic parameters for aceclofenac following a single oral dose of 100 mg alone or coadministered with sucralfate (1gm).

Parameter	Aceclofenac	Aceclofenac + Sucralfate	F- Value	P- Value
C _{max} (µg/mL)	13.39 ± 0.22	12.17 ± 2.35	6.4	0.015
Log C _{max}	1.13 ± 0.01	1.064 ± 0.18	2.75	0.104
AUC _{0-t} (µg/mL. h)	28.99 ± 0.77	61.21 ± 2.25	4384.7	0.000
Log AUC _{0-t}	1.46 ± 0.01	1.787 ± 0.02	6533.0	0.000
AUC _{0-∞} (µg/mL. h)	29.82 ± 0.56	71.48 ± 2.25	7714.3	0.000
Log AUC _{0-∞}	1.47 ± 0.01	1.854 ± 0.01	11852.6	0.000
T _{max} (hr)	1.5 ± 0.000	5.00 ± 0.381	1840	0.000
Lz (1/hr)	0.227 ± 0.07	0.226 ± 0.19	-	-
t _{1/2} (hr)	3.05 ± 0.105	3.06 ± 0.100	133	0.717
MRT	3.18 ± 0.00	8.06 ± 1.040	528.3	0.000

explaining the nature and purpose of the study.

Study Design

This was a conventional, two-way, random, open label and crossover study with a one-week washout period conducted at Ziauddin College of Pharmacy, Ziauddin University. The 24 volunteers were divided into two groups of 12, each receiving one of the two treatments at the first period and the other treatment at the second period in a crossover fashion. All volunteers received treatment I (100mg aceclofenac alone) and treatment II (100mg aceclofenac with sucralfate). After an overnight fasting, subjects were given a single oral dose of 100 mg aceclofenac (Alkeris) either alone, or administered 30 minutes after administration of sucralfate 1g (Ulsanic) in a randomized fashion with 240 mL of water. Intake of food and beverages (other than water, which was allowed after 2 hours) was not allowed until 4 hours after drug administration. Beverages containing xanthine derivatives or alcohol, and intense physical activity were not allowed over the course of the study. Subjects were under continuous medical supervision throughout the study. Five mL blood samples were drawn into heparinized tubes through an indwelling canola at 0, 0.5, 1.0, 1.5, 2, 2.5, 3, 4, 5, 7, 9 and 12 hrs after dosing. The blood

samples were centrifuged at 3500 rpm for 10 minutes within 1 hr of sampling. Plasma samples were stored at -40C until analyzed.

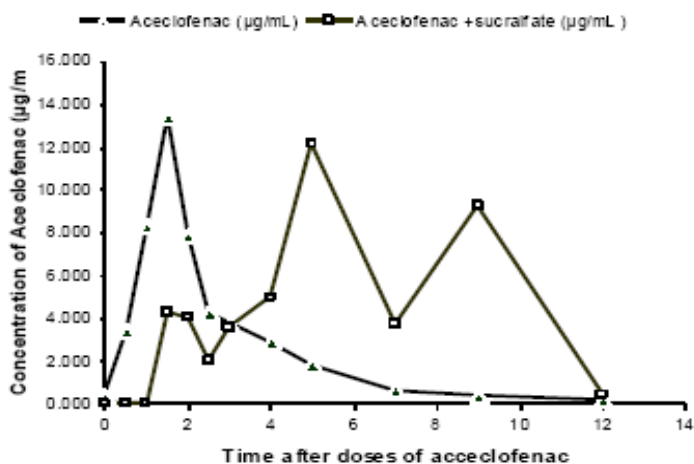
Pharmacokinetic Analysis

Aceclofenac plasma concentration-time data was analyzed with a non-compartmental model using Kinetica 5.0. The area under the curve to the last measurable concentration (AUC_{0-t}) was estimated by the linear trapezoidal rule and AUC_{0-∞} was calculated by equation $AUC_{0-t} + Ct / Lz$, where Ct is the last measurable concentration and Lz is the elimination rate constant, which was obtained from the least square fitted terminal log-linear portion of the plasma concentration-time profile. The peak plasma concentration (C_{max}) and corresponding time to peak (T_{max}) were determined by the inspection of the individual drug plasma concentration-time profiles.

Statistical Analysis

For the purpose of pharmacokinetic analysis, AUC_{0-t}, AUC_{0-∞}, and C_{max} were considered as primary variables. Plasma concentrations in the two groups (with and without concomitant administration of sucralfate) were compared using analysis of variance (ANOVA). The following parameters were compared: maximum plasma concentration, time to reach maximum plasma concentration, cumulative area under the curve

Figure 4. Mean plasma concentrations of aceclofenac following a single oral dose of 100 mg alone or with sucralfate (1.0 gm)



and absolute bioavailability. A difference between two related parameters was considered statistically significant for a P-value equal to or less than 0.05. The 90% confidence intervals of the ratio of pharmacokinetic parameters with and without concomitant administration of sucralfate, as well as those that were logarithmically transformed, were also estimated.¹⁷ All statistical analyses were performed using SPSS¹².

RESULTS

Pharmacokinetic of Aceclofenac

The mean pharmacokinetic parameters of aceclofenac (Alkeris 100 mg) from 24 Pakistani male subjects, including AUC_{0-t}, AUC_{0-∞}, C_{max} and T_{max}, were calculated from the data of aceclofenac plasma concentration at each time of blood collection as shown in table 2. AUC is the prominent parameter indicating that the whole drug exists in the body. C_{max} and T_{max} demonstrate the drug absorption. The rapid absorption with time (T_{max} 1.5 hrs) to peak concentration (C_{max} 13.39 µg/mL) was observed following oral ingestion. The mean (geometrical) plasma elimination half-life, AUC_{0-t}, and AUC_{0-∞}, were 3.05 hrs, 28.99 and 29.82 µg. hr /mL, respectively.

Effect of sucralfate on pharmacokinetic of aceclofenac

All 24 healthy male volunteers completed the study as per the protocol. Both treatments were well tolerated. Adverse effects that occurred during this study were minor. During the aceclofenac run-in period only one subject had complaint of mild nausea that was resolved without treatment. The mean plasma concentration-time profiles for treatment I and II were not identical, as presented in figure 4.

The mean concentration-time profile of treatment II resulted in a two-peak graphical presentation. It illustrates that sucralfate delays the absorption of aceclofenac, as evidenced by a mean increase in the T_{max} of 3.5 h. Results for all subjects showed an increase in this parameter. C_{max} 12.17 µg/mL was achieved at 5 hours post dose in treatment II, versus 13.39 µg/mL at 1.5 hours in treatment I. Mean curve of plasma concentration versus time profile of treatment II indicates the erratic absorption mode of aceclofenac. Figure 4 illustrates that sucralfate delays the absorption of the drug by 1 hour. In addition, the drug concentration increased to its C_{max} 12.17 µg/mL at 5 hours post dose, followed by a sharp decline to 0.74 µg/mL at 7 hours. For a second time, the plasma concentration of the drug sharply increased to 9.23 µg/mL at 9 hours post dose. The concentration gradually decreased

Table 3. Comparison of pharmacokinetic parameters of alkeris, aceclofenac and preservex following a single oral dose of 100 mg.

Parameter	T _{max}	T _{1/2}	Log C _{max}	Log AUC _{0-t}	Log AUC _{0-∞}
Alkeris ^a	1.50	3.05	1.13	1.46	1.47
Aceclofenac ^b	1.58	2.67	1.12	1.39	1.41
Preservex ^c	1.98	2.35	1.07	1.39	1.41
Ratio ^{a/b} (90 % CI)			1.01 (0.97-1.03)	1.05 (0.89-1.14)	1.05(0.89-1.14)
Ratio ^{a/c} (90 % CI)			1.05 (0.86-1.18)	1.06 (0.89-1.14)	1.04 (0.89-1.14)

to the minimum detected, 0.434 µg/mL, at 12 hours.

DISCUSSION

Pharmacokinetic of Aceclofenac

The results of this pharmacokinetic study of aceclofenac (alkeris) compared favorably with those from a previous study [18] conducted on aceclofenac (Sandoz Limited UK) and preservex (Almirall Limited UK) as shown in table 3. The limits of the 90% CIs for the ratios of AUC_{0-t}, AUC_{0-∞}, and C_{max} for log-transformed data fell within 0.80 to 1.25. The secondary efficacy criteria of time to peak plasma concentration (T_{max}) and the half-life (t_{1/2}) were similar for all products. It can be concluded that on the basis of rate and extent of absorption, the generic product (Alkeris) and reference products aceclofenac (Sandoz Ltd.) and preservex (Almirall Ltd.) had equivalent bioavailability and that the study medication was safe and well-tolerated in healthy volunteers at the dose given. In the light of above results we further concluded that the pharmacokinetics of aceclofenac are not different between Pakistani and UK populations.

Effect of sucralfate on pharmacokinetic of aceclofenac

Antacids and sucralfate are known to impair the absorption of ciprofloxacin, norfloxacin, ¹⁹ ketoconazole ²⁰ and phenytoin. ²¹ Sucralfate is a complex salt of sucrose sulfate and aluminum hydroxide. ²² These interactions result from the binding of the affected drug to either the aluminum or sulfated sucrose moiety. However, co-administration of fleroxacin, ²³ ofloxacin and naproxen with sucralfate slightly decreased the absorption.

Sucralfate does not affect the bioavailability of aspirin, cimetidine, diazepam, erythromycin, ibuprofen, ketoprofen, piroxicam, diclofenac, ²⁴ prednisone, propranolol or warfarin ²⁵⁻²⁸. The larger effect of sucralfate on the absorption of norfloxacin compared with that of ofloxacin, or the effect of sucralfate on the absorption of naproxen compared with ibuprofen, ketoprofen or piroxicam, indicates that fluoroquinolones and NSAIDs clearly differ in their potential to interact with metallic cations. ¹⁹ Therefore we determined the extent of sucralfate effect on aceclofenac pharmacokinetic when sucralfate (single dose of 1 g) is administered half an hour before the dose of aceclofenac.

The present study reveals that sucralfate significantly delay the absorption of aceclofenac, as evidenced by a mean increase in the T_{max} of 3.5 hours. Results for all subjects showed an increase in this parameter. This is consistent with the effects of sucralfate administration reported for other medications such as ketoconazole, naproxen and prednisone. ^{2, 8} The erratic absorption is probably due to the formation of an unstable complex between carboxyl and keto groups of aceclofenac and cation of sucralfate. Table 2 summarizes aceclofenac pharmacokinetics in the presence and absence of sucralfate. Table 4 shows the results of the statistical comparison of the pharmacokinetic parameters. Maximum plasma concentration of aceclofenac was, on average, only 6% lower following administration of sucralfate, compared with administration of aceclofenac alone, as shown in table 4. The mean ratio of log C_{max} was 0.94, indicating that the means were within 20%. The 90% CI for

Table 4. Comparison of pharmacokinetic parameters of aceclofenac following a single oral dose of 100 mg alone or coadministered with sucralfate (1 gm).

Parameter	T _{max}	T _{1/2}	Log C _{max}	Log AUC _{0-t}	Log AUC _{0-∞}
Alkeris ^a	1.50	3.05	1.13	1.46	1.47
Aceclofenac ^b	1.58	2.67	1.12	1.39	1.41
Preservex ^c	1.98	2.35	1.07	1.39	1.41
Ratio ^{a,b} (90 % CI)			1.01 (0.97-1.03)	1.05 (0.89-1.14)	1.05(0.89-1.14)
Ratio ^{a,c} (90 % CI)			1.05 (0.86-1.18)	1.06 (0.89-1.14)	1.04 (0.89-1.14)

the mean ratio of product means using log-transformed data ranged from 0.88 to 0.97. The variation between subject coefficients was 17.38%. There was, on average, a 122% delay (90% CI; 3.13, 3.30) in time to reach maximum plasma concentration following administration with sucralfate, compared with the administration of aceclofenac alone. A P-value less than 0.0000 was considered a statistically significant difference. Overall, administration of aceclofenac with sucralfate increased log AUC_{0-∞} 26% on average, relative to results obtained with administration of aceclofenac alone. The 90% CI for the product ratio was 2.36 and 2.43, that is higher than the allowed CI, i.e. 0.80 and 1.25. However, sucralfate does not significantly ($P > 0.20$) decrease the cumulative plasma concentration of aceclofenac. The log-transformed cumulative concentration ratio was 0.984, which indicates a 1.6% decrease in cumulative plasma concentration. Plasma concentrations of aceclofenac declined with a mean t_{1/2} of 3.05 hours when administered alone and 3.06 hours when administered with sucralfate. The data here concludes that a meal interval (0.5 hour) is not sufficient, but separating the administration of two agents by three hours (the half life of aceclofenac) would possibly decrease the potential interaction of sucralfate and aceclofenac.

CONCLUSION

This study indicates that the developed method was linear, accurate, precise and sensitive over a wide range of concentrations. It was also simple and less time consuming. This method was successfully applied to analyze the plasma concentration

of aceclofenac in volunteers without any interference. Comparison of pharmacokinetic aceclofenac between local and UK populations showed no significant difference at the level of $P \leq 0.05$. Pharmacokinetic profiles of Alkeris were comparable to previous studies. One hundred mg of aceclofenac showed delayed and erratic absorption in healthy volunteers when co-administered with sucralfate, which is likely to be of clinical relevance.

ACKNOWLEDGEMENTS

The authors are grateful to Sami Pharmaceutical Pvt. Ltd. Pakistan, for the financial support of this work.

REFERENCES:

1. Rooney PJ, Capell A., Paterson S, Buchanan WW, Dick WC., Continued use of nonsteroidal anti-inflammatory drugs. An index of clinical efficacy. *Br J Clin Pharmacol.* 1978; 5 : 453-455.
2. Menguy R., Masters YF. Effects of aspirin on gastric mucous secretion. *Surg Gynec Obstet.* 1965; 120: 92-98.
3. Lanza F, Royer G, Nelson R. An endoscopic evaluation of the effects of non-steroidal anti-inflammatory drugs on the gastric mucosa. *Gastrointest Endosc.* 1975; 21:103-105.
4. Kent PW, Allen A. The biosynthesis of intestinal mucins. The effect of salicylates on glycoprotein biosynthesis by sheep colonic and human gastric mucosal tissue in vitro. *Biochem J.* 1968; 106: 645-658.
5. Si-Youn Rhim, Jin-Hee Park, Yoo-Sin Park, Min-Ho Lee, Leslie M. Shaw, Ju-Seop kang, Bioequivalence and pharmacokinetic evaluation of two branded formulations of aceclofenac 100mg: A single-dose randomized, open-label, two-period crossover comparison in healthy Korean adult volunteers. *Clinical Therapeutics.* 2008 30: (4) 633-640.
6. Martin F, Farley A, Gagnon M, Benseman D. Comparison of the healing capacities of sucralfate and cimetidine in the short term treatment of duodenal ulcer. A double blind randomized trial. *Gastroenterology* 1982; 82:401-405.

7. Hollander D. Efficacy of sucralfate for duodenal ulcers. A multicenter double – blind trial. *J Clin Gastroenterol.* 1983; 3 (2) 153-157.
8. Martin F, Farley A, Gagnon M, Poitras P, Bensemana D. Short term treatment with sucralfate and cimetidine in gastric ulcer. Preliminary results of a controlled randomized trial. *Scand J Gastroenterol.* 1983; 18 (83) 37-41.
9. Malagelada JR, Arturo Rodriguez de la Serna, Dammann HG, Pons M, Armas C, Sala M, Tena X, Celdran E, Mesa A. Sucralfate therapy in NSAID bleeding gastropathy. *Clinical Gastroenterology and hepatology* 2003; 1: 51-56.
10. Harrington SJ, Schlegel JF, Code CF. The protective effect of sucralfate on the gastric mucosa of rats. *J. Clin. Gastroenterol.* 1981; 3(2) 129-134.
11. Hoogerwerf WA, Pasricha PJ. Agent used for control of gastric acidity and treatment of peptic ulcers and gastroesophageal reflux disease. Joel G. Hardman, Lee E. Limbird (Eds). 10ed. McGraw hill, 2001; 1012.
12. Tarnawski, Hollander D, Krause WJ, Gergely H. Sucralfate protection of gastric mucosa against alcohol injury. Morphologic, ultra structural and function time sequence analysis. *Gastroenterology.* 1983; 84: 1331.
13. Cohen MM, Bowdler R, Gervais P. Sucralfate protects human gastric mucosa from acute ethanol injury (abstr). *Gastroenterology.* 1986; 90: 1376.
14. Caille G, Souich PD, Gervais P, Besner JG, Vezina M. Effects of concurrent Sucralfate administration on pharmacokinetics of Naproxen. *The American Journal of Medicine.* 1987; 83; (3B) 67-73.
15. Mei-Ling Chen, Vinod Shah, Rabindra Patnaik, Wallace Adams, Ajaz Hussain, Dale Conner, Mehul Mehta, Henry Malinowski, John Lazor, Shiew-Mei Huang, Don Hare, Lawrence Lesko, Douglas Sporn, and Roger Williams. Bioavailability and Bioequivalence: An FDA Regulatory Overview. *Pharmaceutical Research,* 18 (12) 2001.
16. Tesler MA, Lim ES. Protection of gastric mucosa by sucralfate from aspirin-induced erosions. *J Clin Gastroenterol.* 1981; 3 (2) 175-179.
17. Westlake WJ. Use of confidence intervals in analysis of comparative bioavailability trials. *J. Pharm. Sci.* 1972; 61(8) 1340-1341.
18. <http://www.mhra.gov.uk/home/groups/lunit1/documents/websitesresources/con2030967.pdf>
19. Lehti P, Kivisto KT. Effect of Sucralfate on Absorption of norfloxacin and ofloxacin. *Antimicrobial Agents and Chemotherapy.* 1994; 248-251.
20. Stephen C. Piscitelli, Thomas F. Goss, John H. Wilton, David T. D'andrea, Harvey Goldstein, And Jerome J. Schentag, Effects of Ranitidine and Sucralfate on Ketoconazole Bioavailability. *antimicrobial agents and chemotherapy,* 1991; 1765-1771.
21. Lubowski TJ, Nightingale CH, Sweeney K, Quintiliani R. Effect of sucralfate on pharmacokinetics of feroxacin in healthy volunteers. *Antimicrob. Agents Chemotherapy.* 1992; 36: 2758- 2760.
22. McCarthy DM, Sucralfate. *N. Engl. J. Med.* 991; 325:1017- 1025.12.
23. Lubowski TJ, Nightingale CH, Sweeney K, Quintiliani R. Effect of sucralfate on pharmacokinetics of feroxacin in healthy volunteers. *Antimicrobial agents chemotherapy.* 1992; 36: 2758 - 2760.
24. Ungethüm W. Study on the interaction between sucralfate and diclofenac / piroxicam in healthy volunteers. *Arzneimittelforschung.* 1991; 41: (8) 797-800.
25. Gambertoglio JG, Romac DR, Yong CL, Birnbaum J, Lizak P, and Amend WJ. Lack of effect of sucralfate on prednisone bioavailability. *Am. J. Gastroenterol.* 1987; 82: 42-45.
26. Hall TG, Cuddy PG, Glass CJ, Srikumaran M. Effect of sucralfate on phenytoin bioavailability. *Drug Intell. Clin. Pharm.* 1986; 20: 607-611.
27. Miller LG, Prichard JG, White CA, Vytala B, Feldman S, Bowman RC. Effect of concurrent sucralfate administration on the absorption of erythromycin. *J. Clin. Pharmacol.* 1990; 30: 39-44.
28. Parpia SH., Nix DE., Hejmanowski LB, Goldstein HR, Wilton JH, Schentag JJ. Sucralfate reduces the gastrointestinal absorption of norfloxacin. *Antimicrob. Agents Chemother.* 1989; 33: 99-102.