Pakistan Journal of Pharmaceutical Sciences
Vol. 18, No.1, January 2005, pp.18-24

PHARMACOKINETICS OF DICLOFENAC SODIUM IN NORMAL MAN

S.M. FARID HASAN, TASNEEM AHMED*, NASIRA TALIB AND FOUZIA HASAN*****

*Jinnah Medical & Dental College, Karachi, *Pharma Professional Services, Karachi*
***Department of Pharmacy, University of the Punjab, Lahore*
****Department of Pharmaceutics, Faculty of Pharmacy*
University of Karachi, Karachi-75270

Diclofenac sodium was administered as 50 mg tablets to four healthy male volunteers in a two-way randomized crossover study in which volunteers were either fasted or were given a standard breakfast immediately prior to dosing. Blood samples were obtained upto 9 hours period and drug concentration were determined by HPLC method.

Besides a significantly delayed (at $p>0.1$) peak in fed state; an increase in absorption rate constant was observed as the only significant (at $p>0.05$) effect of food on biopharmaceutic characteristic of diclofenac sodium. However, the intrinsic absorption of diclofenac sodium is also fast and it is not being the rate limiting factor in the bioavailability of diclofenac sodium, its decrease upto about 18 minutes (0.31 ± 0.05 hr) from 11 minutes (0.19 ± 0.02 hr) produces a null difference as the net effect on bioavailability, particularly when the drug is to be used in multiple dosage regimen.

Keywords: Pharmacokinetics, diclofenac sodium, HPLC method.

INTRODUCTION

The first nonsteroidal anti-inflammatory agent introduced after salicylic acid was phenylbutazone, which made its appearance in 1952. A decade or more later, competitive compounds such as mefenamic acid, ibuprofen, and indomethacin were introduced (Sallmann, 1975).

At this point it was decided to start a project aimed at developing a novel anti-inflammatory drug which should be superior both in activity and tolerability.

Diclofenac sodium has an acidity constant of 4 and a partition coefficient of 13.4. The structural elements include a phenylacetic acid group, a secondary amino group, and a phenyl ring containing chlorine atoms which cause maximum twisting of the ring (Salmann, 1986).

The half-life of diclofenac sodium in plasma varies from 1-3 hours (Adeyeye & Li, 1990; Reynold, 1993; Willis *et al*., 1979; Degen *et al*., 1988; Said & Sharaf, 1981 and Landsdorp *et al*., 1990), with mean peak plasma levels of approximately 0.5 µg/ml and 1.0 µg/ml occurring after about two hours after single doses of 25 mg and 50 mg of enteric-coated tablets respectively (Riess *et al*., 1978).

There are no data available on the distribution of diclofenac in organs or tissues of man. Animal studies have shown that the highest concentrations of diclofenac are found in bile, liver, and kidneys followed by blood, heart and lungs (Riess *et al*., 1978).

Diclofenac, like all NSAIDs, is $\geq$ 99.5% bound to human serum proteins, specifically albumin (Riess *et al*., 1978 and Chamouard *et al*., 1985). It accumulates in synovial fluid after oral administration, which may explain the duration of therapeutic effect that is considerably longer that the plasma half-life (Insel, 1991).

Diclofenac has been marketed since 1973 (Todd & Sorkin, 1988 and Sengupta *et al*., 1985). It has been approved in the United States (Ciba-Geigy, 1988). Experimental and clinical findings obtained to date have indicated that diclofenac sodium was synthesized on well-founded principles (Sallmann, 1986).

In this study, the effect of food on the pharmacokinetic parameters of diclofenac sodium (voltaren 50 mg) was examined in four healthy male volunteers.

MATERIALS AND METHODS

Materials and methods utilized in this study are described elsewhere (Farid *et al*., 2004).

RESULTS AND DISCUSSION

The plasma concentrations of diclofenac sodium in four healthy human volunteers after a single oral administration of 50 mg dose (voltaren 50 mg) in fasting and fed conditions are given in table-1 (mean ± SEM). The mean levels produced by single dose in both the states were subjected to super position method for simulating levels in multi-dose treatment. Table-2 and table-3 report the generated levels after four doses six hourly in fasting and fed conditions. Thus it is clear from these tables that multi-dose usage of the drug will finally produce identical steady state pattern and thus neither the fasting nor fed condition has any beneficial edge over each other as far as the levels are concerned.

Absorption rate is the only parameter in present work which

Table 1
Plasma levels of diclofenac sodium in all human volunteers in control state (fasting) and in treatment state (after food) after oral administration of 50 mg dose in the form of enteric-coated tablet

Time (hours)	Control state (fasting) Mean ± SEM (ug/ml)	Treatment state (after food) Mean ± SEM (ug/ml)
1.00	0.1275 ± 0.0775	0.0975 ± 0.0542
1.50	0.4300 ± 0.3239	0.3300 ± 0.2568
2.00	1.0425 ± 0.6855	0.6300 ± 0.2946
2.50	1.0150 ± 0.2216	0.8925 ± 0.5053
3.00	1.0975 ± 0.4389	0.8375 ± 0.2418
3.50	0.6150 ± 0.2141	0.7525 ± 0.3250
4.00	0.3325 ± 0.1048	0.4500 ± 0.1695
4.50	0.2325 ± 0.0671	0.2450 ± 0.0913
5.00	0.1525 ± 0.0413	0.1675 ± 0.0664
5.50	0.1025 ± 0.0217	0.1150 ± 0.0448
6.00	0.0900 ± 0.0187	0.0875 ± 0.0335
7.00	0.0625 ± 0.0111	0.0650 ± 0.0185
8.00	0.0500 ± 0.0091	0.0500 ± 0.0122
9.00	0.0350 ± 0.0050	0.0375 ± 0.0125

is found significantly different at 0.05 level of significance. The absorption half-lives observed in both the states along with the results of ANOVA and t-tests; paired and unpaired are given in table-4.

As has been discussed previously that peak time in fed state is delayed (Farid *et al*., 2004). However, the absorption rate is significantly (at $p>0.05$) higher in fed state and consequently the half-life is lower. It is thus concluded that the presence of food delays the dissolution which is responsible of longer lag time in fed state, however, once the absorption started it was found faster. The possible reason which may be offered for this rapid absorption is the more blood flow towards, stomach in presence of the food.

Absorption half-life (mean ± SEM) in control as found to be 0.31 ± 0.05 hr where as in treatment it appeared to be 0.19 ± 0.02 hr.

Willis *et al* (1979) examined the pharmacokinetics of diclofenac sodium following intravenous and oral administration, to healthy female volunteers. Individual drug profiles were described by a triexponential function and mean- half-lives of the three exponential phases were 0.05, 0.26 and 1.1 hr. After oral doses of enteric-coated tablets, the lag time between dosing and the appearance of drug in plasma varied between 1.0 and 4.5 hr. Peak plasma diclofenac levels ranged from 1.4 to 3.0 µg/ml. The mean terminal drug half-life in plasma was 1.8 hr after oral doses. Fifty percent of orally dosed diclofenac did not reach the systemic circulation due to first pass metabolism.

Said and Sharaf (1981) gave single oral dose of 10 mg/kg of diclofenac sodium to rabbits and determined serum concentrations by a developed HPLC method. The observed serum levels of rabbits were fitted to a one-compartment open model. The mean values of $t_{1/2}e$, ke, $t_{1/2}a$, ka and t_{max} were 1.98 h, 0.3455h^{-1}, 1.2357 h, 0.5653 h^{-1} and 2.2267 h, respectively.

Thus the value of absorption half-life cited in the above studies were 0.05 hr (Willis, 1979) and 1.2357 hr (Said and Sharaf, 1981) respectively. A large difference in absorption half-lives may be due to physiological variability of subjects participated in the studies.

Distribution half-life (mean ± SEM) in treatment was found to be 0.27 ± 0.05 hr where as in control it appeared to be 0.39 ± 0.06 hr. The distribution half-lives observed in both the states along with the results of ANOVA and t-tests; paired and unpaired are given in table-5.

A previous study (Willis *et al*., 1979) indicates the distribution half-life of diclofenac sodium in normal state

Table 2
Simulation of plasma levels of diclofenac sodium in an 6 hourly 50 mg dose system upto 4 doses generated through superposition technique by utilizing mean levels obtain after single dose oral administration with tablets in control (fasting) state

Time	First dose	Second dose		Third dose		Fourth dose	
0	0						
1	0.1275						
2	1.0425						
3	1.0975						
4	0.3325						
5	0.1525						
6	0.0900	(+0)	0.0900				
7	0.0625	(+0.1275)	0.19				
8	0.0500	(+1.0425)	1.0925				
9	0.0350	(+1.0975)	1.1325				
10	0	(+0.3325)	0.3325				
11		(+0.1525)	0.1525				
12		(+0.0900)	0.0900	(+0)	0.0900		
13		(+0.0625)	0.0625	(+0.1275)	0.19		
14		(+0.0500)	0.0500	(+1.0425)	1.0925		
15		(+0.0350)	0.0350	(+1.0975)	1.1325		
16		(+0)	0	(+0.3325)	0.3325		
17				(+0.1525)	0.1525		
18				(+0.0900)	0.0900	(+0)	0.0900
19				(+0.0625)	0.0625	(+0.1275)	0.19
20				(+0.0500)	0.0500	(+1.0425)	1.0925
21				(+0.0350)	0.0350	(+1.0975)	1.1325
22				(+0)	0	(+0.3325)	0.3325
23						(+0.1525)	0.1525
24						(+0.0900)	0.0900
25						(+0.0625)	0.0625
26						(+0.0500)	0.0500
27						(+0.0350)	0.0350
28						(+0)	0

after intravenous administration, which is 0.26 hr. This value is not in very close agreement with the value estimated in the present work, however; it is not very much different.

The plasma levels versus time profiles in the post-absorptive phases of all subjects were found to have a value of correlation coefficient 0.9. This shows the linear disposition of diclofenac sodium for the dose administered. The biological half-lives (mean ± SEM) in the two states were found to be 2.72 ± 0.29 hr with food and 2.63 ± 0.19 hr without food. The two values are obviously very close and resembling. This indicates that food given in the treatment state has no effect on drug metabolism or drug filtration

Table 3
Simulation of plasma levels of diclofenac sodium in an 6 hourly 50 mg dose system upto 4 doses generated through superposition technique by utilizing mean levels obtain after single dose oral administration with tablets in treatment (after food) state

Time	First dose	Second dose		Third dose		Fourth dose	
0	0						
1	0.0975						
2	0.6300						
3	0.8375						
4	0.4500						
5	0.1675						
6	0.0875	(+0)	0.0875				
7	0.0650	(+0.0975)	0.1625				
8	0.0500	(+0.6300)	0.68				
9	0.0375	(+0.8375)	0.875				
10	0	(+0.4500)	0.4500				
11		(+0.1675)	0.1675				
12		(+0.0875)	0.0875	(+0)	0.0875		
13		(+0.0650)	0.0650	(+0.0975)	0.1625		
14		(+0.0500)	0.0500	(+0.6300)	0.68		
15		(+0.0375)	0.0375	(+0.8375)	0.875		
16		(+0)	0	(+0.4500)	0.4500		
17				(+0.1675)	0.1675		
18				(+0.0875)	0.0875	(+0)	0.0875
19				(+0.0650)	0.0650	(+0.0975)	0.1625
20				(+0.0500)	0.0500	(+0.6300)	0.68
21				(+0.0375)	0.0375	(+0.8375)	0.875
22				(+0)	0	(+0.4500)	0.4500
23						(+0.1675)	0.1675
24						(+0.0875)	0.0875
25						(+0.0650)	0.0650
26						(+0.0500)	0.0500
27						(+0.0375)	0.0375
28						(+0)	0

through kidneys. The difference in this respect apparently is non-existent.

The elimination half-lives observed in both the states along with the results of ANOVA and t-tests; paired and unpaired are given in Table-6.

Elimination half-lives in the normal states reported by other workers ranges between 1-3 hours (Adeyeye & Li, 1990; Reynolds, 1993; Willis *et al*., 1979; Degen *et al*., 1988; Said & Sharaf, 1981 and Landsdorp *et al*., 1990).

Landsdorp *et al* (1990) studied the pharmacokinetics of rectal diclofenac and its hydroxy metabolites in man. When

Table 4
Absorption half-lives of diclofenac sodium in control and treatment states

Volunteer	Absorption half-lives (hr)	
	Control	Treatment
1	0.2800	0.1400
2	0.4600	0.2500
3	0.2700	0.1600
4	0.2100	0.2000
Mean ± SEM	0.3050 ± 0.0539	0.1875 ± 0.0243

Analysis of variance

S.O.V.	S.S.	DF.	M.S.	F
Treatment	0.0276	1	0.0276	--
Residual	0.0420	6	0.0070	3.9470
Total	0.0696	7	--	--

F-ratio = 4.9329 t-test paired = 2.8308 t-test unpaired = 1.9867

Table 5
Distribution half-lives of diclofenac sodium in control and treatment states

Volunteer	Distribution half-lives (hr)	
	Control	Treatment
1	0.4200	0.1600
2	0.5300	0.3000
3	0.3500	0.2300
4	0.2400	0.3800
Mean ± SEM	0.3850 ± 0.0609	0.2675 ± 0.0471

Analysis of variance

S.O.V.	S.S.	DF.	M.S.	F
Treatment	0.0276	1	0.0276	--
Residual	0.0712	6	0.0119	2.3277
Total	0.0988	7	--	--

F-ratio = 1.6682 t-test paired = 1.2918 t-test unpaired = 1.5257

100 mg diclofenac suppository was given to six human volunteers it was well absorbed from the gastrointestinal tract. The apparent half-lives of diclofenac and 4'-hydroxy diclofenac were respectively 1.3 ± 0.3 h and 4.3 ± 1.0 h. When the $t_{1/2}$ values are derived from the renal excretion rate-time profiles, they are as follows: diclofenac 1.8 ± 0.9 h, 3'-hydroxy and 5-hydroxy diclofenac 2.3 ± 1.0 h and 2.5 + 0.4 h respectively, while those of 4'-hydroxy and 4',5-dihydroxy diclofenac are respectively 3.6 ± 0.5 hand 3.1 ± 1.3 h. Diclofenac is excreted for 13.6 ± 6.5%, its renal clearance (Cl_r) = 3.23 ± 1.03 ml/min. The mean metabolite excreted in the urine is 4'-hydroxy diclofenac (27.2 ± 12% dose, Cl_r = 6.14 ± 4.04 ml/min). The total body clearance of the parent drug and the apparent total body clearance of the main metaboilite are similar 28.0 ± 11.9 1/h, and 27.5 ± 10.9 1/h.

Table 6
Elimination half-lives of diclofenac sodium in control and treatment states

Volunteer	Elimination half-lives (hr)	
	Control	Treatment
1	2.5800	2.0500
2	2.1300	3.0100
3	2.7700	2.4600
4	3.0300	3.3600
Mean ± SEM	2.6275 ± 0.1898	2.7200 ± 0.2901

Analysis of variance

S.O.V.	S.S.	DF.	M.S.	F
Treatment	0.0171	1	0.0171	--
Residual	1.4423	6	0.2404	0.0712
Total	1.4594	7	--	--

F-ratio = 0.4277 t-test paired = -0.2894 t-test unpaired = -0.2668

Table 7
Mean residence time of diclofenac sodium in control and treatment states

Volunteer	Mean residence time (hr)	
	Control	Treatment
1	3.7300	3.9500
2	3.9500	4.8200
3	3.2800	3.3200
4	2.4600	2.5300
Mean ± SEM	3.3550 ± 0.3293	3.6550 ± 0.4849

Analysis of variance

S.O.V.	S.S.	DF.	M.S.	F
Treatment	0.1800	1	0.1800	--
Residual	4.1234	6	0.6872	0.2619
Total	4.3034	7	--	--

F-ratio = 0.4611 t-test paired = -1.5461 t-test unpaired = -0.5118

Our value of elimination half-life is in good agreement with the previous findings. Thus the pharmacokinetic parameters found in Pakistani subjects are in close agreement with the previous findings. The observed pharmaceutical data may be used for describing the pharmacokinetic character of the drug in local population. As far as the effect of food is concerned, more or less similar results are obtained as reported by other workers.

The non-compartmental analysis of the data is also performed in order to detect effect of food which might not be reflected from compartmental analysis. The values of mean residence time (MRT) in control and treatment states (mean ± SEM) were found to be 3.3550 ± 0.3293 hr and

3.6550 ± 0.4849 hr respectively, apparently resembling values bearing no significant difference. Mascher (1989) found MRT of 5.5 hours after oral administration of a sustained-release form of the drug to humans. This high value may be attributed to the sustained character of the dosage form. However no other values of MRT have been reported in the literature.

The MRTs, values along with the results of ANOVA and t-tests; paired and unpaired are given in table-7.

CONCLUSION

A possible explanation of these results may be that the presence of food in the gastric pouch lowers the gastric emptying and increases the viscosity of the gastric contents, this in turn causes a hindrance in the transfer of drug from stomach to its site of absorption, intestine. Since the therapeutic action of enteric-coated dosage form depends upon its entry into the intestine which is delayed in the presence of food. This results in increasing the time to reach the peak plasma concentration. But once the drug enters in the intestine it is rapidly absorbed. So in order to obtain a quick effect, diclofenac sodium should be taken in empty stomach or at least one hour before meal may be advised if the treatment consists of only one single dose, however; for multi-dose treatment this precaution seem unnecessary.

REFERENCES

Adeyeye CM and Pui-Kai Li (1990). *In*: Analytical Profiles of Drug Substances (Florey, K. Ed.), Vol.19, Academic Press, San Diego, pp.123-144.

Chamouard JM, Barce J and Urien S *et al* (1985). Diclofenac binding to albumin and lipoprotein in human serum. *Biochem. Pharmaco.,* **34**: 1695-1700.

Ciba-Geigy (1988). Diclofenac package insert. Ardsley, New York.

Degen PH, Dieterle W, Schneider W, Theobald W and Sinterhauf U (1988). Pharmacokinetics of diclofenac and five metabolites after single doses in healthy volunteers and after repeated doses in patients. *Xenobiotica.,* **18**(12): 1449-1455.

Farid SM Hasan, Tasneem Ahmed and Nasira Talib (2004). Effect of food on the bioavailability of diclofenac sodium in local population. Submitted for publication in Journal of Science, University of Karachi.

Insel PA (1991). *In*: Goodman and Gilman's, The Pharmacological Basis of Therapeutics, (Gilman AG, Rall TW, Nies AS and Taylor P Eds.), 8th Edn., Vol.1, Pergamon Press, New York, p.669.

Landsdorp D, Vree TB, Janseen TJ and Guelen PJM (1990). Pharmacokinetics of rectal diclofenac and its hydroxyl metabolites in man. *Int. J. Clin. Pharmacol. Ther. Toxicol.,* **28**(7): 298-302.

Mascher H (1989). The pharmacokinetics of a new sustained-release form of diclofenac sodium in humans. *Drug Des. Deliv.,* **4**(4): 303-311.

Reynolds JEF, Ed (1993). Martindale, The Extra Pharmacopoeia, 30th Edn., The Pharmaceutical Press, London, p.11.

Riess W, Stierlin H, Degen P, Faizle JW, Gerardin A, Moppert Sallmann A, Schmid K, Schweizer A, Sule M, Theobald W and Wagner J (1978). Pharmacokinetics and metabolism of the anti-inflammatory agent Voltaren. *Scand. J. Rheumatol. Suppl.,* **22**: 17-29.

Said SA and Sharaf AA (1981). Pharmacokinetics of diclofenac sodium using a developed HPLC method. *Arzneim.-Forsch.,* **31**(12): 2089-2092.

Sallmann A (1975). *In*: Chronic forms of polyarthritis (Wagenäuser FJ, Ed.). International Symposium, Torremolinos, 1975. Berne: Hans Huber, 1976, pp.196-301.

Sallmann AR (1986). The history of diclofenac. *Am. J. Med.,* **80**(4B): 29-33.

Todd PA and Sorkin EM (1988). Diclofenac sodium; a reappraisal of its pharmacodynamic and pharmacokinetics properties and therapeutic efficacy. *Drugs,* **35**(3): 244-285.

Sengupta Ch, Afeche P, Meyer-Brunot HG and Rensing U (1985). *In*: Anti-inflammatory and Antirheumatic Drugs; Newer Anti-inflammatory Drugs (Rainsford KD, Ed), Vol.2, CRC Press, Inc. Boca Raton, Florida, Chapter 3.

Willis JV, Kendall MJ, Flinn RM, Thornhill DP and Welling PG (1979). The Pharmacokinetics of diclofenac sodium following intravenous and oral administration. *Eur. J. Clin. Pharmacol.,* **16**(6): 405-410