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KINETICS OF ACETYLSALISYLIC ACID IN MALE VOLUNTEERS AFTER ORAL ADMINISTRATION

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ABSTRACT

The kinetics of acetylsalicylic acid, a non-steroidal anti-inflammatory agents, was studied in twelve healthy young males after oral administration of 600 mg aspirin. Blood samples were collected at pre-determined time intervals. The concentration of aspirin as free salicylic acid was analyzed colorimetrially at 530 nm and mean ±SE value in blood was found to be 26.64±0.63 µg mL^{-1}. Individual pharmacokinetic parameters were estimated by using two compartment open model. Mean±SE values were found to be C_{max} 39.40±0.30 mg L^{-1}, T_{max} 1.92±0.05h, $t_{1/2}\mu$ 0.97±0.11 h, Ka 0.80±0.08 h^{-1}, AUC 239.47±4.23 h.mg L^{-1}, V_d 12.96±1.06 L, $t_{1/2}\mu$ 4.85±0.69 h and TBC 1.95±0.08 L h^{-1}. ASA values established in this study were in agreement with those reported by other authors.

Key Words: Acetylsalicylic acid, male volunteer, pharmacokinetics, salicylate, aspirin, volume of distribution, peak plasma concentration, absorption rate constant, half life

INTRODUCTION

Acetylsalicylic acid (ASA), commonly known as aspirin, is one of the most extensively used therapeutic agent which is unique among mild non-steroidal anti-inflammatory agent because of its high efficacy, low cost and low toxicity. It has three major therapeutic action, analgesic (pain relieving), antipyretic (temperature reducing) and anti-inflammatory effects. It is also widely used in the chronic management of rheumatic fever, rheumatoid arthritis and osteoarthritis (Simon and Mills, 1980). The anti-platelet properties of aspirin results from its ability to irreversibly inhibit platelet cyclooxygenase by its acetylation hence diminishes the formation of thromboxane A_2 thus produces anti-coagulant effect by prolonging the bleeding time (Reynolds, 1989). Convincing data exist to show that use of ASA can reduce the risk of ischemic heart disease, the incidence of stroke and myocardial infarction (Stein et al., 1989).

Aspirin is hydrolyzed in the stomach and in the blood to salicylic acid and acetic acid, the biological half life is therefore only 20 min. The plasma salicylate half life following therapeutic dose is 2 to 4.5h, but in over doses increase 18 to 36h (Done, 1960). Usual dose used as analgesic and antipyretic is 300-600 mg every 4-6h (Punnon, 1984).

Approximately 80% of small doses of salicylic acid is metabolized in the liver, conjugation with glycine forms salicyluric acid and with glucuronic acid forms salicylacyl and phenolic glucuronide. Small amount of salicylic acid is also hydroxylated to gentisic acid (Levy and Tsuchiya, 1972).

The studies conducted over several years under indigenous conditions have revealed differences in kinetic behavior metabolism and urinary excretion when compared with values given in literature (Nawaz, 1994). Keeping in view the above mentioned facts, the present study was designed to investigate the pharmacokinetic parameter of acetyl salicylic acid in male volunteers under local conditions.

MATERIALS AND METHODS

Subjects

Twelve healthy male volunteers participated in this study were having age between 20-23 years (mean age 21.4 years), weight 59-72 kg (mean weight 66.3 kg) and height 170.18-182.88 cm (mean height 174.63 cm). All subjects were in good health on the basis of physical examination and medical history.

STUDY PROTOCOL

i. Drug and drug administration

The drug acetylsalicylic acid commercially known dispirin (soluble aspirin) in the dosage form of oral tablets 300 mg each, manufactured by Reckitt Benckiser of Pakistan Ltd., Karachi, were used. The sampling was done in

the month of May.

ii. Blood Sample Collection

After an over night fasting, control blood samples were collected from each volunteer. Each volunteer was given two tablets (2x300 mg) of dispirin and then allowed to take breakfast after 2h following drug administration. The venous blood was drawn in heparinized centrifuged tubes at 0, 15, 30, 45, 60, 90, 120, 150, 180, 240, 360, 480 and 600 min, following oral administration of dispirin tablets. The pH of all fresh blood samples was measured with the help of pH meter. Then each blood sample was centrifuged for 10 min. at 4000 rpm. Plasma was separated and stored at -20^{o}C till further analysis.

Blood Analysis

Stock solution of salicylic acid (SA) equivalent to 1000 mg L^{-1} was prepared in plasma. Different working standard solutions containing 50, 100, 150, 200, 250 and 300 µg mL^{-1} of SA were prepared from stock solution in drug free control plasma. Colorimetric method (Martens and Meyer, 1995) was followed by taking 0.5 ml plasma from each solution in extracting tubes separately and added 0.5 ml of 6N HCl for the deproteinization. The drug was extracted twice with 6 ml $CHCl_3$, shaked and then centrifuged at 3000 rpm for 15 min. To this chloroform layer added 3 ml of 0.1 N NaOH solution and then again thoroughly shaked and centrifuged for 15 min at 3000 rpm. Transferred 2 ml supernatant fluid into a test tube and added 0.3 ml 1N HNO_3 solution and 0.2 ml $Fe(NO_3)_3$ reagent (10%). Violet colour appeared immediately, stay for 15 min. then absorbance was noted at 530 nm with the help of spectrophotometer (Hitachi Model U-2001). Blood samples collected from volunteer after specific time interval were analyzed following the same procedure.

Pharmacokientic Analysis

The Pharmacokinetic parameters C_{max}, T_{max}, volume of distribution, clearance, Area under the curve, elimination half-life, absorption half-life and mean residence time were determined by two compartment open model (Baggot, 1977) using computer program MW/PHARM Version 3.02 (Rombout, 1991).

Statistical Analysis

The results were given as mean ±SE and data was subjected to correlation/regression analysis (Steel and Torrie, 1992).

RESULTS AND DISCUSSION

The mean±SE value for plasma concentration of acetyl salicylic acid as free salicylic acid at various time intervals have been plotted in Fig. **1**.

The plasma concentration at 15 min was 8.88±0.55 µg mL^{-1} which increases with the passage of time due to absorption and mean maximum plasma concentration 43.89±0.79 µg mL^{-1} was achieved at 2 h. The plasma concentration began to decrease due to elimination and reached to a value of 10.40±0.51 µg mL^{-1} after 10 h. The average ±SE for plasma concentration of aspirin as free salicylic acid in male was 26,64±0.63 µg mL^{-1}. While in the male volunteers was 30.33±0.63 µg mL^{-1} (Ambreen, 2002). The pharmacokinetic parameters were determined applying two compartment open model and are presented in Table 1 and 2.

Mean ±SE peak plasma concentration (C_{max}) value in male was 39.40±0.33 mg L^{-1} while in the female volunteer was 44.54±0.46 mg L^{-1}. This difference is due to different genetic make up Siebert *et al*. (1983) calculated C_{max} value 45.59±7.0 mg L^{-1} for 600 mg soluble aspirin. This value is very close to our present value. Time to peak concentration (T_{max}) of salicylic acid in male was 1.92±0.05 h but in female volunteer was 1.87±0.05 h (Ambreen, 2002). Mason and Winer (1981) reported T_{max} value 1.9±0.11 h for 640 mg plain aspirin. The mean value for the area under the curve (AUC) at t=10 (poly exponential) and t=10 (trapezoidal) was 253.66±5.06 and 239.47±4.23 h.mg L^{-1}. The same parameter in healthy female volunteer had mean ±SE values 294.71±6.50 and 275.07±2.73 h mg L^{-1} (Ambreen, 2002). This difference in value for AUC shows that absorption of salicylic acid in female is greater than male. The mean ±SE value for volume of distribution (V_d) was 12.96±1.06 L and same parameter value found in female volunteers was 10.90±0.76. This difference in value is due to difference in body weight and drug metabolism. Furst *et al*. (1979) reported the Vd in L kg^{-1} having value 0.189±0.013 L kg^{-1}. Which is very close to the present value 0.182±0.03 L kg^{-1}. The absorption half life ($t_{1/2ab}$) and elimination half life ($t_{1/2}\mu$)±SE values were 0.97±0.11h and 4.852±0.69 h respectively. The same pharmacokinetic parameter in female had mean ±SE value

1.17±0.025h and 4.69±0.55h respectively (Ambreen, 2002). The total body clearance (CL) was 1.95±0.080 L h^{-1} in female volunteers where as in male it was 1.68±0.06 L h^{-1} (Ambreen, 2002). Montgomery and Sitar (1986) achieved CL value 1.82±0.21 L h^{-1} for 900 mg plain aspirin. The absorption rate constant (Ka) and elimination rate constant (K_{10}) values were 0.85±0.12 h^{-1} and 0.37±0.08 h^{-1} respectively. Elimination rate constant reported by Dubovska *et al*. (1995) was 0.31 h^{-1} after 400 mg dose.

Table. 1. Absorption kinetic parameters of aspirin determined from the plasma concentration following oral dose of 2 x 300 mg tablets to healthy male volunteers

Volunteers	Absorption rate constant (Ka) [1/hr]	Absorption half life [h]	Lag time [h]	Time to peak Tmax [h]	Peak concentration Cmax [mg/l]
1	0.527	1.316	0.139	1.954	37.88
2	0.608	1.141	0.103	2.235	40.80
3	0.880	0.788	0.045	2.114	41.07
4	1.154	0.601	0.071	1.742	39.88
5	0.786	0.882	0.136	1.849	39.12
6	0.983	0.705	0.116	1.705	38.95
7	1.033	0.671	0.087	1.670	39.44
8	0.363	1.909	0.092	1.732	39.32
9	1.224	0.566	0.106	1.967	37.59
10	0.842	0.823	0.119	1.963	39.95
11	0.582	1.190	0.088	2.012	40.74
12	0.665	1.043	0.138	2.130	38.06
Mean	0.804	0.970	0.103	1.923	39.40
SD	0.264	0.382	0.035	0.185	1.158
±SE	0.080	0.110	0.010	0.050	0.33
Min	0.363	0.566	0.045	1.670	37.59
Max	1.224	1.909	0.138	2.235	41.07

The result of this study indicated that pharmacokinetic study of acetylsalicylic acid was found to be slightly different in local subjects (male and female). Moreover, the kinetic data also different when compared with foreign values. So the study supports the need for comprehensive evaluation of drug under our own environmental conditions to obtain pharmacokinetic parameter on which rational dose regimen of drug could be based.

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Table 2. Disposition kinetic parameters of aspirin determined from the plasma concentration following oral dose of 2 x 300 mg tablets to healthy male volunteers.

Volunteer	Mean	Resident AUC	AUC	trapezoidal Clearance (CL)	Vol.	of Vol.	Distr. Vol.	Distr. Half	-life Half -life phase Rate		Rate	Rate
	Time	Polyexponential	(t=10)	[l/h]	distribution	Steady	time [l]	phase 1 [h]	2 [h]	constant	K_{10} constant	constant
	(MRT) (h)	(t=10)			comp.1 [l]	[l]				[1/h]	K_{12}[1/h]	K_{21} [1/h]
1	6.935	248.50	229.80	2.039	5.053	9.989	13.17	0.673	4.477	0.403	0.385	0.394
2	6.778	283.60	263.10	1.797	6.342	9.036	10.27	0.768	3.963	0.283	0.236	0.556
3	6.332	286.50	271.30	1.672	8.666	10.29	10.76	0.811	4.459	0.193	0.128	0.687
4	6.154	246.60	240.50	2.062	9.263	10.76	11.09	0.564	3.727	0.223	0.165	1.025
5	7.825	243.90	231.60	1.912	7.052	12.27	15.02	0.881	5.443	0.271	0.273	0.369
6	6.974	238.60	230.60	2.031	7.988	11.86	13.32	0.747	4.546	0.254	0.269	0.556
7	6.071	234.90	228.80	2.180	8.198	10.94	11.88	0.668	3.777	0.265	0.239	0.715
8	6.343	255.40	230.70	2.113	2.932	7.388	12.75	0.525	4.181	0.720	0.461	0.303
9	6.828	247.90	237.10	1.969	11.160	11.59	11.61	0.168	4.087	0.176	0.151	3.956
10	7.124	256.8	240.50	1.891	7.876	11.00	12.54	0.950	4.596	0.240	0.181	0.458
11	14.64	267.80	247.40	1.340	5.798	17.22	23.60	1.073	12.190	0.231	0.312	0.158
12	5.297	233.40	222.20	2.377	7.149	8.688	9.51	0.725	2.773	0.332	0.154	0.717
Mean	7.36	253.66	239.47	1.949	7.29	10.92	12.96	0.713	4.852	0.299	0.255	0.825
SD	2.39	17.53	14.66	0.264	2.12	2.43	3.67	0.230	2.397	0.145	0.102	1.012
±SE	0.69	5.06	4.23	0.08	0.61	0.70	1.06	0.07	0.69	0.04	0.03	0.29
Min	5.297	233.40	228.80	1.340	2.93	7.39	9.51	0.168	2.773	0.176	0.128	0.158
Max	14.640	286.50	271.30	2.377	11.16	17.22	23.60	1.073	12.190	0.720	0.461	3.956

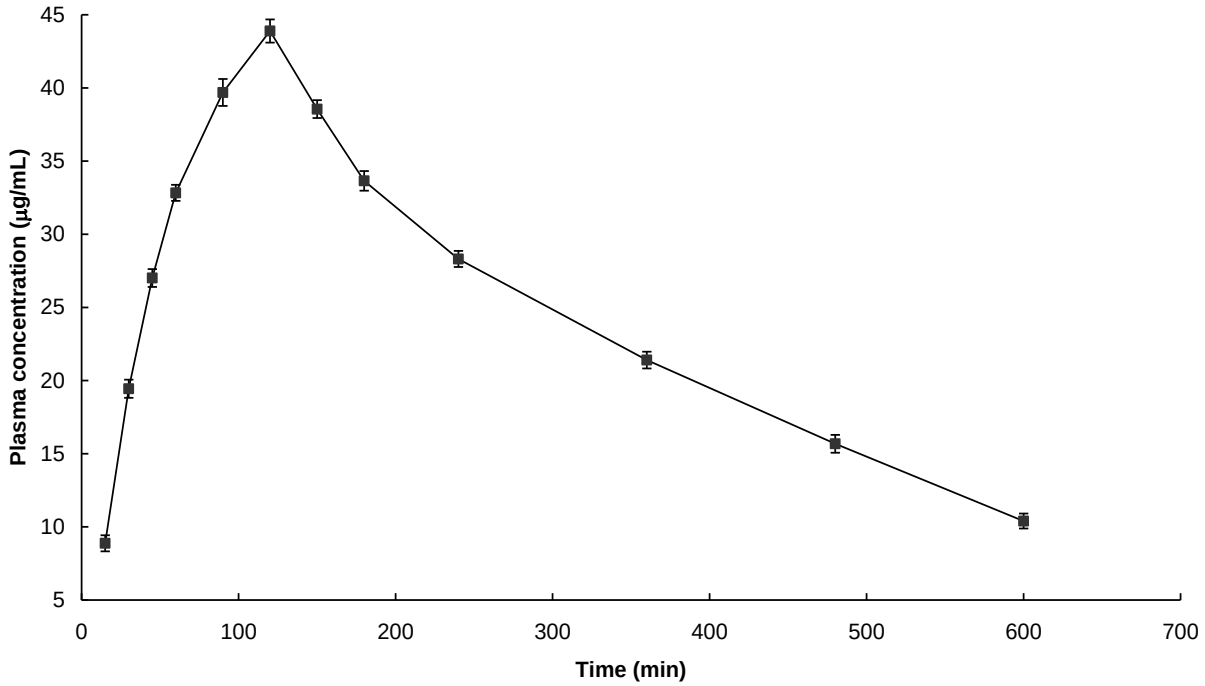

Fig. 1 Plot of plasma concentration of salicylic acid versus time after oral adminnistration of 2 x 300 mg aspirin in male volunteers.

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