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Pharmacokinetic Study of Aspirin in Healthy Female Volunteers

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Abstract: The pharmacokinetics of acetylsalicylic acid, a non-steroidal anti-inflammatory agents, was studied in twelve healthy young females 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 30.33±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} 44.54±0.46 mg L^{-1}, t_{max} 1.87±0.05h, $t_{1/2\alpha}$ 1.17±0.25 h, Ka 0.85±1.12 h^{-1}, AUC 275±2.73 h.mg L^{-1}, V_d 10.90±0.76 L, $t_{1/2\beta}$ 4.69±0.55 h and TBC 1.68±0.06 L h^{-1}. ASA values established in this study were in agreement with those reported by other authors.

Key words: Acetylsalicylic acid, Female 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 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 4.5 h, but in over doses increase 18 to 36 h (Done, 1960). Usual dose used as analgesic and antipyretic is 300-600 mg every 4-6 h (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 female volunteers under local conditions.

Materials and Methods

Subjects: Twelve healthy female volunteers participated in this study were having age between 20-22 years (mean age 21.1 years), weight 50-63 kg (mean weight 57.7 kg) and height 142.24-162.65 cm (mean height 159.39 cm). All subjects were in good health on the basis of physical examination and medical history. They were familiar with the aim and course of study and written consent was signed by each volunteer.

Study Protocol

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.

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 2 h 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. 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°C till further analysis.

Blood analysis: Stock solution of salicylic acid (SA) equivalent to 1000 mg L^{-1} was prepared in distilled water. 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.

Pharmacokinetic 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 9.15±0.45 μg mL^{-1} which increases with the passage of time due to absorption and mean maximum plasma concentration 49.66±1.33 μg mL^{-1} was achieved at 2 h. The plasma concentration began to decrease due to elimination and reached to a value of 12.31±0.48 μg mL^{-1} after 10 h. The average ±SE for plasma concentration of aspirin as free salicylic acid in female was 30.33±0.63 μg mL^{-1}. While in the male volunteers was 26.64±0.63 μg mL^{-1} (Aamir, 2002). The pharmacokinetic parameters were determined applying two compartment open model and are presented in Table 1 and 2.

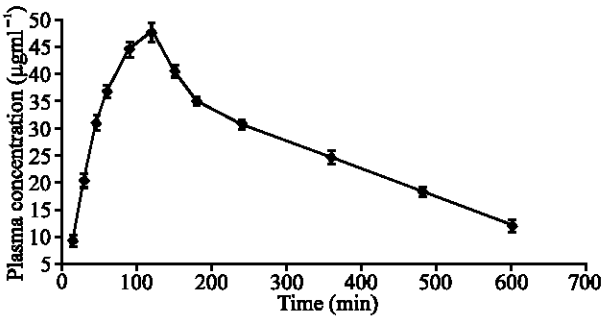

Fig. 1: Plot of plasma concentration of salicylic acid versus time after oral administration of 2x300 mg aspirin in female volunteers

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

Volunteers	Absorption rate constant (Ka) [hr^{-1}]	Absorption half life [h]	Lag Ltime [h]	Time to peak T_{max} [h]	Peak concentration C_{max} [mg L^{-1}]
1	0.780	0.889	0.096	2.216	40.72
2	0.251	2.761	0.145	2.094	42.97
3	0.779	0.890	0.136	2.005	43.44
4	1.247	0.556	0.138	1.847	44.67
5	0.241	2.881	0.113	1.895	46.34
6	1.525	0.455	0.143	1.688	44.43
7	1.158	0.599	0.107	1.653	44.91
8	1.084	0.640	0.114	1.649	45.25
9	0.786	0.882	0.109	1.796	44.92
10	0.360	1.924	0.126	1.809	46.63
11	1.341	0.517	0.158	1.840	44.40
12	0.695	0.998	0.137	1.975	45.80
Mean	0.85	1.17	0.13	1.87	44.54
SD	0.43	0.86	0.02	0.18	1.60
±SE	0.12	0.25	0.01	0.05	0.46
Min	0.241	0.455	0.096	1.649	40.72
Max	1.525	2.881	0.158	2.216	46.63

Mean±SE peak plasma concentration (C_{max}) value in female was 44.54±0.46 mg L^{-1} while in the male volunteer was 39.40±0.33 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 female was 1.87±0.05 h but in male volunteer was 1.92±0.05 h (Aamir, 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 294.71±6.50 and 275.07±2.73 h.mg L^{-1}. The same parameter in healthy male volunteer had mean ±SE values 253.66±5.06 and 239.47±4.23 h.mg L^{-1} (Aamir, 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 10.90±0.76 L and same parameter value found in male volunteers was 12.96±1.06. This difference in value is due to difference in body weight and drug metabolism.

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

Volunteer	Mean resident time (MRT) (h)	AUC Polyexponential (t=10)	AUC trapezoida (t=10)	Clearance (CL) [L h^{-1}}	Vol. of distribution comp. 1 [l]	Vol. Distr. Steady State [l]	Vol. Distr. [l]	Half-life Phase 1 [h]	Half-life phase 2 [h]	Rate constant K_{10} [h^{-1}]	Rate constant K_{12} [h^{-1}]	Rate constant K_{21} [h^{-1}]
1	6.30	269.8	257.1	1.91	8.28	9.43	10.01	0.99	3.62	0.23	0.08	0.57
2	6.30	329.5	280.1	1.75	2.09	3.81	6.79	0.52	2.68	0.83	0.33	0.40
3	7.53	299.8	283.7	1.58	6.37	9.71	10.62	0.59	4.63	0.24	0.36	0.69
4	6.47	281.9	273.9	1.76	9.03	9.78	9.92	0.54	3.89	0.19	0.09	1.15
5	6.28	341.5	290.0	1.68	1.73	3.40	7.77	0.51	3.18	0.97	0.28	0.30
6	7.37	283.6	274.8	1.64	9.80	10.79	11.06	0.89	4.67	0.16	0.06	0.68
7	6.81	280.5	273.4	1.73	7.60	10.13	10.72	0.57	4.28	0.22	0.28	0.85
8	6.39	272.0	264.1	1.84	7.18	9.86	10.68	0.63	4.02	0.25	0.27	0.73
09	9.95	290.5	275.7	1.42	6.01	12.23	14.82	0.86	7.20	0.23	0.33	0.32
10	6.41	300.7	271.9	1.79	2.56	6.29	11.29	0.56	4.37	0.69	0.40	0.27
11	6.67	278.1	268.5	1.76	9.67	10.18	10.44	1.32	4.10	0.18	0.02	0.48
12	12.80	308.6	287.8	1.19	5.75	13.40	16.62	0.99	9.65	0.20	0.32	0.24
Mean	7.44	294.7	275.0	1.68	6.34	9.09	10.90	0.75	4.69	0.37	0.24	0.56
SD	1.98	22.5	9.4	0.20	2.87	3.06	2.65	0.26	1.91	0.29	0.13	0.28
±SE	0.57	6.5	2.7	0.06	0.83	0.88	0.76	0.07	0.55	0.08	0.04	0.08
Min	6.28	269.8	257.1	1.19	1.73	3.81	6.79	0.51	2.68	0.16	0.02	0.24
Max	12.80	341.5	290.0	1.91	9.80	13.40	16.62	1.32	9.65	0.97	0.40	1.15

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 0.17±0.03 L kg^{-1}. The absorption half life ($t_{1/2ab}$) and elimination half life ($t_{1/2\beta}$)±SE values were 1.17±0.25 h and 4.69±0.55 h respectively. The same pharmacokinetic parameter in male had mean ±SE value 0.97±0.11 h and 4.85±0.69 h respectively (Aamir, 2002). The total body clearance (CL) was 1.68±0.06 L h^{-1} in female volunteers where as in male it was 1.95±0.08 L h^{-1} (Aamir, 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.

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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