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Renal Clearance and Urinary Excretion of Clarithromycin in Human Male Volunteers

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Abstract: Following an oral dose of 250 mg of clarithromycin to 14 healthy adult male volunteers, renal clearance and urinary excretion of the drug and that of endogenous creatinine were determined. Before drug administration control samples and after drug administration blood and urine samples were collected, at predetermined time periods. The plasma and urine samples were assayed for endogenous creatinine by spectrophotometric methods and clarithromycin by microbiological assay. Mean \pm SE values for the blood and urine pH mean were 7.9 \pm 0.08 and 5.7 \pm 0.17 respectively. The rate of urine flow (diuresis) was 0.019 \pm 0.003 ml/min/kg and creatinine was cleared at rate of 1.95 \pm 0.164 ml/min/kg of body weight. Average \pm SE value for clarithromycin clearance was 0.54 \pm 0.08 ml/min/kg and mean \pm SE value for clearance ratio was 0.31 \pm 0.061. Cumulative amount of dose excreted until 24 hrs. showed an average value 6.1 \pm 0.76 percent. A significant positive correlation between diuresis and renal clearance of clarithromycin indicate the back diffusion or reabsorption of the drug.

Key words: Renal clearance, Urinary Excretion, Clarithromycin, Male volunteers

Introduction

Clarithromycin (6-0 methylerythromycin) is a broad spectrum antibiotic with a molecular weight of 747.96. Clarithromycin and azithromycin are semisynthetic derivatives of erythromycin (Katzung, 1998). Clarithromycin is rapidly absorbed into the blood and distributed through the blood stream to all parts of the body. Clarthromycin has a significant impact on the treatment of disseminated *Mycobacterium avium* complex infection. Polis *et al.* (1998) analyzed that clarithromycin lowers zidovudine level in persons with immunodeficiency virus infection.

The drug is mainly eliminated via renal route, therefore study of mechanisms involved in the renal handling are of practical importance. The rate of glomerular filtration can be determined by measuring the renal clearance of substances that are neither secreted nor reabsorbed by the tubules and exert no effect on renal function. In all mammalian species, creatinine is freely filtrated in the same concentration as in plasma. Creatinine exists in the body primarily as a high energy phosphate compound. It is an anhydride of creatine and is a highly diffusible substance. The free creatinine occurs in blood and urine. The endogenous creatinine renal clearance is very widely used to estimate the glomerular filtration rate. The present research project was designed to study the renal clearance and urinary excretion of clarithromycin in male volunteers under local environmental conditions.

Materials and Methods

Drug Administration and Sampling: Renal clearance of endogenous creatinine and clarithromycin was determined in 14 healthy adult volunteers following a single dose of 250 mg tablets of clarithromycin. Average body weight of volunteers was $64.5 \text{ kg} \pm \text{SE} 2.14$ while average age and heights were 23 years and 5.7 feet respectively. The blood samples were drawn after 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 hours after the drug administration. Urine samples were taken at 0.75, 1.25, 1.75, 2.25, 2.75, 4, 6, 8, 12 and 24 hours. The blood samples were centrifuged at 4,000 rpm for 15 min to separate plasma from sedimented cells.

Microbiological Assay: Clarithromycin concentration in plasma and urine was determined by microbiological assay according to the method of Arret *et al.* (1971) by using the *Streptococcus fecalus* as test organism. Zone of inhibitions were measured with the help of zone reader. **Analytical Determination:** For the estimation of glomerular filtration rate, the endogenous creatinine renal clearance was measured in plasma and urine samples spectrophotometrically by the method of Bonsnes and Taussky (1945).

0.1% clarithromycin solution in 100 ml of dist. water was used as standard. Clarithromycin concentration in plasma and urine samples was analyzed by following the same procedure of lqbal *et al.* (2000).

Different Parameters were Calculated as: a. Diuresis

Urine volume in collection period (ml)							
Time (min.) × Body wt. (Kg)							
b. Creatinine Concentration Concentration in Plasma (Pc) = Absorbance × Standard Factor × Dilution factor Concentration in Urine (Uc) = Absorbance × Standard factor × Dilution factor							
c. Clarithromycin Concentration Concentration in Urine = Zone size x standard factor Concentration in Plasma = Y = $0.0542e^{0.1715x}$ As; X = Zone of inhibition (mm) Y = Concentration of drug (µg/ml)							
d. Renal Clearance Concentration of substance in urine (Uc) × Diuresis (D)							
Concentration of substance in plasma (Pc)							
e. Clearance Ratio Renal clearance of durg Clearance ratio =							
Renal clearance of creatinine							
f. Urinary Excretion Amount of drug excreted							
Dose of drug							
Cumulative amount excretes							
wage cumulative =							

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Results and Discussion

The results showing mean \pm SE of the experimental periods for pH of blood and urine, diuresis, plasma and urine concentration of creatinine, clarithromycin concentration, clarithromycin clearance and clearance ratio have been presented in Table 1 and graphically shown in Fig. 1-3. In this study the average \pm SE value of pH in blood was 7.9 ± 0.08 . These values are slightly higher than the previously reported value of blood pH 7.73 ± 0.02 in male volunteers. (Rao, 1997). Average t SE value of pH in urine was 5.7 ± 0.17 which is comparable to the value 5.85 ± 0.08 reported earlier on male volunteers. (Rao, 1997). The average \pm SE value for the rate of urine flow (diuresis) recorded in human male volunteers was 0.019 ± 0.003 ml/min/kg. This value is higher than that reported earlier on male volunteers which was 0.012 ± 0.002 ml/min/kg (Rao, 1997). The previous value was recorded in summer while the present value is recorded in winter. The present value is slightly higher from the value reported in summer. This difference is due to environmental difference because in hot climate the evaporation reduces the urine flow during summer while lower environmental temperature increases the rate of urine during winter (Nawaz and Shah., 1984).



Fig. 1: Effect of diuresis on clarithromycin clearance following the oral administration of 250 mg tablet to 14 male volunteers

In the present study the average \pm SE value of creatinine clearance in male volunteers was 1.95 ± 0.164 ml/min/kg. This value is close to the values reported earlier that is 1.73 ± 0.23 ml/min/kg (Edwards and Whyte, 1959) and 1.9 ± 0.27 ml/min/kg (Doolan *et al.*, 1962). The average \pm SE value for the clarithromycin concentration in plasma was $1.26 \pm 0.15 \mu$ g/ml. The value of clarithromycin concentration of the present study is higher than the literature value that is 0.027μ g/ml and 0.062μ g/ml in male volunteers (Chu *et al.*, 1992). The differences in these studies may be attributable to the genetical variation (Nawaz, 1994). Moreover, the previous studies were conducted by high performance liquid chromatographic technique (HPLC) but the present study has been conducted by microbiological assay (Fig. 1).

The average \pm SE value for the renal clearance of clarithromycin was 0.54 ± 0.08 ml/min/kg. This value is higher than renal clearance value calculated by Chu *et al.*



Fig. 2: Effect of clarithrolinycin plasma concentration on renal clearance following the oral administration of 250 mg tablet to each male volunteers



Fig. 3: Effect of urine pH on clarithromycin clearance following the oral administration of 250 mg tablet in 14 male volunteers

(1992) which is 0.069 ml/min/kg due to difference of environment, temperature and other conditions.

The clearance ratio was calculated by dividing drug renal clearance by creatinine renal clearance. Average \pm SE values for the renal clearance ratio was 0.31 ± 0.061 . Clarithromycin clearance was lower than the endogenous creatinine clearance or filtration clearance (GFR) (Fig. 2). This indicates that reabsorption or back diffusion take place (Hardman et al., 1996). Urinary execration of orally administered drug was monitored in total volume of urine voided 24 hrs. of experimentation. Percentage cumulative amount of dose excreted until 24 hours showed an average ± SE value 6.1 ± 0.76 percent. This value is lower than the values given in literature that is 11.5 to 17.5% (Chu et al., 1992) and 18% (Davey, 1991). This decrease in %age due to climatic conditions of our local environment. Usually pH of urine is acidic. The small amount of drug excreted shows the unionized form of drug as clarithromycin is an acidic drug and in acidic urine of human, process of back diffusion of the drug is facilitated due to increase in its permeability across the biomembrane of renal tubules (Fig. 3).

The studies indicate that the renal clearance of endogenous creatinine in male volunteers was lower than the values given

Table 1: Average data of renal clearance of endogenous creatinine and clarithromycin in 14 human male volunteers after the oral dose of 250 mg tablets											
Volunt and Sample No.	Body weight (kg)	Diuresis (ml/min kg)	рН		Concentration (µg/ml)				Renal Clearance		Ratio CL./
			Urine	Blood	Creatinine		Clarithromycin				- Cl _{creat}
					Plasma	Urine	Plasma	Urine	Creatinine	Clarithr- omycin	
1	54	0.037	6.1	8.3	9.583	373.59	0.92	20.35	1.45	0.81	0.60
2	70	0.025	5.5	8.1	11.039	910.21	0.74	22.122	1.72	0.69	0.43
3	70	0.014	5.0	8.2	13.743	1608.64	0.55	25.56	1.39	0.71	0.46
4	70	0.012	5.5	8.1	12.39	2969.45	1.08	45.19	2.83	0.53	0.21
5	70	0.014	5.1	8.1	8.79	948.511	1.437	30.16	1.44	0.28	0.19
6	60	0.017	6.5	8.1	9.913	1254.92	1.90	24.66	2.01	0.25	0.14
7	70	0.018	5.6	8.1	7.660	597.04	1.68	21.48	1.51	0.23	0.19
8	54	0.010	5.0	8.0	10.138	2726.13	0.85	54.03	2.72	0.72	0.25
9	65	0.013	6.7	8.1	8.42	1809.15	0.59	37.001	2.8	0.88	0.29
10	53	0.051	6.8	8.2	10.138	802.06	2.31	27.55	2.78	1.18	0.26
11	75	0.006	4.9	7.9	13.067	3095.62	1.23	36.11	1.51	0.23	0.15
12	71	0.023	6.2	7.3	10.363	1025.11	1.69	30.50	2.09	0.46	0.19
13	55	0.012	5.4	7.3	12.166	1874.49	0.97	18.58	1.95	0.22	0.12
14	67	0.018	6.3	7.6	16.897	891.058	1.38	22.26	1.18	0.49	0.94
Average	64.54	0.019	5.7	7.9	11.02	1491.8	1.28	29.68	1.95	0.54	0.31
±SE	2.14	0.003	0.17	0.08	0.67	247.67	0.15	2.84	0.164	0.08	0.061

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in literature. A positive correlation between diuresis and renal clearance of clarithromycin was indicative of renal tubular back diffusion or reabsorption. There was non-significant positive correlation between urine pH and clarithromycin clearance. The cumulative percentage of dose excreted in the urine was lower than those given in literature. These support that there is a need to evaluate the imported drugs under indigenous conditions for getting optimal therapeutic results.

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