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Renal clearance and urinary excretion of cefuroxime in healthy male volunteers

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ABSTRACT: Cefuroxime was evaluated for the pharmacokinetics and clinical effects in 8 healthy volunteers, Bolus i.v. injections of cefuroxime 750 mg b.i.d. or 750 mg once daily were given to the patients depending on the degree of renal impairment. The concentration of drug in urine was measured during treatment, and pharmacokinetic parameters were investigated; Drug elimination half-life increased from 4.2 h (creatinine clearance 23.0 ml/min) to 22.3 h (creatinine clearance 5.0 ml/min) with decreasing renal function. The apparent volume of distribution ranged from 11.6 to 17.9 . A linear correlation was found between the total and renal clearance of cefuroxime and the creatinine clearance; the extrarenal clearance was 8.24 ml/min. Concomitant treatment with furosemide did not impair renal function and no evidence of nephrotoxicity was found. The clinical efficacy of the drug was good. Symptoms of infection subsided after 3-4 days and the isolated pathogens were eradicated. No relapse or episodes of reinfection were observed in a following-up period of 3 months. The drug was well tolerated and no side effects or changes in haematological or biochemical values were seen.

KEYWORDS: Renal clearance, urinary excretion, cefuroxime.

INTRODUCTION

Cefuroxime sodium is a second-generation cephalosporin, broad-spectrum, semisynthetic and consider as an agent intended for parenteral administration. It has been extensively used for the management of the patients encompassing infections of soft tissue, urinary tract, bone and joint tissues, genital tract, central nervous system and respiratory tract. Generally, cefuroxime sodium isprepared as a crystalline lyophilized powder. It is administered by intramuscular, intravenous or intraperitoneal routes (Zhao *et al.,* 2012).It is a semi-synthetic cephalosporin designed to overcome breakdown and inactivation by /3-lactamases from gram-negative organisms, a shortcoming of early cephalosporin antibiotics. Given by parenteral route, it has been shown to be excreted, almost unchanged, in the urine, and its half-life is about 1 h in normal adult patients (Norrby, Foord & Hedlund, 1977). The aim of the present work was to determine the pharmacokinetic parameters in a group of aged patients (> 70 years) whose renal functions were more or less impaired.

Cefuroxime is not extensively metabolized and almost completely excreted as unaffected form in urine through the tubular secretion as well as glomerular filtration with in individuals owing normal renal function. In renal impairment with creatinine clearance less than 40ml /min, cefuroxime is excreted only by the glomerular filtration (El-Gindy *et al*., 2000). Basically, renal clearance of cefuroxime depends on the urine flow and creatinine clearance both in normal and impaired renal function subjects. Hemodialysis is moderately significant route of elimination of cefuroxime (Van *et al*., 1979).

The present project was designed to assess the renal clearance and urinary excretion of cefuroxime in local population of Pakistan.

MATERIAL AND METHODS

This study was conducted to analyze the urinary excretion and renal clearance of cefuroxime and endogenous creatinine in blood and urine samples of healthy male volunteers after the I/V administration of 750 mg cefuroxime were collected. The

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experiments were conducted on 8 male volunteers. The volunteers who offered to participate was included in this study. Blank blood and urine samples were taken from each male.

SAMPLING PROCEDURE

COLLECTION OF BLOOD SAMPLES

Blood samples were collected at specific time intervals in EDTA tubes. The first blood sample was collected before the administration of Cefuroxime sodium injection as a control sample from each volunteer. The blood samples were collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8 hours after administration of the dose. Blood samples were then centrifuged at 4000 rpm for 30 minutes, the plasma was separated and stored at -20^{0}C until further analysis.

COLLECTION OF URINE SAMPLES

The control urine sample was collected from each volunteer before administration of the drug. For the study of renal clearance and urinary excretion, the urine samples after drug administrationwere collectedin 45, 75, 105, 135, 165, 240,360 and 480 minutes after administration of drug in plastic bottles containing 1 Mol/L Na_2CO_3 to buffer the urine above pH 7 for preventing acidic degradation of the drug.

HPLC ANALYSIS

Concentration of cefuroxime was determined by HPLC.

CHROMATOGRAPHIC SYSTEM

Chromatography was performed with a high performance liquid chromatography. The HPLC system was consisted of Shimadzu SCL-10A system controller, UV visible SPD-10AV detector and LC-10AT pump with FUC-10AL VP flow controller wall. Separation was achieved at ambient temperature with Hypersil C18 BDS 250x4.6 column pore size of 5 micron. Chromatographic data was collected and analyzed using CSW32 software.

CHROMATOGRAPHIC CONDITIONS

Quantitative analysis of allopurinol was achieved by using an isocratic mode. UV detector was used for the detection of allopurinol. Hypercil C18 BDS 250*4.6 column was used. Flow rate was maintained at 1ml/min.

PREPARATION OF MOBILE PHASE

The mobile phase consists of Acetonitrile and 0.05 M Disodium hydrogen phosphate buffer (pH 6) in the ratio of 25:75 v/v. The mobile phase was filtered and degassed before use. The mobile phase was filtered in vacuum filtration assembly having cellulose filter which have pore size 0.45um (Sartorius company). Filtered mobile phase was sonicated for the removal of bubbles for 10 minutes (eyela sonicator).

STANDARDS PREPARATION

STOCK OR WORKING SOLUTIONS

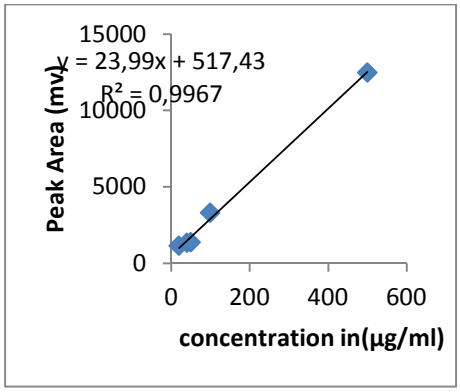
Stock or working solution of Cefuroxime sodium was made up by dissolving equivalent to 10 mg cefuroxime in 100 ml of deionized water.

CALIBRATION STANDARD FOR URINE SAMPLES

Calibration standards for urine samples were prepared by adding the required amount of Cefuroxime sodium working solution added to drug free urine samples to achieve the Cefuroxime sodium concentrations of 20, 40, 50, 100, 500µg /ml were extracted and analyzed as described above,These solutions were filtered through through HA 0.45µm membranes filter having a pore size (25 mm filter) and 20 µL was injected into the HPLC for analysis. Calibration graph was prepared by using peak area verses concentrations of calibration standards.

Table 1: Concentration and peak area of standard solution of Cefuroxime sodium

Concentration (µg/ml)	Peak Area (mv)
20	1139
40	2232
50	2773
100	5300
500	12476



CALCULATIONS

DIURESIS

The rate of urine flow in a time period was calculated as the volume of urine in a collection time period

$$\text{Diuresis (mL/min/kg)} = \frac{\text{Volume of urine in a collection time period (mL)}}{\text{Time (min) x body weight (kg)}}$$

RENAL CLEARANCE

It may be defined as the volume of plasma being cleared of drug per unit time per kg of body weight by the kidneys. The renal clearance of endogenous creatinine was used for the estimation of glomerular filtration rate (GFR). Renal clearance of Cefuroxime sodium and endogenous creatinine was calculated by the following formula.

Where $cl_R$is the renal clearance, U_c and $P_c$are concentrations of a substance in urine and plasma respectively. U_v is urine rate flow (Diuresis, ml/min/kg).

DETERMINATION OF CONCENTRATION OF CEFUROXIME SODIUM IN URINE AND PLASMA SAMPLES

Concentration of Cefuroxime sodium in plasma and urine by HPLC method mentioned above (El Gindy et al., 2000). The concentration of Cefuroxime sodium in urine and plasma samples was determined byfollowing relationship:

$$y = a + bx$$

Where a = slope, b= intercept, y = absorbance in nm, x = concentration of drug (µg/ ml)

CREATININE ANALYSIS

Creatinine analysis was performed by creatinine colorimetric detection kit of (merck company). Some important parameters due to which this method was preferred upon conventional method. The Creatinine colorimetric detection kit utilizes a single-step liquid detection reagent that is safer and less time consuming than other assay methods. This kit is calibrated against the NIST standard and offers reproducible results with less than 6% inter- and intra-assay variation.

STATICAL CALCULATIONS

STATISTICAL ANALYSIS

Correlations of renal clearance with pH, diuresis and drug concentrations were obtained through regression analysis at 5% level of significance (P < 0.05) (Steel *et al*., 1997).

RESULTS AND DISCUSSION

RENAL CLEARANCE

Values of diuresis, plasma and urine concentration as Mean± SD and renal clearance of cefuroxime and endogenous creatinine in eight volunteers are presented in Table 1.

In present study, the rate of urine flow was recorded to be 0.016 ± 0.002 ml/min/kg.

Values for pH of blood and urine of volunteers of our study were 7.43±0.007 and 6.13±0.21

respectively. Mean ± SE value for renal clearance of endogenous creatinine was recorded as 7.65±0.37 and 572.2 ±3.39ml/min/kg in blood and urine samples present study.

However, the clearance value in present study is 1.315±0.103. No significant correlation was observed between diuresis, plasma concentration of cefuroxime and urine pH with the renal clearance of drug in male subjects of present study through regression/correlation analysis (Figure1)

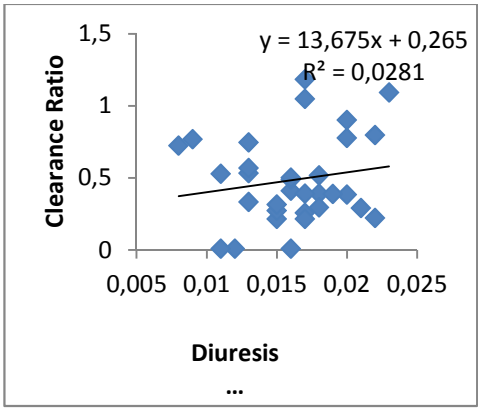


Figure 1: Effect of diuresis of ciprofloxacin on its renal clearance in sheep.

Each data point shows one of the 32 experiments, each comprised of 4 experimental periods.

Sr No	Body weight (Kg)	Diuresis (ml/min/Kg)	pH		Creatinine Conc. (µg/ml)		Renal Clearance of Creatinine (ml/min/kg) cl_{CR}	Cefuroxime Conc. (µg/ml)		Renal Clearance of Cefuroxime (ml/min/kg) $cl_{Cefuroxime}$	Clearance Ratio $cl_{cef.}/cl_{CR}$
			Blood	Urine	Plasma	Urine		Plasma	Urine		
1	74	0.016	7.43	6.63	8.2	494.0	1.36	26.527	998.675	0.593	0.436
2	70	0.016	7.42	6.03	6.9	565.7	1.39	27.100	983.000	0.571	0.411
3	68	0.017	7.45	6.90	7.3	461.7	1.01	27.482	992.650	0.605	0.599
4	75	0.018	7.40	6.24	9.1	599.5	1.13	25.613	1011.825	0.691	0.612
5	65	0.018	7.46	5.39	6.9	621.5	1.54	25.815	1012.050	0.715	0.465
6	72	0.017	7.44	6.01	8.0	751.0	1.55	25.835	1003.475	0.660	0.426
7	69	0.015	7.43	5.45	9.0	474.2	0.85	26.740	991.675	0.557	0.655
8	70	0.014	7.42	6.90	6.4	609.7	1.69	26.210	998.075	0.514	0.304
Mean ±SD	70.375 ±3.248	0.016 ±0.002	7.43 ±0.007	6.13 ±0.21	7.65 ±0.37	572.2 ±3.390	1.315 ±0.103	26.415 ±0.664	998.928 ±10.041	0.613 ±0.069	0.488 ±0.121

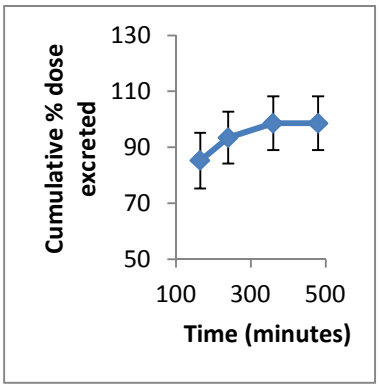


Figure 2: Mean cumulative% amount of dose excreted in urine after intramuscular administration of cefuroxime sodium 750 mg in male subjects at different time intervals

URINARY EXCRETION

Mean ± SD values for urinary excretion of cefuroxime in sheep have been shown in Figure 2. These values are expressed as cumulative percent of cefuroxime dose excreted in the urine at different time intervals following its intramuscular administration which was observed as 100 % at 480 min post drug administration in the urine of sheep.

DISCUSSION

RENAL CLEARANCE

The renal clearance and urinary excretion of Cefuroxime were investigated in eight healthy male subjects in present study after intramuscular administration of Cefuroxime 750 mg to each volunteer. The pH of the urine of the current study was 6.13±0.21 which is correlated to previously calculated pH of urine 6.13±0.185 (Ghani et al., 2003). Besides these pH of urine is influenced by the seasonal changes, type of food intake, summer and winter season.

The pH of the blood of the current study was 7.43±0.004 which was correlated to previously studied pH of urine 7.43±0.021 (Ran et al., 2010)

The mean±SD value of urinary creatinine was 57.2±0.329 mg/dl, which was within range (30-300 mg/dl) as mentioned by (WHO, 1996) also correlated by previously finding 49.32±6.25 mg/dl reported

The mean±SD value of renal clearance of endogenous creatinine of the present study was 1.315±0.103 which is correlated with previously reported 1.025±0.3062 in male volunteers by (Foord .1976) and 1.28±0.09 reported by (Bundtzenet al.,1981) in male volunteers. Another study was carried out in Belgium in elderly patients and young adults reported (2.07±1.03) and (1.02±1.08) respectively (Broekhvysen , 1981).

The mean±SD value of the renal clearance ratio of Cefuroxime to creatinine of the present study was 0.488±0.121 ml/min/ kg value is correlated with reported earlier 1.37±0.14ml/min/ kg by (Foord et al., 1976) in male volunteers. A study was conducted by (Gower, 19) reported 1.5±0.15. However the value of clearance ratio of drug to creatinine is greater than 1 indicating most of drug excreted unchanged in urine (Hardman et al., 1996).

There is a significant (P< 0.05) negative correlation (r= -0.718) between plasma concentration and clearance ratio of renal clearance of Cefuroxime and renal clearance of endogenous creatinine presented in (Fig 12). It reflects the saturation of excretory mechanism at higher plasma concentration of drug which is indicative of involvement of active tubular secretion.

There is the positive correlation (r= 0.327) between the pH of the urine clearance ratio of renal clearance of Cefuroxime and renal clearance of endogenous creatinine as P>0.05 showing a highly non significant relationship between these two parameters presented in (Fig 13). As Cefuroxime is acidic drug by decreasing the pH of the urine the urine became acidic the drug became ionized so does not reabsorbed and excretion increases. As according to data basic drugs are more readily ionized in acidic urine and vice versa. Only ionized form of drug is reabsorbed while ionized or polar drugs are more soluble in water so readily dissolve in body fluids for excretion.

There is a non-significant positive correlation (r=0.167) between diuresis and clearance ratio of renal clearance of Cefuroxime and renal clearance of endogenous creatinine presented in (Fig 14). As the rate of urine flow increases, the rate

of Cefuroxime clearance also increases. This observation indicates that at increase diuresis, the drug has less time to stay in the tubules from where it would be excreted unchanged.

The cumulative percentage of dose excreted in 8 hours in urine of eight healthy male subjects of the present study was 98.599±9.594%. Previously reported the excretion of Cefuroxime during the first 12 hours is 101.9% of a given dose (Foord , 1976).The cummulative percentage of dose excreted after administration of 750 mg Cefuroxime was 96 ± 10 (Bundtzenet al.,1981).

CONCLUSION

It was concluded that Glomerular filteration was involved in the renal handling of cefuroxime while back diffusion was not involved and the renal clearance of endogenous creatinine in indigenous species was lower than their foreign counterparts.

REFERENCES

[1] Bundtzen, Toothaker, Nielson, Madsen, Welling, Craig. Pharmacokinetics of cefuroxime in normal and impaired renal function: comparison of high-pressure liquid chromatography and microbiological assays. Antimicrob Agents Chemother. Mar; 19(3):443-9. (1981).

[2] Broekhuysen, Deger, Douchamps, Freschi, Mal N, Neve, Parfait, Siska, Winand. Pharmacokinetic study of cefuroxime in the elderly. British Journal of Clinical Pharmacology. Dec; 12(6):801-5.(1981).

[3] El-Gindy, Fattah, Walily and Bedair. First-derivative spectrophotometric and LC determination of cefuroxime and cefadroxil in urine. Journal of Pharmaceutical and Biomedical Analysis: 1016. (2000).

[4] Foord, Cefuroxime: Human Pharmacokinetics. Journal of Antimicrobial agents and chemotherapeutics. May:9(5):471-747,1(976).

[5] Ghani, Glichberg, sahagian. High incidence of resistant pathogens in community acquired bscteriuria from patients in the Jerusalem area with lower urinary tract infections. Dec: 14(12)1032-5, 1091-1090, (2002).

[6] Gower, Kennedy, Dash. The effect of renal failure and dialysis on the pharmacokinetics of Cefruroxime. Proc R Society of Medicine.70(9): 151-157, (1981).

[7] Hardman, Fisher, Patel, Neale, Chambers, Lane, Appleberg. Ruptured abdominal aortic aneurysms: who should be offered surgery? Journal of vascular surgery.Jan:23(1)123-9, (1996).

[8] Norrby, Foord, & Hedlund,. Clinical and pharmacokinetic studies on cefuroxime. Journal of Antimicrobial Chemotherapy's, 355-62. (1977).

[9] Ran, Jimbo. Distribution of cefuroxime sodium in mice and tissue pharmacokinetics. Heilongjiang medical science. 4:969, (2010).

[10] Steel, Dickey and Torrie. Linear regression. In: Principles and Procedures of Statistics: A biometrical approach. 3rd Ed. McGraw-Hill series in probability and statistics. London : 253-285.(1997).

[11] Van, Vree, Hafkenscheid & Gimbere. Determination of plasma and renal clearance of cefuroxime and its pharmacokinetics in renal insufficiency. Antimicrobial Chemotherapy., 5,281-292.(1979).

[12] Zhao, Qing, Xingang, Ran, Xiaohui, Lulu, Kaishun. Bioequivalence and Population Pharmacokinetic Modeling of Two Forms of Antibiotic, Cefuroxime Lysine and Cefuroxime Sodium, after Intravenous Infusion in Beagle Dog. Journal of Biomedicine and Biotechnology, 2012 :9 (2012).