International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

A comparative study of renal clearance of cefaclor and creatinine in male volunteers

Munazza Noor, Muhammad Adeel Shahid*, Shahzad Ali Shahid Chatha, Siddique Yaseen

Department of Applied Chemistry and Biochemistry, Government College University Faisalabad, Pakistan

Abstract

Renal clearance of a substance is the volume of plasma completely cleared of that substance by the kidneys per unit time and by measuring the renal clearance, the rate of glomerular filtration can be determined. It is generally apprehended that creatinine clearance is the best measure of glomerular filtration rate. This study is an organized appraisal to work for the renal clearance of creatinine and cefaclor in 12 healthy male volunteers followed by oral administration of 375 mg tablets of cefaclor to each volunteer. Blood and urine samples were collected at specific time intervals and concentration of drug was measured by creatinine analysis and microbiological assay. Renal clearance of creatinine and cefaclor was 3.39 and 0.76 mL/min/kg body weight respectively. The clearance ratio was 0.05. A significant negative correlation was observed between plasma concentration and clearance ratio and also a significant negative correlation was found between plasma concentration and drug clearance. These observations assists to endure the need for comprehensive evaluation of drug under indigenous circumstances to obtain pharmacokinetic parameter on which the rational dose regimes of drug could be based.

Key words: Cefaclor, Creatinine, Renal Clearance, Pharmacokinetic, Drug Therapy

Full length article Received: 13-11-2014 Revised: 05-04-2015 Accepted: 15-04-2015 Available online: 31-05-2015

*Corresponding Author, e-mail: adeelchemist@gmail.com, Phone: 0092-3457833772

1. Introduction

The aim of drug therapy is to prevent, cure or control various disease states. To achieve this goal, adequate drug doses must be delivered to the target tissues so that therapeutic, yet non-toxic levels are obtained [1]. Cefaclor is a second generation cephalosporin antibiotic used to treat certain infections caused by bacteria such as pneumonia, ear, lung, skin, throat, and urinary tract infections. Cefaclor, 3-choloro-7-D-(2-phenylglycinamido)-3-cephem-4-carboxylic acid, is a new cephalosporin related to cephalexin. Its formula is C_{15} H_{14} N_3 ClO_4 S and molecular weight is 367.808 g. Cefaclor is active against Staphylococci, streptococii, and uphalothin susceptible *Enterobacteriaceae* [2]. Cefaclor has become widely used in the range of pedliatric infections including otitis media, tonsillitis and skin infections. Cefaclor has been as relatively safe drug [3]. Renal clearance of a substance is an estimation of volume of plasma cleared of a substance by a kidney in a unit time for a given body weight while urinary excretion gives total amount of drug excreted in urine as parent drug or metabolites. The glomerular filtration rate can be determined by measuring renal clearance of a substance that freely filtered at glomerulus and is neither absorbed nor reabsorbed [4]. The plasma and urine concentration of cefaclor were measured after oral administration of single and multiple doses to volunteers. Cefaclor was rapidly excreted in the urine, well tolerated without toxicity, and failed to accumulate in plasma with choronic dosing [5]. The biochemical parameters recorded under indigenous condition, pH of blood and urine and drug metabolism. The difference has been shown to affect fate of drug, therapeutic standards and dose segments on the basis of indigenous investigation [6-7]. The project was planned to study the renal clearance of creatinine and cefaclor in male human volunteers to optimize the use of cefaclor under local environmental conditions.

2. Materials and methods

2.1. Subject:

The experiment was conducted on 12 healthy male volunteers of age between 25 to 30 years. On the basis of physical examination and medical history it was determined that all subjects were in good health. No other medications were permitted one week prior to and during the study. Body weight, height, age of each volunteer was recorded.

2.2. Drug used:

Cefaclor was obtained as film coated tablets by the name of ceclor from ELI LILLY-GOHAR (Pvt.) Ltd. Each tablet

contains cefaclor 375 mg was used for oral administration to volunteers.

2.3. Collection of samples:

After an overnight fastening control blood and urine samples were collected from all volunteers at 0, 0.5, 1.0, 1.5 and 3.0 hours' time intervals. Each volunteer was given a tablet of cefaclor (375 mg) with 240 mL orally. The volunteers were allowed to take breakfast two hours following drug administration.

2.4. Blood collection:

The 5 mL venous blood from each volunteer was drawn at 0.25, 0.5, 0.75 and 1.0 hours' time intervals in heparinized centrifuge tubes, following oral administration of cefaclor tablets. The blood samples were centrifuged at 4000 rpm for 10 minutes and plasma was separated and stored in plastic bottles kept in freezer at -20°C till further analysis.

2.5. Urine collection:

The urine samples were taken at 0, 0.5, 1.0, 1.5 and 3.0 hours' time intervals after oral administration of cefaclor. The total volume of urine voided during this time period was recorded. The pH of fresh urine sample was recorded with pH meter. A 40 mL of each sample was stored in plastic bottles and preserved in freezer at -20°C for further analysis.

2.6. Analytical procedure:

2.6.1. Creatinine analysis:

For the estimation of glomerular filtration rate, the endogenous creatinine renal clearance was measured in plasma and urine samples spectrophotometrically by the method of Bonsons and Tausky (1945) using Jaffer-reaction [8].

2.6.2. Microbiological assay:

Cefaclor concentration in blood determined by microbiological assay according to disc agar diffusion method describe by Arret *et al*., (1971) using *E. Coli* as test organism [9].

2.7. Statistical calculation:

The data are reported as ± SE of twelve observations. The correlation between the diuresis, pH and plasma concentration of drug with its renal clearance were determined by means of regression/correlation analysis and are shown in the figures 1-7 [10]. All the results are represented in table 1.

3. Results and discussion

Renal clearance of endogenous creatinine and cefaclor was investigated in 12 healthy human male volunteers after oral dose of 375 mg tablet. Blood and urine samples were analyzed for creatinine and cefaclor by microbiological assay [11]. Their renal clearance was determined.

The mean ± SE for the rate of urine flow (diuresis) was 0.07±0.01 mL/min/Kg, pH of blood was 7.51±0.01 and of urine was 5.83±0.06. Concentration of creatinine in plasma and urine was 3.39±0.38 and 813.57±138.29 µg/mL respectively. The mean ± SE value of cefaclor in plasma and urine was 2.93±0.06 and 17.13±1.17 µg/mL respectively. Renal clearance of creatinine and cefaclor was 3.39 ± 0.38 and 0.76 ± 0.14 mL/min/Kg body weight respectively. The clearance ratio was 0.05 ± 0.01.

The study indicated that the renal clearance of endogenous creatinine in male volunteers was less than the values given in literature. A significant positive correlation between diuresis and renal clearance of cefaclor is indicative of renal tubular back diffusion or reabsorption [12]. There is a non-significant negative correlation between urine pH and cefaclor clearance. So, pH of urine does not have any influence on the renal clearance of drug. There is non-significant negative correlation between diuresis and clearance ratio and also non-significant negative correlation between pH of urine and clearance ratio. There is significant negative correlation between plasma concentration and clearance ratio and also significant negative correlation between plasma concentration and drug clearance as shown by results and graphs.

4. Conclusion

It is concluded that besides glomerular filtration, mechanism of back diffusion and active tubular secretion was also involved in cefaclor excretion. This observation enables to endure the need for comprehensive evaluation of drug under indigenous circumstances to obtain pharmacokinetic parameter on which the rational dose regimens of drug could be based.

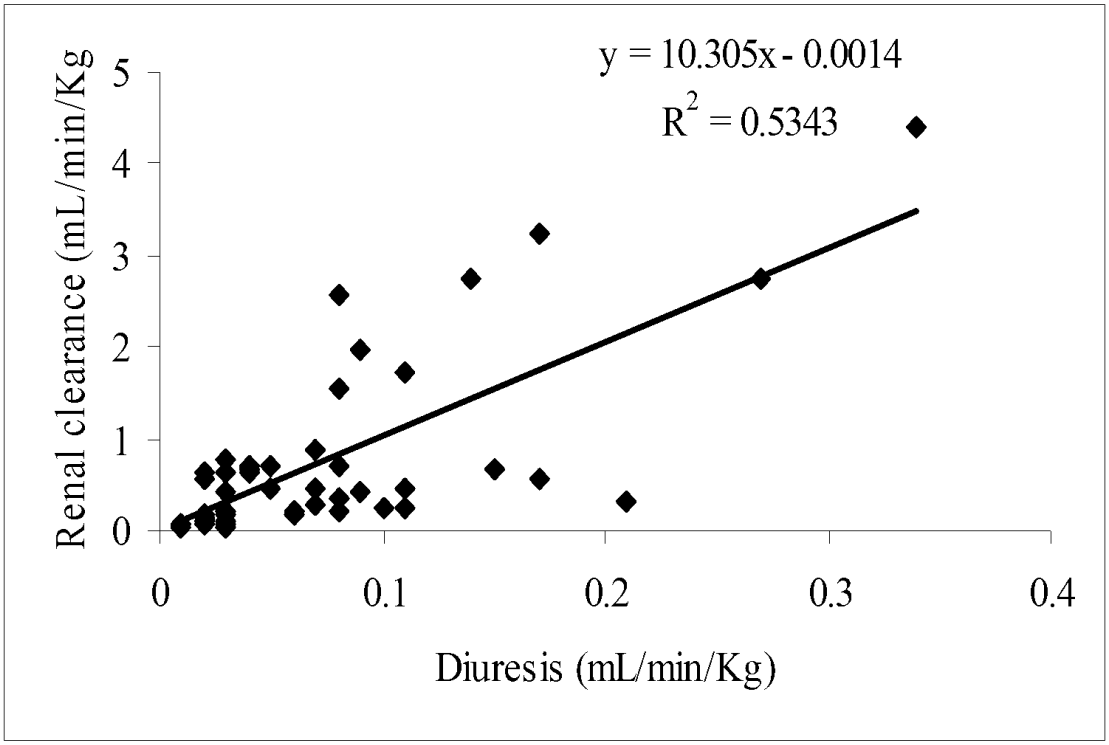

Figure 1. Relationship between diuresis and renal clearance of cefaclor in 12 healthy male volunteers

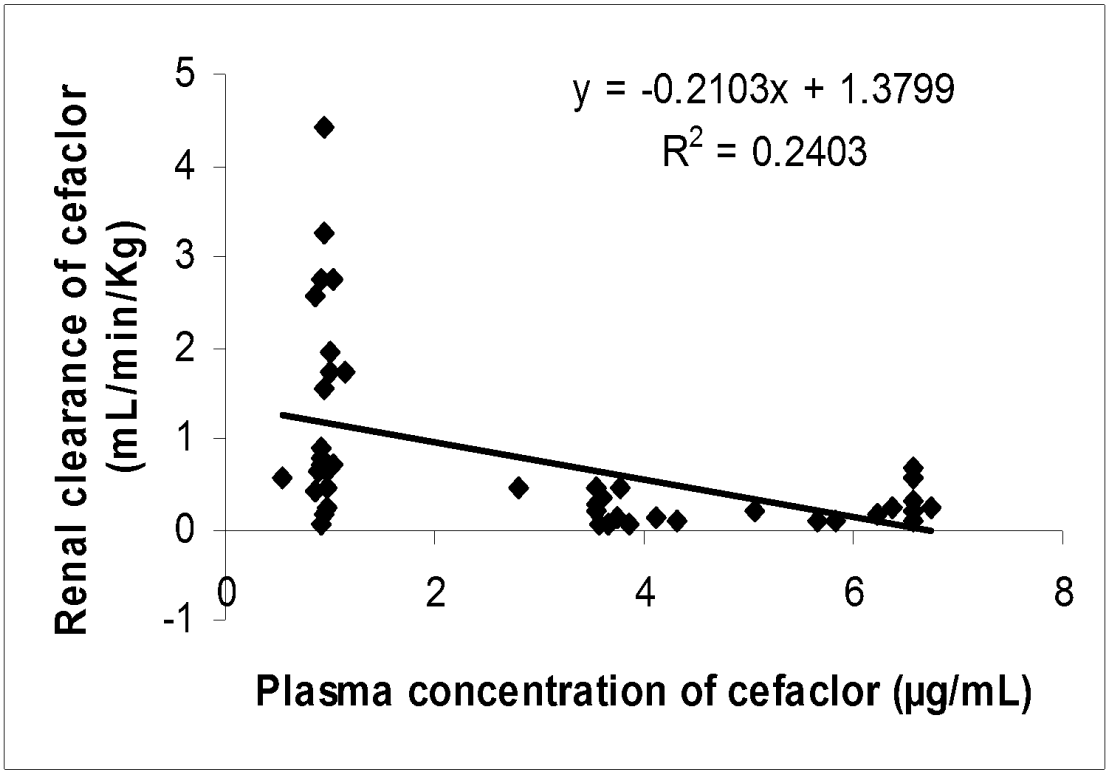

Figure 2. Relationship between plasma concentration of cefaclor and its renal clearance in 12 healthy male volunteers

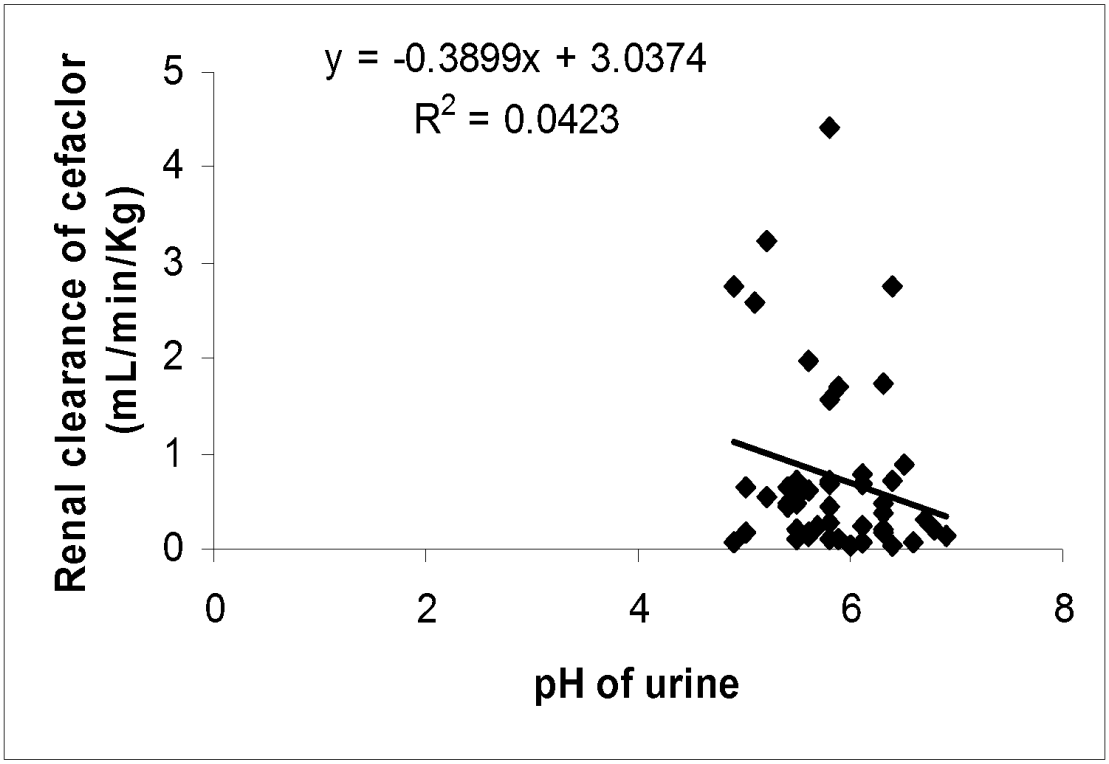

Figure 3. Relationship between pH of urine and renal clearance of cefaclor in 12 healthy male volunteers

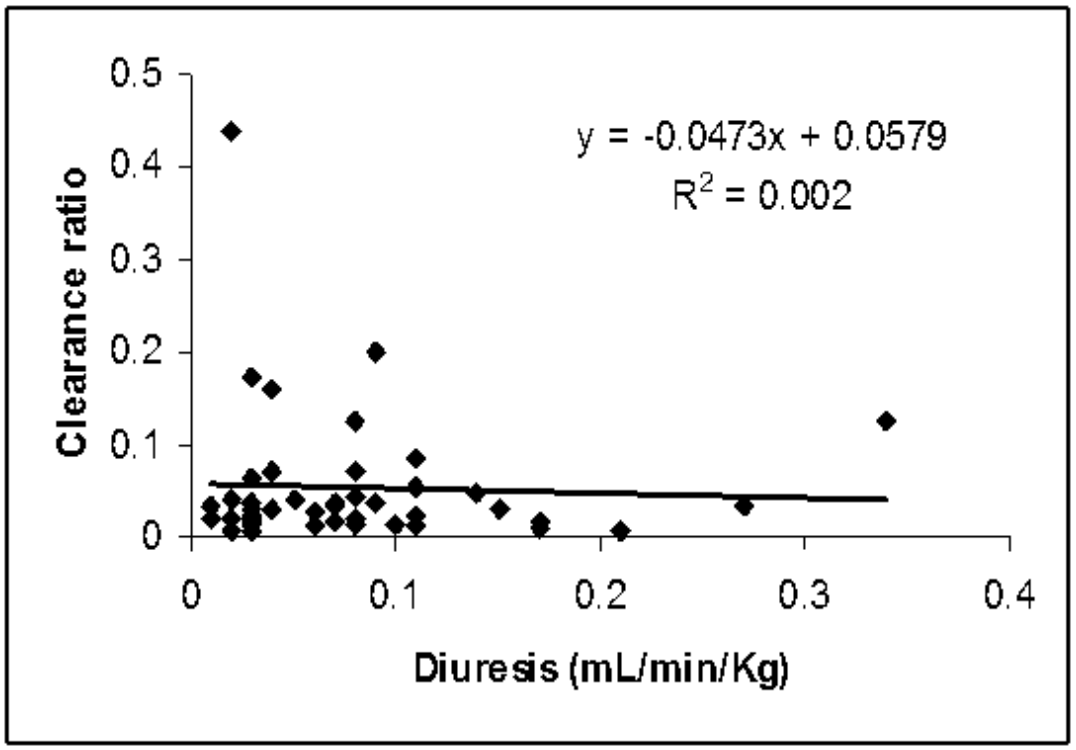

Figure 4. Relationship between diuresis and cefaclor clearance ratio in 12 healthy male volunteers

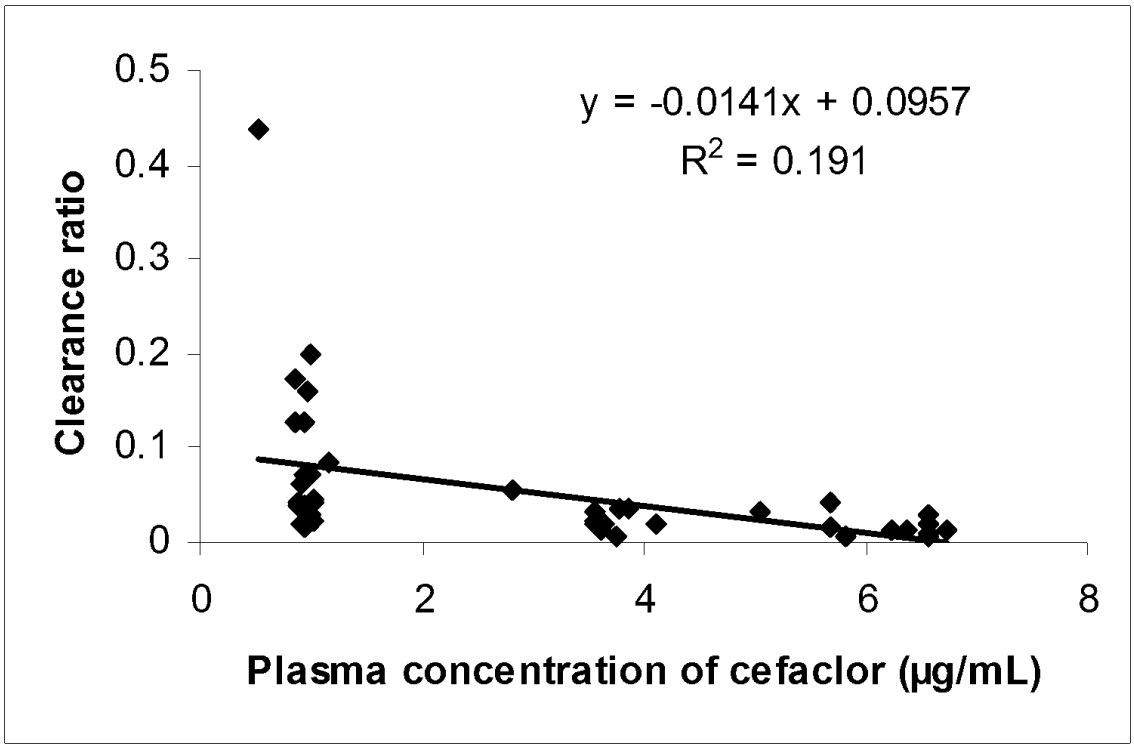

Figure 5. Relationship between plasma concentration of cefaclor and its clearance ratio in 12 healthy male volunteers

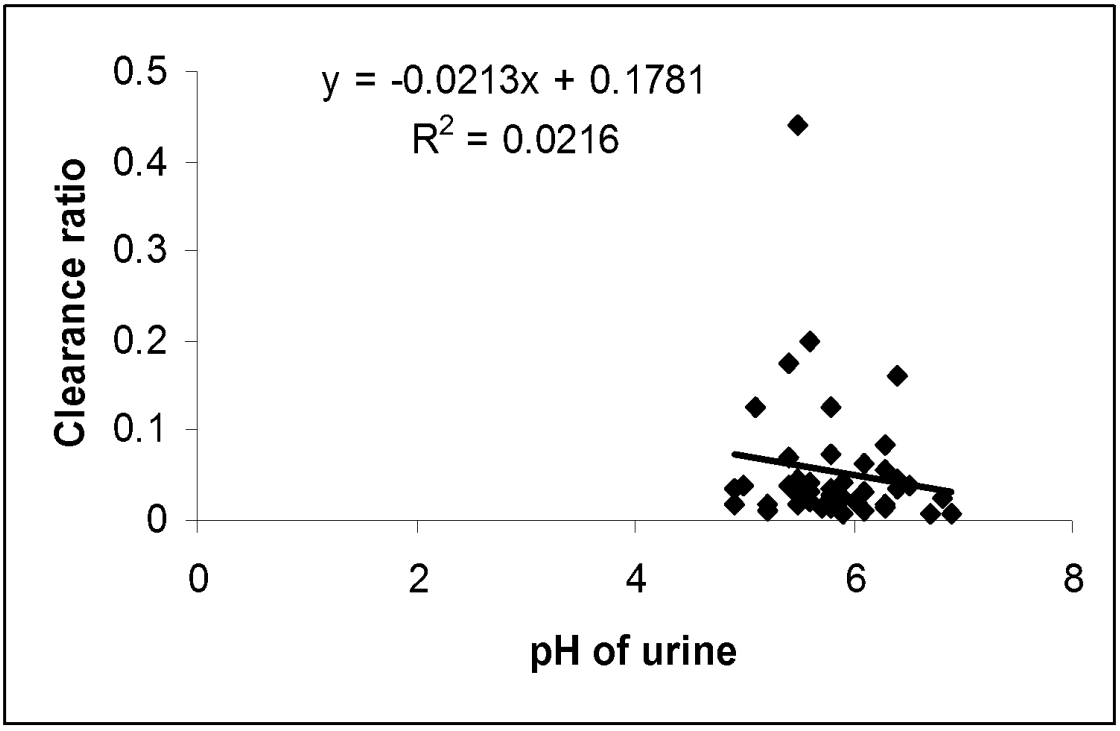

Figure 6. Relationship between pH of urine and cefaclor clearance ratio in 12 healthy male volunteers

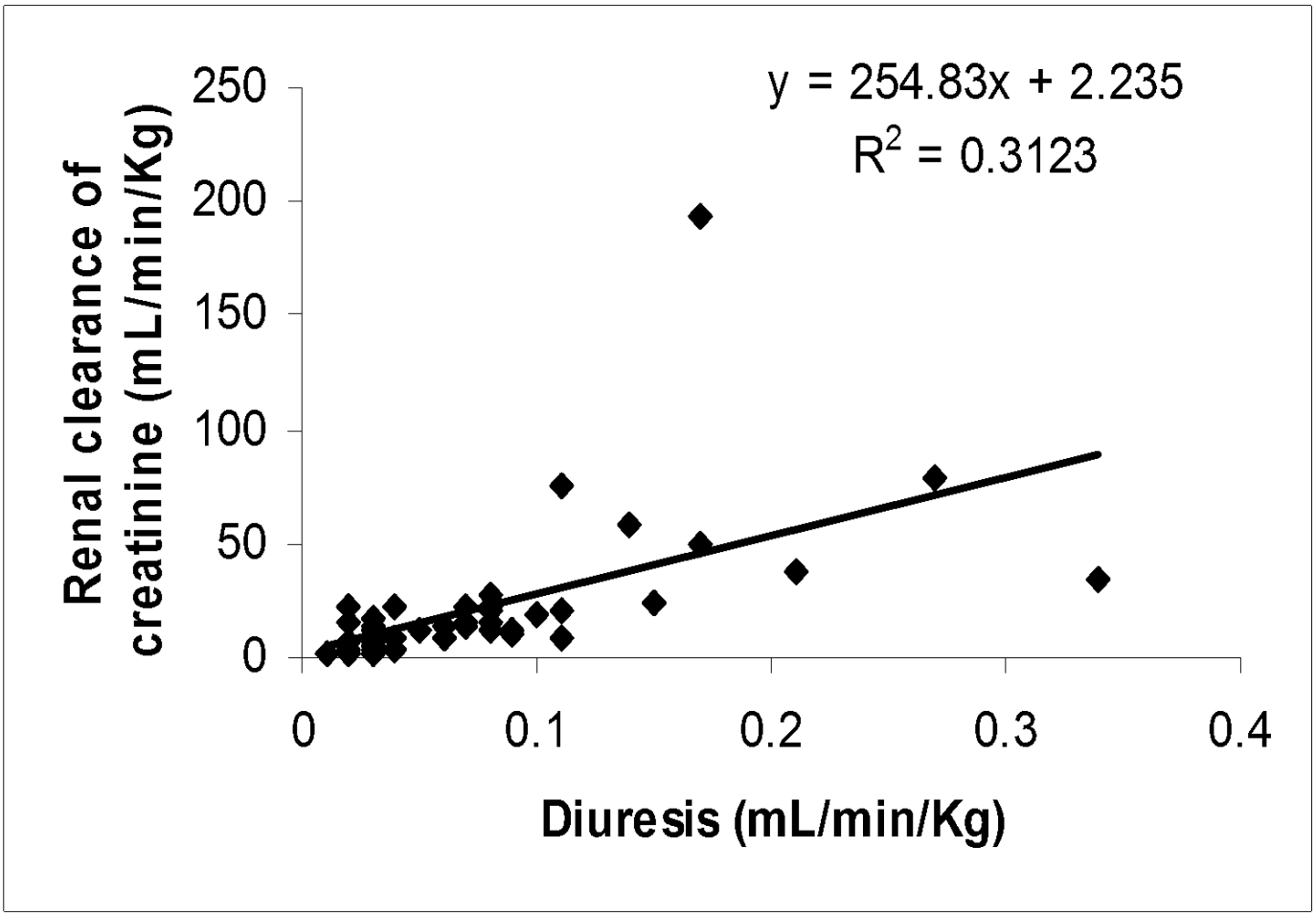

Figure 7. Relationship between diuresis and creatinine in 12 healthy male volunteers

Table 1: Average data of renal clearance of endogenous creatinine and cefaclor in male volunteers after oral dose of 375 mg tablets.

Volunteers	Body weight (Kg)	Diuresis mL/min/Kg	pH		Concentration (µg/mL)				Renal clearance (mL/min/Kg)		clearance ratio Cldrug/Clcr
					Creatinine		Drug				
			urine	blood	Urine	Plasma	urine	plasma	creatinine	drug	
1	59	0.026	5.38	7.54	1193.89	6.296	14.03	2.983	8.24	0.21	0.026
2	79	0.049	5.78	7.49	584.11	3.646	19.50	2.510	10.95	0.52	0.136
3	54	0.098	5.90	7.50	906.39	3.046	22.24	3.213	31.44	1.07	0.039
4	52	0.024	6.03	7.50	607.98	5.505	18.38	2.833	2.62	0.32	0.103
5	64	0.153	5.73	7.58	406.61	3.205	17.33	3.020	18.97	1.76	0.094
6	63	0.071	6.05	7.48	730.93	1.992	22.61	2.813	25.40	1.40	0.051
7	51	0.097	5.95	7.52	559.34	2.178	13.27	3.013	22.70	0.60	0.033
8	55	0.099	5.55	7.50	614.11	2.751	12.61	2.815	25.88	0.90	0.029
9	52	0.075	5.88	7.50	511.61	3.969	11.57	2.833	9.22	0.39	0.043
10	80	0.049	6.08	7.54	949.57	2.610	18.56	2.920	16.04	0.48	0.031
11	54	0.095	5.73	7.52	2158.43	2.774	22.05	3.035	69.86	1.14	0.019
12	50	0.057	5.98	7.49	539.80	2.733	13.36	3.230	15.80	0.37	0.026
Average	59.42	0.07	5.83	7.51	813.57	3.39	17.13	2.93	21.43	0.76	0.05
±SE	3.00	0.01	0.06	0.01	138.29	0.38	1.17	0.06	5.03	0.14	0.01

References

[1] J.M. Mary, A.H. Richard, C.C. Pamela and D.F. Bruce. (1997). Lippincott's illustrated reviews pharmacology. 2nd Edition. Lippincott-Raven Philadelphia, New York. 1-9.

[2] J. Santoro, B.N. Agarwal, R. Martinelli, N. Wenger and M.E. Levison. (1978). Pharmacokinetics of cefaclor in normal volunteers and patients with renal failure. Antimicrobial Agents and Chemotherapy. 13(6): 951-954.

[3] B.A. King and G.C. Gellhoed. (2003). Adverse skin and joint reactions associated with oral antibiotic in children: the role of cefaclor in serum sickness like reactions. Journal of Oaediatrics and Child Health. 39: 677-681.

[4] J.G. Hardman, L.E. Limbird and A.G. Gilman. (2001). Goodman and Gilman's the pharmacological basis of therapeutics. 10th Edition. Jaypee Brothers. 1274-1277.

[5] G.R. Hodges, L. Chien, R.H. Daniel, L.H. Jane and L.D. David. (1978). Pharmacological evaluation of cefaclor in volunteers. Antimicrobial Agents and Chemotherapy. 14(6): 454-456.

[6] M. Nawaz and B.H. Shah. (1984). Renal clearance of endogenous creatinine and urea in sheep during summer and winter. Research in Veterinary Science. 361: 220-224.

[7] M. Nawaz. (1994). Geonetical factors affecting biodisposition of drugs. Canadian Journal of Physiology and Pharmacology. 12: 257-259.

[8] R.M. Bonsens and H.M. Tausky. (1945). On the colorimetric determination of creatinine by Jaffe reaction. The Journal of Biological Chemistry. 158: 581-591.

[9] B. Arret, D.P. Johnson and A.K. Krishdan. (1971). Outlines of detail for microbiological assay of antibiotic. Journal of Pharmaceutical Sciences. 60(11): 373-378.

[10] R.G.D. Steel, J.H. Torrie and D.A. Dickey. (1997). Principles and procedures of statistics. 3rd Edition. McGraw-Hill, New York.

[11] S. Amalthes and V.K. Guptas. (1988). Spectrophotometric determination of trace amounts of hydrazine in polluted water. Analyst. 113: 1481-1483.

[12] J.G. Hardman, L.E. Limberd, P.B. Molinoff and R.W. Ruddon. (1996). Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 9th Edition. McGraw-Hill, New York.