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ELIMINATION KINETICS OF CEFACLOR IN MALE HUMAN BEINGS

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ABSTRACT

Elimination kinetics of cefaclor was investigated in twelve male healthy volunteers after 375 mg single dose oral administration of the drug. Elimination kinetics parameters revealed that the mean value for rate constant (K_{10}) was 0.30, mean value for elimination half-life was 2.25h, mean value for rate constant (K_{21}) was 0.30, mean value for clearance was 4.04 1/h, mean value for mean residence time was 6.73h. No relation was found regarding age, weight, height and body temperature considering elimination kinetics

Key Words: Blood plasma, *E.Coli*, Cefaclor, Elimination kinetics.

INTRODUCTION

The body defends itself against potentially harmful compounds like drugs, toxic compounds and their metabolites by elimination (Masereeuw and Russel, 2001). Drug includes all chemical substances except foods that are used to promote or safeguard the health of man or animals (Jones, 1965).

Cefaclor is a widely used life saving antibiotic belonging to the class of cephalosporin (Kemperman *et al.,* 2000). It is a second generation semi-synthetic cephalosporin antibiotic with a broad spectrum activity against Gram positive and Gram negative bacteria (Anon, 1989). Cefaclor is highly active, equally or more so than the other oral cephalosporins, against several gram-negative species including *Escherichia coli, Enterobacter aerogens,* and *Klebsiella pneumoniae*. None of the cephalosporins were particularly active against *Enterobacter cloacae*. Cefaclor is active against *Proteus mirabilis* (Smith *et al.,* 1977). Cefaclor is used orally. The concentrations in plasma after oral administration are about 50% of those achieved after an equivalent oral dose of cephalexin. However, cefaclor is more active against *H.influenzae* and *M.catarrhalis*, although some b-lactamase producing strains of these organisms may be resistant (Jorgenson *et al.,* 1990). Cefaclor has become widely used in the range of pediatric infections including otitis media, tonsillitis and skin infections (Joubert *et al.,* 1999). It does not have a significant effect on theophylline pharmacokinetics (Jonkman *et al.,* 1986). Cefaclor was eliminated more rapidly than other cephalosporins from serum (Welling 1979).Cefaclor have serum elimination half-lives of less than or equal to 1h. The urinary recovery of this agent is 54% (Barbhaiya *et al.,* 1990).It degrades chemically in the body with an approximate half-life of 2.3 hours. Most of the drug is excreted unchanged in the urine (Brown *et al.,* 2007).

The drug often but not always is distributed to certain body compartments that bio transform it, which is to say that molecular structures of drug is changed. The chemical nature of the drug strongly influences its ability to cross cell membranes (Mary *et al.,* 1997). Smith has phrased, "The composition of blood is determined not by what the mouth ingests but by what the kidney keeps" (Chatterjee *et al.,* 1983). The most marked pharmacokinetic effect of renal failure is delayed renal elimination of drugs. However, urenic patients manifest abnormalities in drug absorption, metabolism and protein binding and in the distribution space, each of which affects plasma water concentrations. These patients also have abnormal pharmacodynamics (Maher JF, 1984). β –lactum antibiotics are frequently prescribed for a wide range of bacterial diseases in human and veterinary medicine. The most important classes of β –lactum antibiotics are the penicillins and cephalosporins, which have the β –lactum ring as a common part of their molecular structure (Mason *et al,*. 1999). From a pharmacodynamic perspective, cephalosporin antibiotics exhibit time-dependant antibacterial activity (Gibson, 1986). Pharmacologically, cephalosporins bind to peptidase enzyme target sites (i.e., penicillin-binding proteins) in the outer cytoplasmic membrane of bacteria. This binding impairs integration of bacterial peptidoglycan into a lattice forming the structural support of the bacterial cell wall (Karchner *et al.,* 2000). An antibacterial effect is exerted when the concentration of cephalosporin at the infection site exceeds the minimum inhibitory concentration (MIC). Raising the concentration more than 2-4 folds above the MIC provide no additional antibacterial effect (Craft *et al,* 2000). Elimination half-lives, protein binding does not explain all the variability in elimination half-life among cephalosporins (Rosin *et al.,* 1993).

MATERIAL AND METHOD

Drug Administration and Sampling: The body weight, temperature, height and blood pressure of 12 healthy adult male volunteers were recorded in the month of January, 2007 (Table 1). The drug "Ceclor MR" 375mg

tablet was given to each volunteer orally with 240ml of water after being kept fasting for 12 hrs. Blood samples were taken in sterilized test tubes at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10hrs and each sample was centrifuged immediately for 15 minutes. Plasma was separated with the help of micro-pipette and stored at -10ºC until assay.

Drug Analysis: The concentration of cefaclor in plasma was determined by microbiological assay according to Disc Agar Diffusion method (Hodges *et al.,* 1978) using *E.Coli* as test organism.

Table 1. Demographic data of Volunteers.

Subject		Age	Weight	Height	Blood Pressure mm of Hg		Body Temperature
No	**ID**	**Years**	**Kg**	**Inches**	**Systolic**	**Diastolic**	**ºF**
1	MJ	36	59	69	110	80	98.4
2	AS	30	79	68	120	80	98.0
3	QA	28	54	67	110	80	98.0
4	MR	21	52	68	110	75	98.2
5	AM	35	64	65	120	80	99.2
6	SR	28	63	65	110	80	98.4
7	AR	23	51	68	120	80	98.0
8	MI	36	55	64	100	75	98.2
9	SA	27	52	66	100	80	98.6
10	IA	28	80	69	140	90	98.4
11	MA	34	54	68	130	90	98.2
12	BM	25	50	68	110	80	98.5
Mean		**29.3**	**59.4**	**67.1**	**115.0**	**80.8**	**98.3**
±S.D		**5.1**	**10.4**	**1.7**	**11.7**	**4.7**	**0.3**
Minimum		**21.0**	**50.0**	**64.0**	**100.0**	**75.0**	**98.0**
Maximum		**36.0**	**80.0**	**69.0**	**140.0**	**90.0**	**99.2**

Bioassay of Cefaclor Activity: Disc diffusion tests for cefaclor against *E.Coli* were performed precisely as described by the National Committee for Clinical Laboratory Standards (NCCLS 1984). Nutrient agar (Oxoid) was used at a concentration of 28g/L of distilled water and autoclaved. *Escherichia coli* (100µl) obtained from Biochemistry Department, University of Agriculture, Faisalabad grown in broth culture for two weeks was added in 300ml of autoclaved solution. Glass petri plates (14 cm in diameter), pipettes, cylinders, test tubes, filter paper, discs (10mm) and tips were autoclaved at 121ºC and 15psi used in the experiments. 40ml of media along with *E.Coli* suspension was poured in sterilized Petri plates which were kept on leveled table for solidification. A 100µl volume of plasma samples were impregnated per 10mm disc.plates having antimicrobial discs were incubated at 37ºC for 24hrs. Zones of inhibition were measured with zone reader scale in mm. All determinations were done in triplicate and the results are averaged.

Estimation of Cefaclor Concentration: Concentration of cefaclor in each sample was determined by microbiological assay (Kitaura *et al.,* 1989). A 100µl volume of these dilutions was loaded and Petri plates were incubated. Zones of inhibition were obtained by the above same procedure. The value of cefaclor in plasma was estimated by the help of standard curve against zone obtained by unknown samples.

Statistical Analysis: Data is presented in the form of mean and standard deviation (Steel *et al.,* 1997).

RESULTS AND DISCUSSION

Plasma concentration was found maximum (Table-2) at 90 minutes in all volunteers having minimum 13.4µg/ml in AR and maximum in BM volunteer 14.88 µg/ml**.** After 2 hrs the concentration of cefaclor in plasma started decreasing to reach 4.5µg/ml after 10hrs.

No relation between age, weight, height, blood pressure and body temperature was found regarding elimination of cefaclor (Table 1 and Table 2).

Clearance: Clearance (Cl) is the volume of blood plasma completely cleared off a drug per unit time through all means and mechanism of eliminations. The values of clearance for all twelve volunteers were 4.21, 4.10, 4.00, 4.02, 4.09, 4.04, 4.04, 3.98, 4.05, 3.96, 3.98, and 3.99 [1/h] respectively. Its mean ± S.D value is 4.04 ± 0.07 [1/h] (Table 3).

Table 2. Plasma concentration (µg/ml) of Cefaclor after oral dose (375mg) to each healthy male.

Volunteer ID	15 min	30 min	45 min	60min	75 min.	90 min	2 hr	3 hr	4 hr	6 hr	8 hr	10 hr
MJ	0.91	0.88	3.57	6.57	9.60	14.73	11.12	9.66	8.4	6.93	5.60	4.29
AS	0.90	0.53	3.55	5.06	8.46	14.12	11.10	9.59	8.84	6.57	5.82	4.68
QA	1.01	1.15	4.12	6.57	9.60	14.10	11.39	10.35	8.74	7.66	5.79	4.55
MR	0.85	0.96	3.85	5.67	9.50	14.25	11.20	10.45	8.84	7.64	5.93	4.45
AM	0.94	1.00	3.78	6.36	9.59	14.15	11.86	10.40	8.84	7.36	5.82	4.28
SR	1.03	0.85	3.55	5.82	10.80	14.23	11.28	10.35	8.84	7.26	6.00	4.40
AR	0.94	0.94	3.60	6.57	9.59	13.40	11.39	9.91	8.84	7.07	5.89	4.61
MI	0.91	1.03	3.65	5.67	11.10	14.09	10.99	9.72	8.64	7.33	6.18	4.63
SA	0.98	0.98	2.80	6.57	9.59	14.34	11.12	9.85	8.40	7.20	5.95	4.58
IA	0.99	0.90	3.55	6.24	10.63	14.12	11.86	10.24	8.68	7.32	5.98	4.68
MA	0.94	0.88	3.75	6.57	10.54	14.40	11.80	9.97	8.68	7.33	6.34	4.45
BM	0.98	0.90	4.31	6.73	9.85	14.88	12.23	10.34	8.68	7.41	6.15	4.40
Mean	**0.95**	**0.92**	**3.67**	**6.20**	**9.9.00**	**14.23**	**11.44**	**10.07**	**8.7**	**7.26**	**5.95**	**4.50**
±S.D	**0.05**	**0.15**	**0.37**	**0.52**	**0.73**	**0.36**	**0.39**	**0.32**	**0.16**	**0.30**	**0.20**	**0.14**

Elimination Half-Life: Biological half-life or elimination half-life represents the elimination of drug from the body. Shorter half-life shows rapid elimination of drug and longer half-life indicates delayed elimination from the body. The values for the elimination half-life (hour) for cefaclor were 2.56, 2.45, 2.21, 2.29, 2.09, 2.28, 2.43, 2.48, 2.31, 2.74, 2.29 and 2.22 respectively. Mean ± S.D value was 2.36 ± 0.18 (Table 3).

The mean value of half-life of cefaclor is 2.25h, which is greater as compared to an earlier report in which the eliminative half-life of cefaclor after the oral administration of 250mg is 0.69h and 40 to 60 min in normal subjects by Bloch (1977). Values are different due to the food difference, genetical difference and local temperature conditions.

Table 3. Elimination kinetics parameters of cefaclor from the plasma concentrations following oral administration.

Volunteers	Rate Constant (K10) [1/h]	Elimination half-life [h]	Rate Constant (K21) [1/h]	Clearance (Cl) [1/h]	Mean Residence Time (MRT) [h]
MJ	0.28	1.97	0.27	4.21	6.63
AS	0.28	2.46	0.28	4.10	7.23
QA	0.32	2.23	0.32	4.00	6.55
MR	0.31	2.28	0.30	4.02	6.73
AM	0.33	2.36	0.33	4.09	6.57
SR	0.30	2.29	0.31	4.04	6.74
AR	0.29	2.19	0.29	4.04	6.74
MI	0.29	2.16	0.28	3.98	6.76
SA	0.30	2.33	0.30	4.05	6.85
IA	0.29	2.21	0.26	3.96	6.78
MA	0.30	2.25	0.30	3.98	6.69
BM	0.31	2.22	0.31	3.99	6.56
Mean	**0.30**	**2.25**	**0.30**	**4.04**	**6.73**
± S.D	**0.02**	**0.12**	**0.02**	**0.07**	**0.18**

Mean residence time: Mean residence time (MRT) gives us the time required to eliminate specific amount of drug. The values for MRT were 6.63, 7.23, 6.55, 6.73, 6.57, 6.74, 6.74, 6.76, 6.85, 6.78, 6.69 and 6.56 respectively. The Mean ± S.D value was 6.73 ± 0.18 (Table 3).

Mazzei in 2000 presented that with the new sustained-release formulation, the time of peak and mean residence time (MRT) values are significantly longer than those observed with the standard cefaclor IR, He determined that the MR formulation improves the kinetic properties of the cefaclor molecule with a prolonged MRT which allows a daily dosage of 750mg every 12h, which is similar to my value, 6.73, the difference is only due to the administered dose of the cefaclor MR.

Rate constants K10 and K21: The value of K10, K21 (1/h) were determined. The Mean ± S.D values for those rate constants were 0.30 ± 0.02 and 0.30 ± 0.02 (Table 3).

Kuroda in 2005 determined that cefaclor was cleared from the cerebrospinal fluid (CSF) more rapidly than cefalexin after intracerebroventricular administration and the elimination rate constant of cefaclor was 0.11 which is smaller than the value recorded in this study, 0.30. This difference may presumably be due to the different passage of administration (oral and in the acerebroventricular) and the differences in the environmental conditions.

REFERENCES

Anonymous, (1989). USPDI, Vol. I 18th edn. Rockville, MD. United States pharmacoprial convention, Inc and Englewood, Co. Micromedex Inc. 740-750.

Barbhaiya, H., U.A. Shukla, C.R. Gleason, W.C. Shyu, R.B. Wilber and K.A. Pittman (1990). Comparison of cefprozil and cefaclor pharmacokinetics and tissue penetration. *Antimicrobial Agents and Chemotherapy*, 34(6): 1204-1209.

Bloch, R., J. J. Szwed, R. S. Sloan and F. C. Luft (1977). Pharmacokinetics of cefaclor in normal subjects and patients with chronic renal failure. *Antimicrobial Agents and Chemotherapy*, 12(6): 730-732.

Brown, S.A., J.F. Boucher, V.L. Hubbard, M.J. Prough and T.F. Flook (2007). The comparative plasma pharmacokinetics of intravenous cefpodoxime sodium and oral cefpodoxime proxetil in beagle dogs. *J. Veterinary Pharmacology and Therapeutics*, 30: 320-326.

Chatter-jee C. C., B. N. Koley. J. Koley. S. Dasgupta and S. C. Ray (1983). Human physiology Vol. 2. Introduction to kidneys. 725-805.

Craft, J C, and L.C. Panish (2000) Systemic antimicrobial therapy. In: *Drug therapy in dermatology* (Milikan LE, ed). New York, NY. Marcel Dekker, pp.57-78.

Gibson, T.P. (1986). Renal disease and drug metabolism. An overview. *American Journal of Kidney Diseases*, 8: 7-1.

Hodges, G. R., L. Chien, R. H. Daniel, L. H. Jane and L. D. David (1978). Pharmacological evaluation of cefaclor in volunteers. *Antimicrobial Agents and Chemotherapy*, 14(3): 454-456.

Jones L. M. and N.M. Booth (1965). *Veterinary pharmacology and therapeutics* 3rd ed. Low A University Press. USA; 7-29.

Jonkman, J. H., W. J. van der Boon, R. Schoenmaker, A. Holtkamp and J. Hempenius (1986). Clinical pharmacokinetics of theophylline during co-treatment with cefaclor. *Int. Journal of Clinical Pharmacy and Therapeutics. Toxicol*., 24(2): 88-92.

Jorgenson, J. H, G.V. Doein, L.A. Maher, A.W. Howell and J.S. Redding (1990). Antimicrobial resistance among respiratory isolates of pneumoniae in the United States. *Antimicrobial Agents and Chemotherapy*, 34: 2075-2080.

Joubert, G., I K. Hadad, D. Matsui, J. Gloor and M. J. Rieder (1999). Selection of treatment of cefaclor associated urticarial, serum sickness like reactions and erythema multiforme by emergency pediatricians. Lack of a uniform standard of care. *Can. Journal of Clinical Pharmacology*. 6: 197-201.

Karchner A W. Cephalosporins (2000). In. *Principles and practice of infectious diseases*. 5th ed (Mamdell G L, Bennett G E, Dolin Rr, eds). Philadelphia, Pa. Chunchill living store; 274-291.

Kemperman, G. J. (2000). *Induced fit phenomena in clathrate structures of cephalosporins*. The Royal Society of Chemistry. 1425-1429.

Kitaura, T., S. Tsukiai, S. Arai, K. Miyake, M. Kimura and H. Fukuchi (1989). Ocular pharmacokinetics of latamoxef and cefaclor . Antibiot. Khimioter cefaclor in humans. Penetration into aqueous humor. *Journal of Pharmacobio-dynamics*. 12(1): 60-6.

Kuroda, M., H. Kusuhara, H. Endou and Y. sugiyama (2005). Rapid elimination of cefaclor from the cerebrospinal fluid is mediated by a Benzyl penicillin-sensitive mechanism distinct from Organic Anion Transporter. *Journal of Pharmacology and Experimental Therapeutics Fast Forward*, 314: 855-861.

Maher, J.F. (1984). Pharmacokinetics in patients with renal failure. *Clinical Nephrology*. 21: 39-46.

Marry, J. M., A. H. Richard, C. C Pamella and D. F Bruce (1997). *Lippincott's illustrated Reviews pharmacology*. 2nd ed. Lippincott Raven Publishers Philadelphia. New York. 1-9.

Mason I. S and M. Kietzmann (1999). Veterinary dermatology, 10, Cephalosporins-pharmacological basis of clinical use in veterinary dermatology.pp.187-192.

Masereeuw, R and F. G. Russel. (2001). Mechanisms and Clinical implications of renal drug excretion. *Drug Metabolism, Rev*. 33(3-4): 229-351.

Mazzei, T, A. Novelli, S. Esposito and P. Periti (2000). New insight into the clinical pharmacokinetics of cefaclor: tissue penetration. *Journal of Chemotherapy*. 12(1); 53-62.

Rosin, E., T.S. Uphoff, N.J. Schultz-Darken and M.T. Collins (1993). Cefazolin antibacterial activity and concentrations in serum and the surgical wound in dogs. *American Journal of Veterinary Research*, 54: 1317-1321.

Smith, S., W. Gerald and C. Melinda (1977). In vitro activities of five oral cephalosporins against aerobic pathogenic bacteria. *American Society for Microbiology*. 12(15): 609-613.

Steel R. G. D., J. H. Torrie and D. A. Dickery (1997). *Principles and procedures of statistics*. McGraw Hill Companies, Inc., New York. Pp.672.

Welling, P. G., S. Dean, A. Selen, M. J. Kendall and R. Wise (1979). The pharmacokinetics of the oral cephlosporins cefaclor, cephradine and cephalexin. *Int. J.Clin. Pharmacol Biopharm*. 17(9): 397-400.

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