Pharmacokinetics of Cloxacillin in Humans

Pages with reference to book, From 299 To 303

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Abstract

Urinary excretion data were obtained after oral administration of a single dose of 250 mg of Cloxacillin in six healthy young men volunteers. The excretion rate data were fitted to single and two compartment open models and the pharmacokinetic parameters were determined. The drug showed a rapid absorption and fast distribution. The time of appearance of peak renal excretion was 45 minutes in all the volunteers. The biological half-life (47 ± 3.6 min.) and total renal recovery (31.43 ± 2.5%) was in good agreement with the reported values. Although both the single and two compartments model fitting was not possible. One compartment model was found to be more suited as the generated data through this model bears close resemblance with the experimental data(JPMA 33:299, 1983).

Introduction

The mathematical characterization of blood, serum, or plasma drug concentration and time data and data on excretion of drug has become one of the most important areas of research in Pharmaceutics, particularly in clinical Pharmacokinetics where the drug monitoring is the vital part of health care. Much useful informations can be derived from a pharmacokinetic analysis, which helps to evaluate the proper dosage regimen as well as to design a better bioavailable formulation.

Among the semisynthetic penicillins produced since 1961, the isoxazolyl penicilins have contributed substantially to the control of penicillin-resistant staphylococcal infection in human clinical practice. Cloxadilin is an isoxazolyl penicillin widely used for the treatment of penicillin-resistant Staphylococcus aureus infections.

The pharmacokinetics of cloxacillin in humans has been determined by many investigators (Modr and Dvoracek, 1969; Rosenblatt et al., 1968; Nauta et al., 1973; Hellstrom et al., 1974; Nauta and Mattie, 1975, 1976; Oe et al., 1973; Gibaldi and Schwartz. 1968; Barza and Weinstein, 1976). The determination of a generalised optimum dosage regimen in Pharmacokinetic studies are relevant in local human population and with the environment in which the drug is to be used to achieve clinically effective and safe drug concentration in the body. Since no such efforts have yet been made in Pakistan, the kinetic studies of different drugs were undertaken. The present work is a part of such studies and reports the pharmacokinetics of cloxacillin in local population of Pakistan.

Material and Methods

Six healthy young men volunteered for the study after the nature of the experiment had been explained to them. The volunteers ranging in age from 21 to 34 years and weighing between 51 to 68 kg, had a normal renal function. The volunteers had not taken any drug during two weeks before the study. The volunteers reported the laboratory after an overnight fast and each of them was given a single oral dose of cloxacillin (the monohydrate sodium salt equivalent to 250 mg of cloxadillin in gelatin capsules, Orbenin). A light breakfast was served 2 hours after administration. Urine samples were collected just before administration of the drug and then after half an hour for 2 hours and at 1 hour intervals till 4th hour. The volunteers were asked to take 250m1 of water between sampling interval to improve urine flow. rate. The volume of each void was recorded and an aliquot of 25m1 was retained for submission

in screw capped test tube, and stored at 4°C for the analysis on the same day.
The antibiotic was assayed microbiologically by the disc plate diffusion method using Sarcina lutea (ATCC 9341) on nutrient agar as reported by Sutherland and Rolinson (1978), with some modifications to increase the sensitivity and precision. The diameters of inhibition-zones obtained for the control dilutions of the antibiotic were plotted on semiogarithmic scale against the concentration. From the regression line obtained antibiotic concentration in the urine specimens were estimated by interpolation. The appropriate dilutions of the control and samples were made in 0.05M-phosphate buffer at pH 7.0. The urinary excretion rate-time data were analysed separately for each volunteer. The mean value and standard error of mean (SEM) were calculated using a programmable calculator Casio FX-602P.

Results

Values of kinetic parameters which describe absorption, distribution, and elimination of cloxacillin in healthy volunteers are reported in Table I.

Table – I

Mean Pharmacokinetic Parameters (±SEM) of Cloxacillin in Humans After Oral Administration of a Single Dose of 250 mg.

Pharmacokinetic Parameters	Mean	± SEM
One Compartment Model		
λ_z, hour^{-1}	0.91	0.07
$t_{½\ z}$, minutes	47.0	3.60
K_a, hour^{-1}	5.48	0.83
$t_{½a}$, minutes	8.41	1.23
Two Compartment Model		
λ_1, hour^{-1}	1.58	0.28
$t_{½\ 1}$, minutes	29.5	4.95
K_a, hour^{-1}	4.50	0.68
$t_{½a}$, minutes	1.10	1.10
λ_z, hour^{-1}	0.78	0.11
$t_{½\ z}$, minutes	57.0	7.00
K_{12}, hour^{-1}	0.18	0.06
K_{10}, hour^{-1}	1.10	0.19
K_{21}, hour^{-1}	1.00	0.07
K_e, hour^{-1}	.007	.002

To avoid ambiguity the pharmacokinetics symbols prescribed by the Committee for Pharmacokinetic Nomenclature, Philadelphia (Allen et al., 1982) were used in the present paper. The mean distribution halftime, t½ 1' was found to be 295 ± 4.9 (SEM). The mean biological half life, t%, by fitting the renal excretion data to single and two compartment open model were found to be 47.0 ± 3.6 (t¼, K) minutes

and 57.0 ± 7.0 (t1/2 Tz minutes, respectively. Absorption half-life, t1/2a was found to be 10.0 ± 1.1 minutes when the data was fitted to triexponential equation (two compartment), whereas absorption half-life, t½a, was equivalent to 8.41 ± 1.23 minutes, when calculated by biexponential equation (single compartment). The renal excretion rates versus time proffle for all the volunteers are shown in Figure 1.

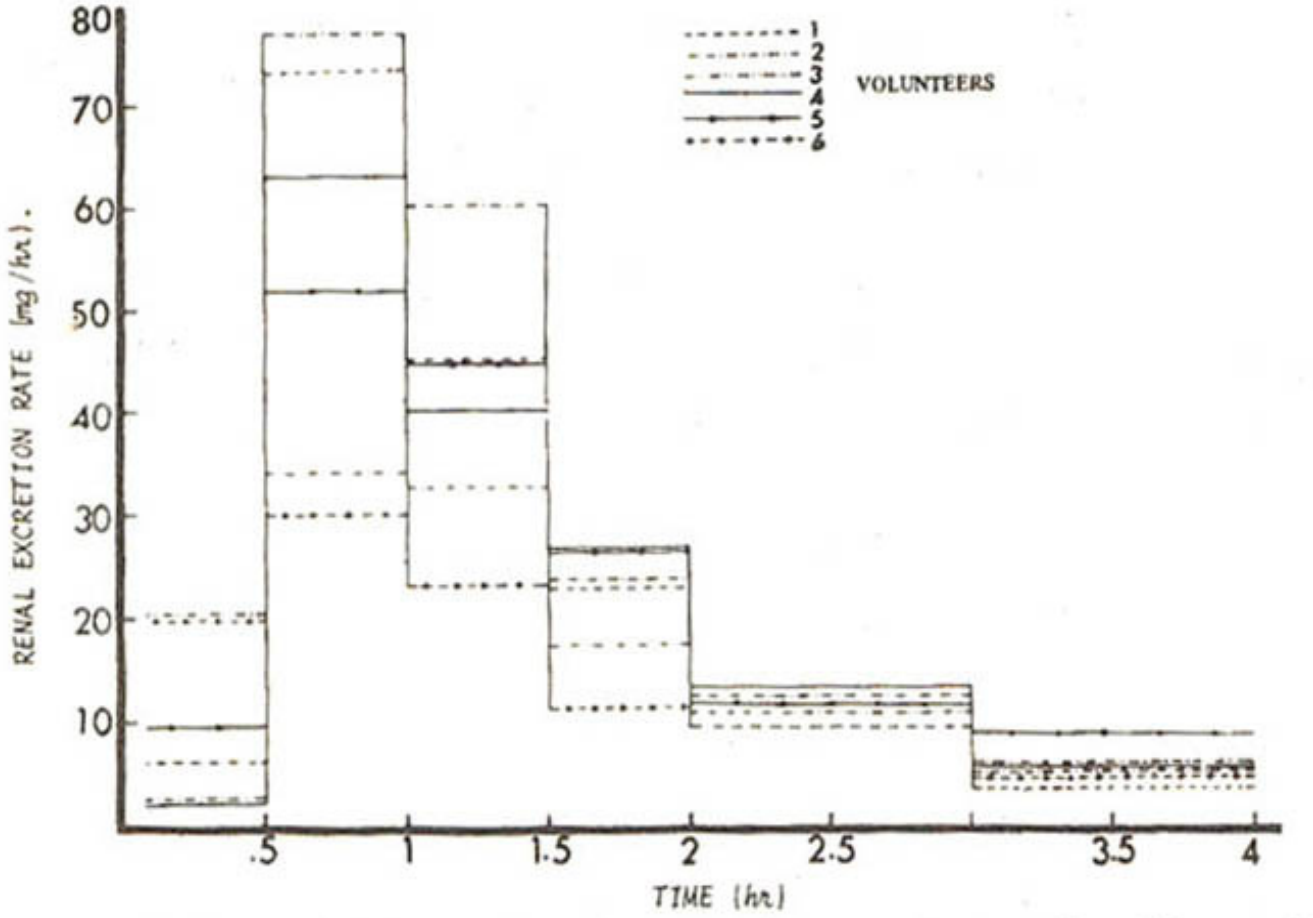

Fig.1. Renal Excretion Rate Versus Time Profiles of Cloxacillin in Six Human Volunteers After Oral Administration of a Single Dose of 250mg.

Bioavailability parameters like percent recovery, peak-time, and peak-value are reported in Table II.

Table – II

Mean Bioavailability Characteristics (± SEM) of Cloxacillin in Human Volunteers After Oral Administration of a Single Dose of 250 mg.

Bioavailability Parameters	Mean	± SEM	Range
Peak time, min.	45.00	0.0	
Peak renal excretion rate, mg. hour $^{-1}$	54.76	8.06	30.0–77.0
Total % urinary excretion	31.43	2.50	21.2–38.15

In present study, it is found that the mean total percent renal recovery of the unchanged drug administered to human volunteers is 31.43 ± 2.5% (± SEM) within a range of 21.2 to 38.15%, out of six volunteers three showed almost identical 34% renal recovery and in the other three values were found to be 21.2%, 27.22%, and 38.15%.

The time of appearance of renal excretion rate in all the volunteers is found uniformally to be 45 minutes. The peak renal excretion rate is variable and the mean peak renal excretion rate is 54.76 + 8.06/mg hour -1 SEM).

Discussion

The selection of appropriate compartment model among single and two compartment was a difficult task in the present investigation. Renal excretion rate versus time profiles on semiogarithmic scale of few volunteers reveal two distinct phases in post absorptive portion i.e., T1 and 42 exponents. However, other volunteers do not show such two distinct phases emphasising for single compartment fitting. For many reasons there is no clear cut idea about the selection of model in reported studies (Modr et al., 1969; Nauta et al., 1973; Hellstrom et al., 1974; Nauta and Mattie, 1975, 1976; Barrelet et al., 1977; Burckart et al., 1978). Firstly there are relatively few studies which describe the pharmacokinetics, secondly, the many studies describing the kinetic behaviour of drug in the body mentioned only the half-life from the slope of post absorptive phase instead of fitting the data to appropriate model. Thirdly the very few studies which suggest any kinetic model are not of uniform opinion about its type. In present investigation, we attempted to fit the data to single and two compartment open model. Both single and two compartment model can be fitted to excretion rate data of all the volunteers with the exception of volunteer No. 4, on which application of two compartment

model was not possible. Mean renal excretion rate (± SEM) versus time profile of all the six volunteers alongwith the simulated values generated by biexponential and triexponential equations are illustrated in Figure-2.

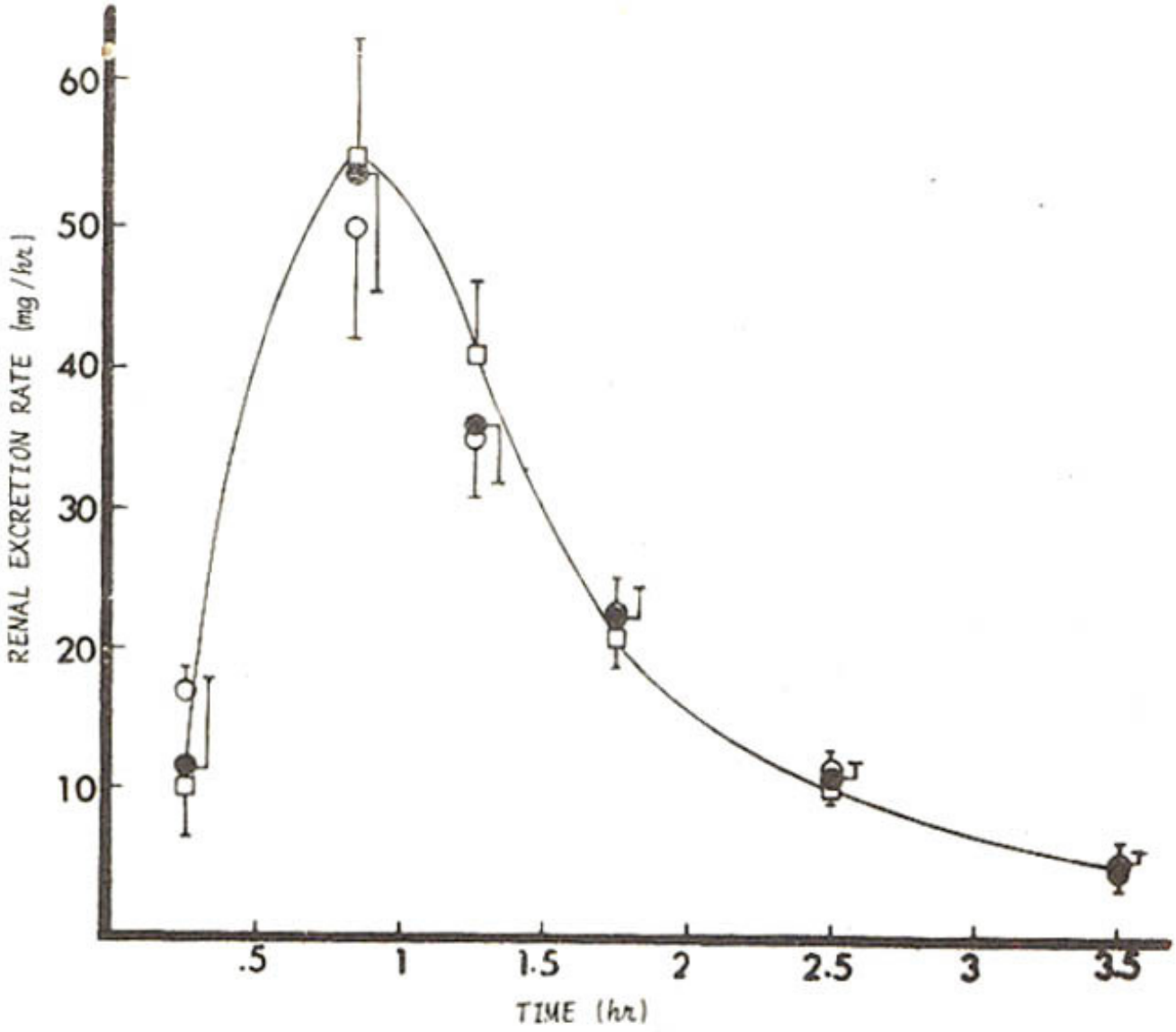

Fig.2 Mean Renal Excretion Rate (± SEM) Versus Time Profile of Cloxacillin After Administration of a Single Dose of 250mg. to Human Volunteers (n=6).

The experimental rate data bears a close resemblance with the data of both the models. However the correlation between the experimental values and the values generated by single compartment was 0.995 in comparision with 0.985 found between experimental and two compartment values. The peak time found (~- 45 min.) in present study is in good harmony with the reported values ranging from 0.5 to 1 hour. The rapid achievement of peak levels in all the volunteers indicates that the absorption of cloxacillin is fast and quite uniform.

There exists a great deal of discrepancy in the reported values of the biological half-life of cloxacillin

in humans. This might be attributed to the physiological, pathological, biochemical, environmental, and nutritional variations. Nevertheless, the majority of the workers reported its half-life about 30 minutes. In present investigation we determined a biological half-life 47 ±3.6 minutes (single compartment) and 57.0 + 7.0 minutes (two compartment), which is in the range of reported values (25-150 minutes).

The reason for a greater half-life in two compartmental analysis is obvious because here the post absorptive phase is further divided into two distinct phases, the fast disposing and slow disposing ones. The elimination half-life is calculated from the latter phase which obviously would be greater than the half-life calculated from the whole post absorptive phase as done in single compartmental analysis due to its slow disposing nature.

The mean total renal recovery of the drug during a four hour period was 31.43 ± 2.5% (± SEM). This is again in close agreement with the reported values of 30-40% (Kunin, 1967; Bennett et al., 1964; Bodey et al., 1972) after oral administration. Although parentral administration of the drug results in more renal excretion due to complete bioavailability of the drug and less degradation as compared with oral administration.

A very short absorption half-life (> 10 minutes) as determined in the present investigation indicates a rapid and fast absorption of the drug.

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