Fate of Cravit, One of the Most Active Antibiotic for Urinary Tract Infection in Body

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Summary: The fate of cravit was determined in 9 female volunteers following oral administration of 500 mg tablets. The blood samples were collected at specified time intervals. Concentration of cravit in plasma was determined by microbiological assay, that was 2.39 µg/ml having 1.75 SD and 75% CV values. The pharmacokinetic parameters were determined according to single compartment open model. The average absorption rate constant was 2-0 1/hr, while absorption half-life was 0.34 hours. Average C_{max} and T_{max} values were 2.43 mg/l and 1.60 hours while volume of distribution was 177 1. From T_{max} studies it is concluded that absorption is delayed due to non-fasting. So cravit can be administered orally in the presence of food. The elimination half life and total body clearance values were 7.40 and 16.54 hours respectively while total area under the plasma drug level-time curve was 30.2 h. mg/1. It is clear that elimination half-life is not affected by the presence or absence of food.

Introduction

Different bacteria show variation in sensitivity against different antibiotics. Infection with bacteria is a problem, as the organism has intrinsic resistance several antibiotics and capability in acquiring resistance during antibiotic therapy. Antibiotics are anti-indicative agents of biological origin, used either prophylactically or therapeutically.

Cravit is a well tolerated antibiotic, with no potential serious adverse effects involving the kidney, while other antimicrobials have long been known to cause various forms of nephrotoxicity occurring as allergic interstitial nephrites, granulomatous or tubular necrosis.

Cravit is a fluoroquinolone and is the L-isomer of ofloxacin [1]. It has broad spectrum of *in-vitro* activity and is significantly more active against bacterial pathogens. Cravit is more potent than other quinolones and exerts its antibacterial effect through inhibition of DNA-gyrase type II topo-isomerase [2-4].

Results and Discussion

Among the different antibiotics (chloremphenicol, erythromycin, cravit and ampicillin) tested for microbiological assay, cravit showed maximum antibacterial activity (Table-1) and was further used in the study.

Plasma concentration of cravit was measured in 9 female volunteers and the results with SD and CV values are given in Table-2. A gradual increase in plasma concentration (C_{max}) was reached after which a decline was observed These results are in agreement with the findings of Fish and Chow [2] and Gomez-Lus [4].

Table-1: Antibiotic sensitivities of some common pathogenic bacteria

Antibiotics	Pathogens			
	Bacillus subtilus	*Exchirichea coli*	*Staphylo-coccus aureus*	*Strepto-coccus aureus*
Chloremphenicol	x	+	+	+
Erythromycin	0	0	+	+
Cravit	+	+	+	+
Ampicillin	0	x	+	+

+ = > 80% sensitive
o = < 25 % sensitive
x = Variable sensitivity

The pharmacokinetic parameters were 'determined following one compartment open model (Table-3). Absorption half-life is the time in which half of the drug is absorbed. In the present study its average value was 0.34 hours. The absorption of cravit was slightly delayed by food, although overall bioavailability of the drug following a high fat meal was not altered [5]. The changes in cravit absorption were not clinically significant Fish and Chow [2] reported that the drug could be administered orally in the presence of food. The average absorption rate constant ($K\alpha$) was 2/hour, which is known as rate constant for absorption of drug.

Table-2:Plasma concentration ofcravit (μg/ml) in female volunteers

Volunteer number	Plasma concentration (μg/ml) at different time intervals (hours)										
	0.5	1.0	1.5	2.0	2.5	3.0	4.0	5.0	6.0	8.0	12.0
1	1.62	5.27	5.39	4.64	5.62	6.26	5.62	5.16	3.74	3.66	2.49
2	1.59	2.54	2.89	2.44	2.14	2.49	1.43	1.59	1.81	1.46	0.91
3	2.71	2.60	2.71	2.85	2.54	2.14	1.92	1.52	1.20	1.15	1.08
4	4.16	4.54	3.82	4.08	5.62	3.99	3.99	3.82	3.29	2.05	1.55
5	0.73	1.59	1.18	0.79	1.20	1.03	0.77	1.15	ND	ND	0.32
6	0.38	0.53	1.15	1.18	0.46	0.47	1.00	0.78	0.99	0.93	0.42
7	ND	ND	0.82	1.18	1.46	1.62	1.31	1.06	1.28	0.70	0.20
8	0.35	0.49	0.99	U.19	0.95	1.13	1.23	1.28	0.93	0.58	0.35
9	2.66	1.59	0.91	0.87	0.99	0.87	ND	ND	0.52	0.67	0.32
Average	1.73	2.39	2.21	2.12	2.33	2.22	2.17	2.13	1.72	1.40	0.91
SD	1.34.	1.75	1.61	1.45	1.97	1.85	1.72	1.53	1.17	1.04	0.73
CV%	75.20	75.00	72.90	68.60	84.40	83.20	79.40	71.30	68.20	74.00	80.20

ND= Not detected
SD = Standard deviation
CV =- Coefficient of variance
pharmacokinetic parameters of carvit in female volunteers

Table-3: Pharmacokinetic parameters of carvit in female volunteers

Parameters	Units	Volunteers									
		1	2	3	4	5	6	7	8	9	Aver
T_{max}	hours	1.89	1.10	0.61	1,26	0.70	3.11	5.17	0.57	3.54	1.60
C_{max}	mg/1	5.82	2.57	2.72	4.18	1.40	0.85	1.51	1.45	1.1	2.45
K_a	h^{-1}	2.23	6.30	7.77	2.62	21.50	0.93	1.20	74.40	0.28	2.00
$T_{1/2\alpha}$	H	0.31	0,11	0.89	0.26	0.03	0.74	0.56	0.00	2.41	0.34
AUC	H mg/1	77.30	28.60	28.30	50.80	11.40	16.70	17.20	10.80	10.50	30.20
$T_{1/2\beta}$	H	8.08	7.22	6.80	6.36	5.47	11.10	6.20	5.11	2.39	7.40
V_d	L	0.15	182.00	173.00	90.40	345.00	480.00	260.00	340.00	163.00	177.0
Cl	1/h	0.01	7.40	17.60	9:84	43.70	29.10	29.10	46.20	47.30	16.50

T_{max} : Time to peak absorption
C_{max} : Peak concentration
K_a : Absorption rate constant
$T_{1/2\alpha}$: Absorption half-life
AUC : Area under the plasma drug level-time curve
$T_{1/2\beta}$: Elimination half life
V_d : Volume of distribution
Cl : Ttoal body clearance

In the present study the average time to peak (T_{max}) was 1-60 hours. Fish and Chow [2] reported 1,80 hours as average peak time in 5 healthy non-fasting volunteers and it was 1.0 and 2.0 hours for non-fasting and fed condition [5], Chien *et al.*, [6] found these values as 1.3 hours in 10 healthy male volunteers. T_{max} value from these studies is in accordance, but the only difference is due to non-fasting conditions. So it may be concluded that absorption is delayed due to non-fasting.

Peak concentration (C_{max}) is defined as the maximum concentration given by drug in plasma and it is 2.4 mg/1. According to Fish and Chow [2], C_{max} was 2.6 and 5.2 mg/I within 1 to 2 hours after oral administration of levofloxacin 250 and 500 mg tablets respectively. Lower values of C_{max} in these studies are due to non-fasting and application of microbiological assay while in all the other studies HPLC was used.

Area under curve (AUC) is the total area under plasma concentration-time curve and the average value was 30.20 h, mg/l. Chien *et al.*, [7] reported that in 16 healthy volunteers, administered with 750 mg levofloxacin, AUC value was 7.13 h μg/ml and 90.7 h, μg/ml when one gm dose was given. Fish and Chow [2] reported that AUC increased linearly in a dose proportional fashion.

In the present study the average value of elimination half-life ($T_{1/2\beta}$) was 7.40 hours. Fish and Chow [2] reported 6-8 hours in individuals with normal renal function. Lee *et al.*, [9] reported that the mean $T_{1/2\beta}$ was not affected by the presence or absence of food when the drug was administered. The average value of volume of distribution was 177 1. According to Chien *et al.*, [6] and Lomaestro [8] there was not much variation from single to multiple dosages, the mean study state value of V_d following 750 mg dose was 105 in 16 volunteers. The variation in results may be due to average body weight, active body metabolism, etc.

Total clearance of drug obtained was 16.50 Vhr from 9 volunteers. Chien *et al.*, [7] reported

13.40 l/hr in 5 non-fasting volunteers. So it may be concluded that the results obtained from pharmacokmetics parameters are appropriate and any difference in results, is due to analytical or biological conditions.

Experimental

Drug Administration and Sampling

Pharmacokinetics of cravit was investigated following a single oral dose of 500 mg in 9 healthy female volunteers, aged between 21-25 years having 55 kg of average body weight. Blood samples were drawn intravenously at 0, 0.5, 1.5, 2.0, 2.5, 3, 4, 5, 6, 8, and 12 hours after the drug administration. Blood samples were centrifuged at 4000 rpm for 15 min., then plasma was carefully separated from the sedimented cells.

Microbiological Assay

Cravit concentration in plasma was determined following microbiological assay by agar diffusion technique using *Staphylococcus aureus* as test organism [9]. Medium containing bacteria was incubated for 24 hours then growth was washed with 50 ml, normal saline. 100 µl spore suspension was added in 100 ml nutrient agar medium. It was poured on petri dish and 100 µl of each standard was added on to disc and incubated for 24 hours. Zones of inhibition due to activity of drug after 24 hours were measured by zone reader

Preparation of Standard Curve and Analysis of Plasma Samples

0.1% cravit solution in distilled water was prepared and a standard curve was plotted between the log concentration (µg/ml) and zone of inhibition (mm). Plasma samples from cravit were analyzed by following the same procedure as mentioned above.

Pharmacokinetics of Cravit

The pharmacokinetics parameters were determined by single compartment open model [10]. Parameters such as peak concentration (C_{max}). time to peak (T_{max}), absorption rate constant (K_a), absorption half-life ($T_{1/2a}$), area under the plasma drug level-time curve (AUC), volume of distribution (V_d), elimination half life ($T_{1/2\beta}$) and total body clearance (Cl) were determined by using computer programme Nw/PHARM version 3.02 [11].

Statistical Analysis

Regression line, standard deviation (SD) and co-efficient of variation (CV) values were determined [12].

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