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PHARMACOKINETIC PROFILE OF AMPICILLIN AND CLINDAMYCIN IN RABBITS

BY

A. RAMADAN*, NEHAL A. AFIFI*, T. ABBAS**, A.F. EMARA**
Department of Pharmacology*, Faculty of Veterinary medicine, Cairo University, Giza, Egypt. Department of Oral Surgery**, Faculty of Oral and Dental Medicine, Cairo University, Giza, Egypt.

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SUMMARY

Ampicillin and clindamycin were once administered in rabbits via oral and i.v. routes in doses of 25 and16 mg/kg b.wt., respectively, to determine blood concentration, kinetic behaviour and bioavailability. Following a single i.v. injection, the blood concentration-time curve indicated a two compartment open model, with an elimination half-life value ($t_{0.5}$, (β),) of 103.03 and 209.41 minutes for ampicillin and clindamycin, respectively. The apparent volume of distribution of ampicillin in rabbits was less than 1 litre/kg and suggesting a lower distribution in tissues than in blood. While, the apparent volume of distribution of clindamycin in rabbits was more than 1 litre/kg and suggesting a higher distribution in tissues than in blood. After oral administration the peak plasma concentration of ampicillin and clindamycin were 11.03 and 2.25ug/ml at 2.45 and 0.96 hours, respectively. The average bioavailability of ampicillin and clindamycin given by oral administration, were 0.44 and 0.56%, respectively.

INTRODUCTION

Ampicillin is probably one of the most interesting and valuable of the semi-synthetic penicillins, similar to amoxicillin in structure and activity, because it retains the typical Gram-positive of the penicillins and possesses greatly enhanced activity against Gram-negative bacteria (Brander and Pugh 1982).

Clindamycin is a semi-synthetic antibiotic derived from the parent compound lincomycin and is indicated for the treatment of many infectious diseases (Goodman and Gilman 1980).

In spite of the great economic value of rabbits as food producing animals in several parts of the world, few literature is available on kinetics of ampicillin and clindamycin in this species. The present work was thus initiated to explain certain pharmacokinetic aspects of these antibiotics in rabbits to be helpful during its application in therapy.

MATERIAL AND METHODS

Drugs:

1. Ampicillin (Amphiben®), was obtained from Misr Company for Pharmaceutical Industries, Materia, Cairo, Egypt. It is available in vials of 250mg each.

2. Clindamycin (Dalacin-C®), was obtained from Memphis Chemical Company, Cairo, Egypt (under licence from Upjohn, Belgium). It is available in capsules of 150 mg each.

Experimental animals:

Ten clinically healthy rabbits (Boskat breed), each weighing from 1,98 to 2.02 kg were obtained two weeks before the studybegan. food and water *ad libitium* were provided.

Grouping of rabbits and drug administration:

The rabbits were divided into two equal groups (5

each). Aniamls of the first group were administered a single dose of ampicillin (25 mg/ kg body weight) orally, whereas those of the second group were administered a single dose of clindamycin (16 mg/kg body weight) via oral route. Two weeks later, all the rabbits were injected with the same dose intravenously with each drug and the same way of sampling was applied to reveal the bioavailability of the tested drugs.

Blood sampling:

Blood samples were obtained from ear vein prior to and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12 and 24 hours after respective drug administration. Each blood sample was collected in a clean centrifuge tube containing heparine and centrifuged at 3000 rpm for 15 minutes to separate plasma. These samples were then used to determine the antibiotic concentrations in plasma.

Analytical methods:

Estimation of ampicillin and clindamycin concentrations in blood plasma samples were carried out by microbiological assay technique described after Bennett et al. (1966) using *Micrococcus luteus* (ATCC, 9341) as the test organism.

Statistical calculations:

The pharmacokinetic data were calculated according to the method of Baggot (1978). The obtained data were statistically analysed and the results are given as mean ± s.e.m.

RESULTS

The mean plasma concentrations of ampicillin and clindamycin in rabbits following single i.v. injection of 25 and 16 mg/kg body weight, respectively are illustrated in Fig 1 and 2. Values for the kinetic constants describing the absorption and disposition of the drugs in rabbits are tabulated in Table 1 and illustrated in Fig 1 and 2. Following i.v. injection of ampicillin and clindamycin in rabbits in a single dose of 25 in 16 mg/kg body weight, respectively, their concentration revealed a biexponential decline that can be described by the open two-compartment model (Fig. 1 and 2). In addition, both drugs were rapidly distributed ($t_{1/2\alpha}$ 37.88 and 9.96 minutes) and eliminated ($T_{1/2}$ β 103.03 and 209.41 minutes), respectively. The lower distribution for ampicillin than 1 litre/kg indicated lower distribution in tissues than blood. While, the higher distribution for clindamycin

Table 1: Pharmacokinetic parameters of ampicillin and clindamycin in rabbits after a single i.v. injection of 25 and 16 mg/kg body weight, respectively (n = 5).

Parameter	Unit	Ampicillin	Clindamycin
B.wt.	Kg	2.00±0.04	2.01±0.04
C°	ug/ml	125.20±0.64	55.20±2.13
A	ug/ml	76.60±0.93	53.99±2.12
α	min^{-1} 10^{-2}	1.80±0.04	7.00±0.04
$t_{1/2(\alpha)}$	min	37.88±0.08	9.96±0.05
k_{12}	min^{-1} 10^{-2}	0.30±0.01	2.00±0.10
K_{21}	min^{-1} 10^{-2}	1.10±0.02	0.50±0.01
B	ug/ml	48.60±0.43	1.22±0.05
β	min^{-1} 10^{-3}	6.70±0.10	3.00±0.02
$t_{1/5(\beta)}$	min	103.03±0.82	209.41±1.23
K_{el}	min^{-1} 10^{-2}	1.10±0.02	4.80±0.10
Vc	ml/kg	99.96±1.63	144.69±4.25
$V_{d(area)}$	ml/kg 10^{-3}	0.165±0.01	2.108±0.04
$V_{d(\beta)}$	ml/kg 10^{-3}	0.163±0.003	2.106±0.04
$V_{d(B)}$	ml/kg 10^{-3}	0.258±0.01	6.576±0.20
$V_{d\ (ss)}$	ml/kg 10^{-3}	0.125±0.002	0.747±0.03
Cl (B)	ml/kg/min	1.11±0.03	6.97±0.12

Table 2: Pharmacokinetic parameters of ampicillin and clindamycin in rabbits after a single oral administration of 25 and 16 mg/kg body weight, respectively (n = 5).

Parameter	Unit	Ampicillin	Clindamycin
B.wt.	Kg	1.99±0.03	1.98±0.03
A	ug/ml	6.62±0.12	1.48±0.04
$K_{(ab)}$	min^{-1} 10^{-2}	1.10±0.01	3.20±0.04
$t_{1/2(ab)}$	min	62.63±0.48	21.50±0.28
C(max)	ug/ml	11.03±0.09	2.25±0.02
t(max)	hr	2.45±0.01	0.96±0.44
B	ug/ml	33.10±0.53	3.50±0.03
$t_{1/2(\beta)}$	min	93.52±0.19	92.69±0.24
K_{el}	min^{-1} 10^{-2}	0.80±0.002	1.00±0.004
F*	%	44.47±1.06	45.10±1.28

* Systemic bioavailability percent.

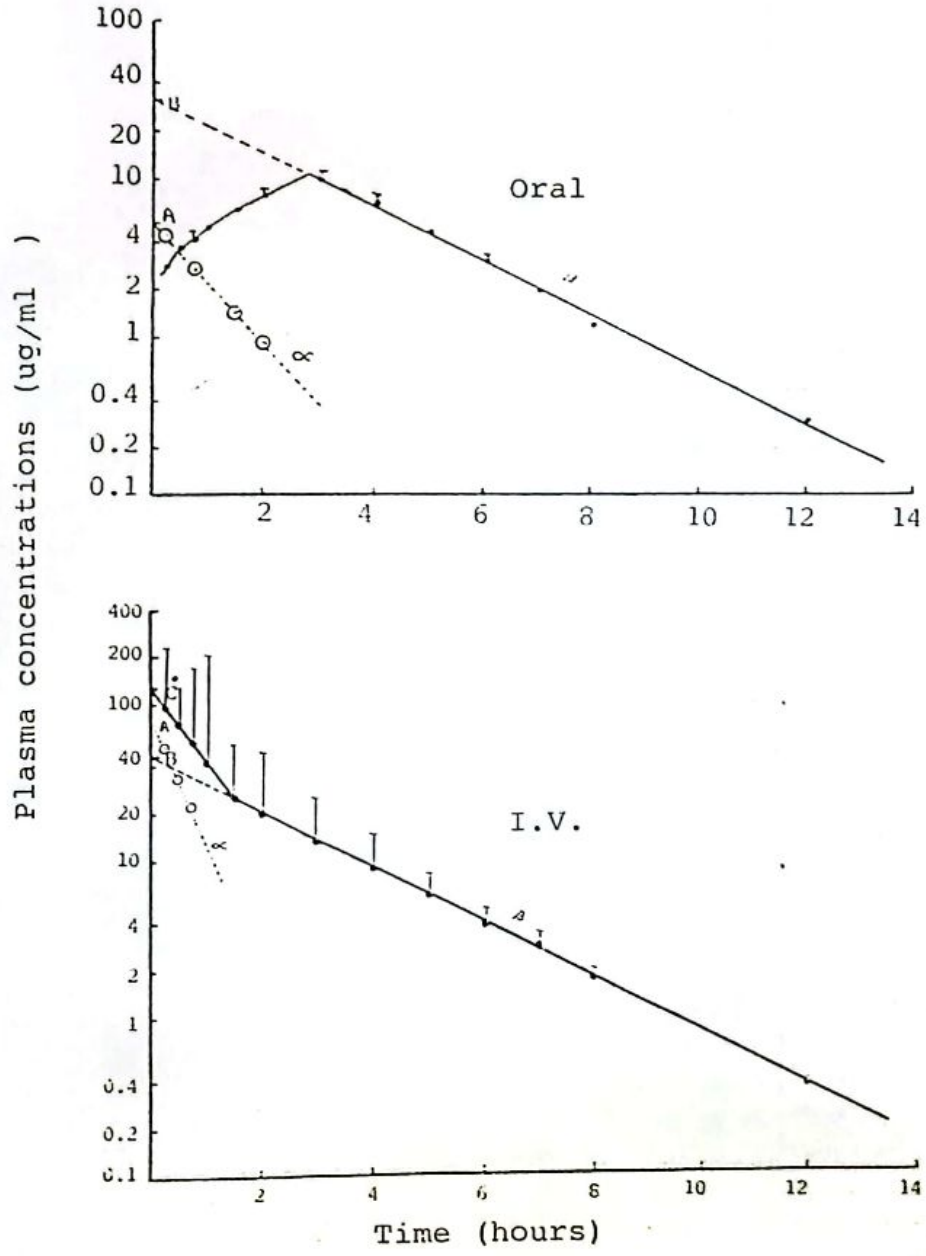

Fig. 1: Semilogarithmic graph depicting the timeconcentration course of ampicillin in plasma of rabbits after a single oral and I.V. injection of 25 mg/kg body weight

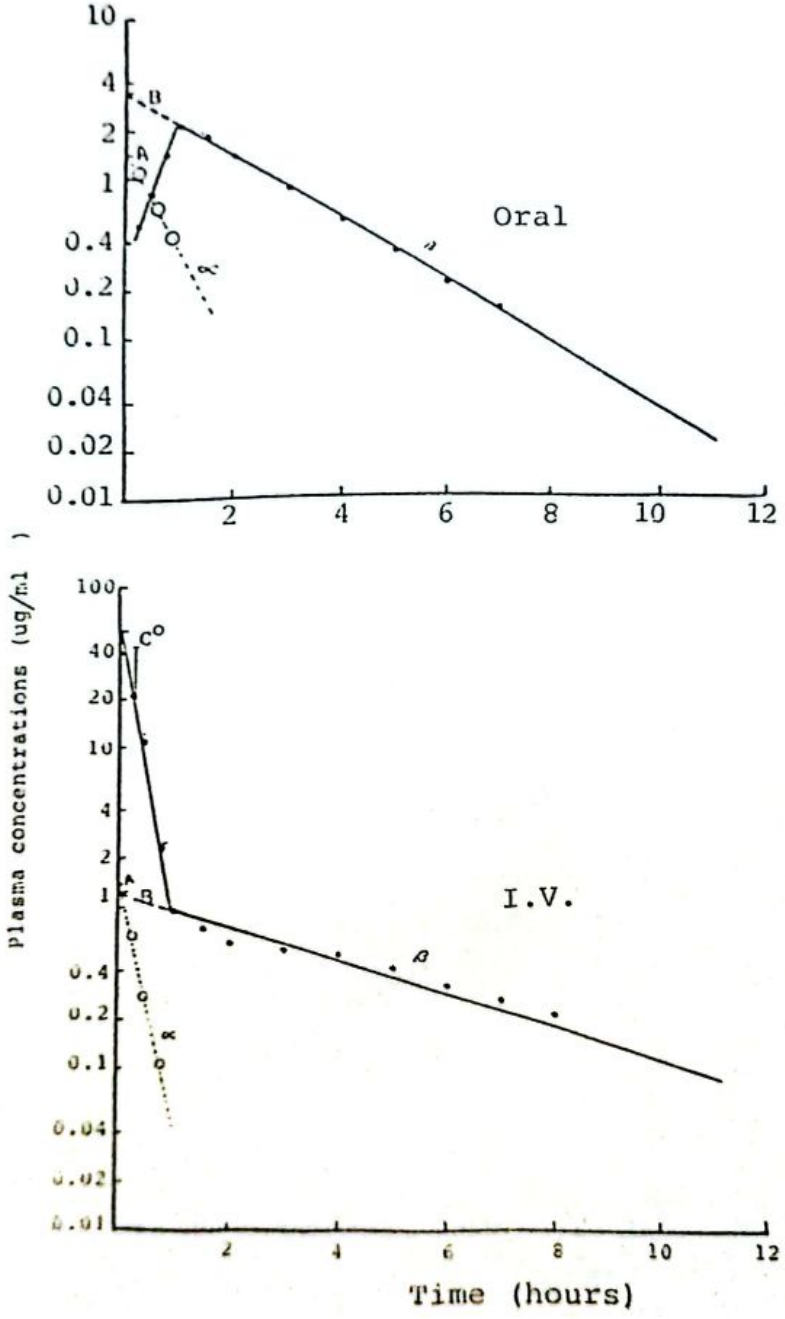

Fig. 2: Semilogarithmic graph depicting the time concentration course of clindamycin in plasma of rabbits after a single oral and I.V. administration of 16mg/kg body weight.

than 1 litre/kg indicated higher distribution in tissues than blood. The total body clearance of ampicillin (1.11 ml/kg/min), while for clindamycin 6.97 ml/kg/min) following the single i.v. injection is related to the eliminantion half-life calcuated in the tested rabbits. The bioavailability of ampicillin and clindamycin in rabbits following oral administration was 44.47 ± 1.06 and 45.10 ± 1.28%, respectively. The mean plasma concentrations of ampicillin and clindamycin in rabbits following single oral administration of 25 and 16 mg/kg body weight, respectively are illustrated in Fig. 1 and 2. The mean ampicillin and clindamycin peak concentration (C_{max}, 11.03 and 2.25 ug/ml) was reached at 2.45 and 0.96 hours after oral administration, respectively. As shown in Table 2 and Fig 1 and 2 these tested drugs were rapidly absorbed from the administration sites. This can be expressed by its higher absorption rate constant (K_{ab}, mean value of 0.011 and 0.032/min, respectively). The mean elimination of half-life ($t_{1/2}$ β) for ampicillin following oral administration was 93.52 minutes, indicating the faster elimination of the tested drug $t_{1/2}$ β) 10.3.03 minutes).

DISCUSSION

The present study indicated that the blood concentrations of ampicillin and clindamycin in rabbits were superior to the minimum inhibitory concentrations (MICs) for more sensitive bacteria, for 12 and 7 hours after a single oral administration and for 12 and 8 hours after a single i.v. injection, respectively. Furthermore, Cruickshank et al. (1975) considered that a bacterium might be sensitive to an antibiotic if the MIC was not more than a quarter to a half its average concentration in blood. Plasma concentration data for ampicillin and clindamycin were best fitted to a two-compartment pharmacokinetic model after i.v. dosing. The oral absorption for ampicillin and clindamycin was fairly rapid with $t_{1/2\ (ab)}$ of approximately 62. 63 and 21.50 minutes and peak levels occurring at 2.45 and o.96 hours, respectively. Ziv. et al. (1977) found that plasma half-life for ampicillin was 101.3 minutes in calves. In this study, the peak plasma concentrations after oral administration of ampicillin and clindamycin were 11.03 and 2.25 ug/ml, respectively. These results were similar to those of lenampicillin 11.55 ug/ml in man (Akimoto et al., 1990); talampicillin 9.64 ug/ml in man (Akimoto et al., 1985); and clindamycin 1.9 ug/ml in man (Walker et al., 1981). On the other hand, these values are inconsistent with those recorded in human (2.01 ug.ml), Akimoto et al., 1985) following administration of ampicillin.

Our experiment has demonstrated that ampicillin was rapidly disappeared (Short elimination half-life) from the plasma of rabbits and had an average half-life of 103.03 minutes after single i.v. injection, whereas clindamycin was slowly disappeared (long elimination half-life) from the plasma and had an average half-life of 209.41 minutes after single i.v. dosage. These values were correlated with ampicillin in humans (93.5 minutes, Assael et al., 1979 and 1.3 hours, Benet and Sheiner 1980); horses, cows, dogs and cats (1.55, 1.2, 0.8 and 1.2 hours, Baggot 1978, respectively) and bacampicillin in human (0.9 hour, Benet and Sheiner,1980). The elimination half-life for clindamycin was 2.5 and 2.7 hours in humans (Goodman and Gilman 1980 and Benet and sheiner 1980, respectively).

The slower elimination of clindamycin in rabbits could be explained on the basis of its high pka (7.5, Benet and Massoud 1984) and protein binding (90%) or more (Goodman and Gilman, 1980).

The low apparent volume of distriution {V_d (β)} value of ampicillin (163.42 ml/kg) than one litre following its i.v. dosage in rabbits obtained in the present work indicates the lower distribution of this drug in tissues than in plasma (Baggot 1978). On the other hand, clindamycin showed higher {V_d (β)} value (2.106 L/kg) more than one litre indicated the higher distribution of clindamycin in tissues than in plasma. These values were consistent with those previously reported by Benet and Massoud 1984 (0.03L/kg) and Assael et al., 1979 (0.68 L/kg) in human and Baggot (1978) in dogs (0.27 L/kg) after i.v. injection of ampicillin. The higher distribution of clindamycin in tissues than in plasma, was anticipated, since the drug is a lipophilic compound can diffuse readily through cell membranes after oral administration (Goodman and Gilman 1980). On the other hand, clindamy-

cin showed a height body clearance rate (6.97 ml/kg/min) than ampicillin (1.11 ml/kg/min) and this value was also correlated with the half-lives value of both tested drugs in rabbits. The bioavailability of ampicillin and clindamycin after oral aministration were incomplete, with 44.74 and 45.10% of the doses being absorbed, respectively. Similar results were reported by Ziv et al. (1977) in calves (43%) after oral administration of ampicillin derivatives.

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