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PHARMACOKINETIC PROFILE OF PIPEMIDIC ACID IN NORMAL AND NEPHRITIC RATS

ATEF M., AMER AZIZA M. M., El- BANNA H. A. and SOLIMAN G. A.

Department of Pharmacology, Faculty of Veterinary Medicine, Cairo University

SUMMARY

The pharmacokinetic profile, tissue distribution and residual content of pipemidic acid were studied in normal and nephritic rats. The maximum serum concentration was reached after 1 hr in both normal and nephritic rats folowing oral administration of 50 mg/kg b. wt.

Lower serum concentrations were detected in nephritic rats at corresponding time intervals as compared with healthy ones. Following the intravenous injection of pipemidic acid, the resulting curves were best fitted to follow two compartment open model. The drug was highly distributed in all tested tissues and completely disappeared from all tissues after 9 and 15 days in healthy and nephritic rats following its oral administration in a dose of 50 mg/kg b. wt. twice daily for 5 successive days.

INTRODUCTION

Pipemidic acid is one of pyrimidine drivatives (**Matsumoto and Minami, 1975**) showing activity against Gram negative bacteria and staphylococci and has been used in the intestinal and urinary tract infections (**Shimizu et al., 1975B**).

As the pharmacological aspects of the drug differ in diseased subjects than in normal ones (**Baggot, 1980 and Burrows, 1980**), the present work was thus initiated to elucidate the pharmacokineric aspect, tissue level and with-holding time of pipemidic acid in normal rats and those with experimentally-inducted kidney damage.

MATERIAL AND METHODS

Drug:
Pipemidic acid trihydrate was obtained in a pure form from Cid Chemical Company, Giza, Egypt.

Animals:
Apparently healthy and experimentaly inducted renal failure rats of 150-200 g. b. wt. were used.

Experimental induction of renal failure:
Acute renal failure was induced according to the method described by Thiel et al., (1967). Male albino rats were dehydrated for 24 hours then injected intramuscularly with glycerol 50% in normal saline (10 ml/kg b. wt.). Serum creatinine level was measured 48 hours post injection to insure that they have renal failure.

Experiments:

1- Pharmacokinetic profile (Single dose study):
Two groups of 10 rats each from both healthy and diseased animals were injected intravenously with a single dose of pipemidic acid (50 mg/kg. b. wt). Blood samples were collected from the inner eye canthus at 15, 30 minutes. 1, 2, 4, 6 and 8 hours. The rats were left for 3 weeks to insure that the

drug was totally cleared from their bodies then given the drug orally in the same dose and blood samples were collected at the corresponding times as in the intravenous route.

II. Tissue distribution and residual content (multiple dose study):

Two groups of 24 healthy and 27 diseased rats were used. Rats of each group were given pipemidic acid orally in a dose of 50 mg/kg b. wt. twice daily for 5 successive days. Blood samples were collected daily for assaying the blood concentration of the drug. Three rats from each group were sacrificed at 1 hour, 1st, 3rd, 5th, 7th, 9th, 11th, 13th, and 15th day post-dosing and blood and tissue samples (liver, kidney, lung, spleen, heart, muscle and intestine) were taken from all animals till the disappearance of the drug from their bodies.

Analytical method:

The obtained blood samples were left to clot then centrifuged at 3000 r. p. m. for 15 minutes to obtain clear sera. Appropriate part of each organ (about 1 g) from each rat was weighed, homogenized with 0.067 N phosphate buffer, of pH 7.5 (1:5 v/v) and heated at 80°C for 15 minutes then cooled and centrifuged. The supernatent was transferred to sterilized tubes.

Estimation of pipemidic acid concentration in serum and tissues was carried out using the microbiological assay technique described by Arret et al., (1971) using E. coli (ATCC 1129) as standard test organism (Goss and Deitz, 1963).

The protein binding tendency was assayed as applied by Lorian (1980).

Statistical analysis:

The pharmacokinetic parameters were calculated according to Baggot (1978) wheras statistical analysis were carried out according to Snedecor and Cochran (1976).

RESULTS

The obtained results revealed higher creatinine concentration with a mean value of 18.01± 0.85

Table (1): Serum concentrations of pipemidic acid (µg/ml) in normal and nephritic rats after a single oral and intravenous administration of 50 mg/kg body weight. ($\bar{x} \pm$ S.E., n = 10)

Time	Intravenous		Oral	
	Normal	Nephritic	Normal	Nephritic
15 min	26.10 ± 0.17	24.40 ± 0.27**	6.40 ± 0.16	5.20 ± 0.13**
30 min	18.40 ± 0.27	16.70 ± 0.13**	17.00 ± 0.33	10.80 ± 0.13**
1 h	13.30 ± 0.15	11.85 ± 0.15**	31.60 ± 0.69	16.20 ± 0.25**
2 h	11.10 ± 0.23	9.60 ± 0.16**	20.10 ± 0.23	10.30 ± 0.15**
4 h	6.75 ± 0.11	5.90 ± 0.06**	9.70 ± 0.26	6.6 ± 0.16**
6 h	4.90 ± 0.10	3.89 ± 0.07**	4.70 ± 0.11	4.15 ± 0.05**
8 h	3.69 ± 0.06	2.96 ± 0.08**	2.54 ± 0.01	2.5 ± 0.17

Significant at :

* $P < 0.05$

** $P \leq 0.01$

Table (2): Pharmacokinetic parameters following pipemidic acid administration (50 mg/kg b.wt) in normal and nephritic rats ($\bar{x} \pm$ S.E., n = 10).

Parameter	Intravenous			Parameter	Oral		
	Unit	Normal	Nephritic		Unit	Normal	Nephritic
C_P^o	ug/ml	62.59±1.34	56.96±1.29**	B.Wt.	kg	1.61±0.02	1.58±0.01
A	ug/ml	46.83±1.25	42.73±1.16*	A	ug/ml	48.83±0.99	23.29±0.51**
α	h^{-1}	5.93±0.16	5.66±0.31	$K_{(ab)}$	h^{-1}	1.64±0.04	2.35±0.09**
$t_{0.5(\alpha)}$	min	7.06±0.18	7.32±0.24	$t_{0.5(ab)}$	h	0.425±0.01	0.300±0.01**
B	ug/ml	15.56±0.14	14.19±0.13**	B	ug/ml	38.597±0.68	20.14±0.23**
β	h^{-1}	0.187±0.001	0.205±0.003**	Kel	h^{-1}	0.320±0.002	0.24±0.07
$t_{0.5(\beta)}$	h	3.71±0.03	3.36 ±0.05**	$t_{0.5(el)}$	h	2.198±0.01	2.99±0.1**
K 12	h^{-1}	3.82±0.13	3.61±0.14	$c_{max(cal)}$	ug/ml	25.92 ±0.31	14.08±0.09**
K 21	h^{-1}	1.62±0.03	1.59±0.03	$t_{max(cal)}$	h	1.24±0.01	1.07±0.01**
Kel	h^{-1}	0.69±0.008	0.74±0.02*				
Vc	L/kg	0.8 ±0.1	0.88±0.02	F	%	91.76±3.20	96.40+2.71
$Vd_{(\beta)}$	L/kg	2.94±0.02	3.17±0.03**				
$Vd_{(ss)}$	L/kg	2.69±0.01	3.22±0.10**				
$Cl_{(tot).}$	L/kg/min	32.97±0.4	38.94±0.70**				

Significant at:

* $P < 0.05$

** $P < 0.01$

Table (3): Serum pipemidic acid concentration in normal and nephritic rats following oral administration of 50 mg/kg b.wt. twice daily for 5 successive days ($\bar{x} \pm$ S.E., n = 10)

Time after first administration	Normal	Nephritic
24 h	-	-
48 h	2.3 ± 0.01	2.2 ± 0.01
72 h	4.2 ± 0.15	3.8 ± 0.01 *
96 h	6.3 ± 0.23	5.2 ± 0.15 **
120 h	9.6 ± 0.27	6.4 ± 0.16 **

Significant at:

* $P < 0.05$

** $P < 0.01$

Table (4): Tissue concentration of pipemidic acid (ug/g) in normal and nephritic rats following oral administration of (50 mg/kg b.wt) for 5 successive days. n = 5.

Tissue	Time of slaughter after the last dose															
	1 h		1 D		3 D		5 D		7 D		9 D		11 D		13 D		15 D	
	N	Neph.	N	Neph.	N	Neph.	N	Neph.	N	Neph.	N	Neph.	N	Neph.	N	Neph.	N	Neph.
Serum	42.4 ± 0.33	23.6** ± 0.65	13.1 ± 0.44	5.3** ± 0.33	2.67 ± 0.1	-	-	-	-	-	-	-	-	-	-	-	-	-
Liver	6.3 ± 0.33	13.67** ± 0.37	4.3 ± 0.58	8.67** ± 0.67	3.0 ± 0.28	5.67** ± 0.33	2.33 ± 0.18	5.0** ± 0.33	1.5 ± 0.19	3.67** ± 0.27	-	2.0 ± 0.10	-	1.67 ± 0.07	-	-	-	-
Kidney	9.33 ± 0.67	15.0** ± 0.0	5.0 ± 0.01	8.67** ± 0.67	3.0 ± 0.27	5.17** ± 0.37	- ± 0.07	3.67** ± 0.18	1.67 ± 0.17	2.33** ± 0.26	-	2.0 ± 0.08	-	-	-	-	-	-
Heart	8.33 ± 0.88	12.5** ± 0.29	5.33 ± 0.49	7.33** ± 0.07	2.67 ± 0.13	4.33** ± 0.33	1.67 ± 0.15	3.33** ± 0.23	1.33 ± 0.03	2.67** ± 0.09	-	1.7 ± 0.0	-	-	-	-	-	-
Spleen	8.67 ± 0.88	9.33** ± 0.76	5.33 ± 0.18	6.67** ± 0.13	2.67 ± 0.07	5.5** ± 0.29	2.0 ± 0.09	4.0** ± 0.08	1.33 ± 0.03	3.2** ± 0.08	-	2.47 ± 0.08	-	1.33 ± 0.07	-	-	-	-
Lung	6.33 ± 6.7	12.53** ± 0.33	3.67 ± 0.53	9.33** ± 0.67	2.33 ± 0.18	7.4** ± 0.29	2.67 ± 0.07	6.5** ± 0.58	-	5.33 ± 0.33	-	4.0 ± 0.31	-	2.8 ± 0.17	-	1.67 ± 0.08		
Muscle	6.0 ± 0.67	8.2** ± 0.58	3.33 ± 0.13	4.3** ± 0.14	1.67 ± 0.09	2.9** ± 0.18	1.33 ± 0.07	2.0** ± 0.13	-	1.67 ± 0.13	-	-	-	-	-	-	-	-
Intestine	4.67 ± 0.23	5.33** ± 0.33	2.67 ± 0.13	4.33** ± 0.27	2.0 ± 0.08	3.0** ± 0.18	1.3 ± 0.08	2.67** ± 0.13	-	2.0 ± 0.07	-	-	-	-	-	-	-	-

-- : undetectable
N = Normal
Neph.= Nephritic

Significant at: * $P < 0.05$ ** $P < 0.01$

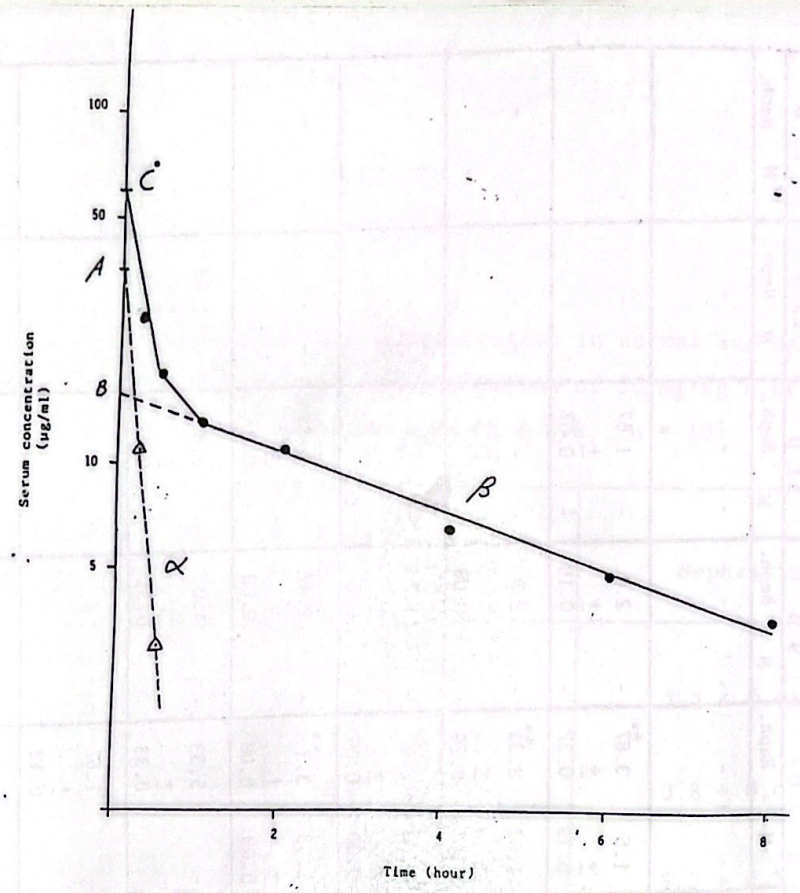

Fig. (1): Semilogarithmic graph depicting the time course of pipemidic acid in serum of normal rats after single intravenous injection of 50 mg/kg b.wt.

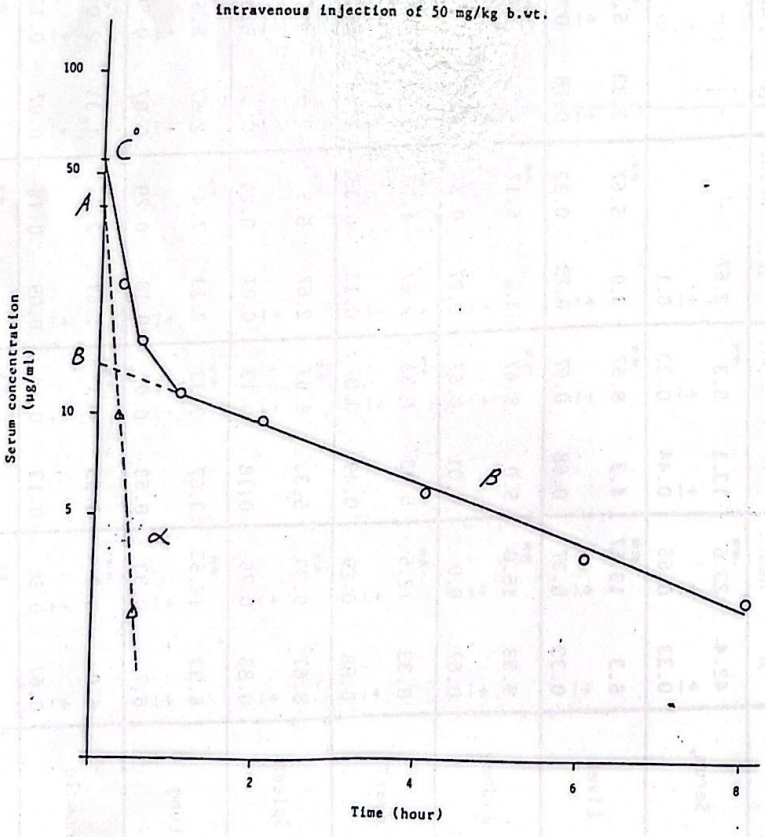

Fig. (2): Semilogrithmic graph depicting the time course of pipemidic acid in serum of nephritic rats after single intravenous injection of 50 mg/kg b.wt.

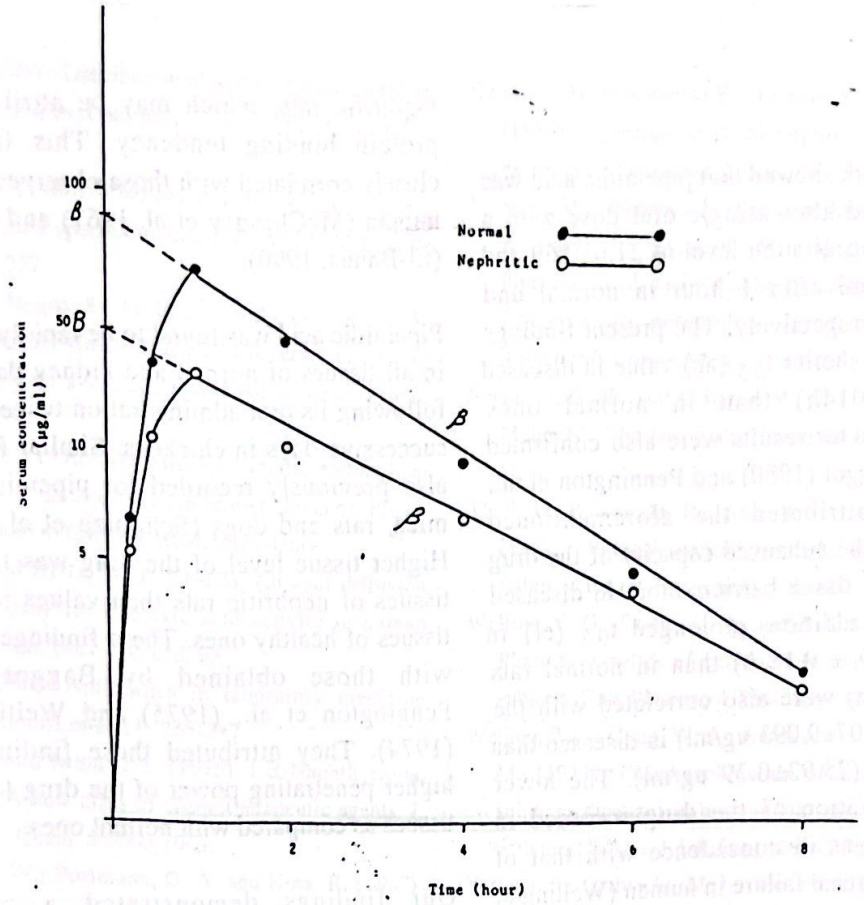

Fig. (3): Semilogarithmic graph depicting the time course of pipemidic acid in serum of normal and nephritic rats after a single oral administration of 50 mg/kg b.wt.

mg/100 ml blood in rats injected with glycerol in comparison with those obtained from normal rats (1.10±0.06 mg/100 ml blood) reflecting the induction of acute renal failure.

Single dose study:

The mean serum concentration of pipemidic acid in normal and nephritic rats following a single oral and intravenous administration of 50 mg/kg b. wt. recorded in table (1). Lower serum concentration was detected in diseased rats as compered with the normal ones.

The kinetic parameters describing the disposition of the drug in rats are tabulated in table (2) and illustrated in Fig (1, 2 and 3). Pipemidic acid showed delayed absorption, higher volume of distribution and faster clearance rate in nephritic rats than normal ones.

Multiple dose studies:

Pipemidic acid had the ability to accumulate in the blood of normal and nephritic rats during the course of treatment (Table 3). Tissue levels and withdrawal time of the drug in normal and diseased rats are incorporated in table (3). The obtained data indicated long withdrawal time in nephritic rats than normal ones.

Protein binding tendencey:

Pipemidic acid showed higher protein binding tendency in nephritic rats with a mean value of 20.41% than in normal ones (13.26%).

DISCUSSION

The present work showed that pipemidic acid was highly absorbed after asingle oral dose with a peak blood concentration level of 31.6±0.69 and 16.2±0.13 ug/ml after 1 hour in normal and nephritic rats, respectively. The present findings demonstrated a shorter $t_{0.5}$ (ab) value in diseased rats (0.30±0.014h) than in normal ones (0.425±0.01h). Our results were also confirmed by those of Baggot (1980) and Pennington et al., (1975) who attributed the aforementioned observation to the enhanced capacity of the drug to penetrate the tissue barriers more in diseased conditions. In addition, prolonged $t_{0.5}$ (el) in diseased (2.989 ± 0.18 h) than in normal rats (2.189 ± 0.01 h) were also correlated with the lower C_{max} (14.07±0.093 ug/ml) in diseased than in normal rats (25.92±0.39 ug/ml). The lower serum concentration of the drug recorded in nephritic rats was in consistence with that of trimethoprim in renal failure in human (Welling et al., 1975) and methicillin in patients suffering from cystic fibrosis (Yaffe et al., 1977).

Pipemidic acid concentration data following the intravenous injection of 50 mg/kg body weight in normal and nephritic rats were best fitted to follow a two compartment open model. This finding was consistent with that previously recorded for pipemidic acid in human (Cadoringa et al., 1987), for flumequine in chickens (Atef et al., 1987) and for nalidixic acid in chickens (El-Banna 1990). Our data showed that higher volume of distribution and faster clearance rate of pipemidic acid in nephritic rats (V_{dss} 3.22±0.1 & $Cl_{(tot)}$ 38.94±0.70) as compared with normal ones (V_{des} 2.69±0.01 & $Cl_{(tot)}$ 32.97 ±0.4). These findings were consistent with the lower serum concentration of the drug recorded here in nephritic rats than normal ones.

Repeated oral administration of pipemidic acid showed a cummulative behaviour in normal and nephritic rats, which may be attributed to the protein binding tendency. This finding was closely correlated with those observed for acid in human (McChesney et al.,1967) and in chickens (El-Banna, 1990).

Pipemidic acid was found to be rapidly distributed in all tissues of normal and kidney damaged rats following its oral administration twice daily for 5 successive days in chickens. Simllar finding was also previously recorded for pipemidic acid in mice, rats and dogs (Schimizu et al., 1975 A). Higher tissue level of the drug was recorded in tissues of nephritic rats than values recorded in tissues of healthy ones. These findinge correlated with those obtained by Baggot, (1980), Pennington et al., (1975) and Welling et al., (1974). They attributed these findings to the higher penetrating power of the drug to diseased tissues as compared with normal ones.

Our findings demonstrated a prolonged withdrawal time of pipemidic acid in tissues of diseased rats (15 days) than values recorded in tissues of healthy ones (9 days), this may be attributed to the high rats of the drug distribution in tissues of diseased rats than normal ones (Pennington et al., 1975) and to the higher protein binding tendency of pipemidic acid in nephritic rats (20.41%) than in normal ones (13.26%).

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