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Comparative pharmacokinetic profiles of cinoxacin and pipemidic acid in humans

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SUMMARY

Serum and urinary levels of Cinoxacin and pipemidic acid were determined at 7-day intervals in the same 10 healthy volunteers after a single oral dose of respectively 500 and 400 mg of the drugs.

Comparison of results shows that Cinoxacin was absorbed faster (absorption half-life, ta $\frac{1}{2}_{cin} = 0.25$ h) than pipemidic acid (ta $\frac{1}{2}_{pip} = 0.37$ h) and distributed in a smaller apparent volume ($AVD_{cin} = 23.5$ l/1.73 m2; $AVD_{pip} = 60.1$ l/1.73 m2). Biological half-lives were identical (tb $\frac{1}{2}_{cin} = 2.10$ h; tb $\frac{1}{2}_{pip} = 2.15$ h). On the other hand, serum levels for Cinoxacin at 1, 2 and 4 hours (8.1 ± 1.5 µg/ml, 10.6 ± 1.5 µg/ml, 5.6 ± 1.3 µg/ml respectively) were higher than those for pipemidic acid (3.3 ± 0.3 µg/ml, 3.4 ± 0.5 µg/ml, 2.1 ± 0.5 µg/ml respectively). Urinary excretion of the two derivatives during the 12 hours following their administration was similar ($U^{cin}_{0\text{-}12h} = 86\%$; $U^{pip}_{0\text{-}12h} = 83\%$). Mean urinary concentrations were particularly high, still attaining respectively 90 ± 29 µg/ml and 131 ± 38 µg/ml in samples collected between the 9th and the 12th hours; these levels were well above the M.I.C. for the Gram-negative organisms included within the spectrum of activity of these two quinolones. In addition, predictive calculations of serum levels reached after multiple dosing indicate that at an administration rate of 500 mg every 6 or preferably every 4 hours, Cinoxacin concentrations should be sufficiently high to be of interest in the treatment of systemic infections by sensitive organisms.

Cinoxacin (Cinobac®) is a new synthetic antibacterial agent belonging to the quinolone family. Like nalidixic, oxolinic, piromidic and pipemidic acids, it is structurally centered by the cinnolin ring (Figure 1). Its antimicrobial spectrum includes the majority of gram-negative bacteria (except for Pseudomonas aeruginosa), in particular enterobacteriaceae (1,9,11,14,16). Furthermore, Cinoxacin seems to inhibit the transfer of a number of R-factors, even in cases where either the donor or the recipient organism is nalidixic acid-resistant (19). This drug shoud thus be of particular interest in the treatment of urinary infections.

The purpose of this study was to determine the Cinoxacin pharmacokinetics and to compare them with those of another derivative of this same quinolone group, pipemidic acid (Pipram®), whose characteristics are already well defined (8,17,21,22).

An attempt was also made to predict theoretical serum levels (5) of these two drugs to be achieved after repeated dosing, using pharmacokinetics data previously established after a single dose administration of Cinoxacin and of pipemidic acid to healthy volunteers.

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MATERIALS AND METHODS

Standards

Cinoxacin [1-ethyl-4(1H)-oxo-[1,3]dioxolo[4,5-g] cinnoline-3-carboxylic acid] was kindly supplied by Eli Lilly and Compagny, Indianapolis, U.S.A., as 250 mg capsules of Cinobac, and pipemidic acid [ethyl-8 oxo-5 piperazinyl-2 dihydro-5,8 pyrido-(2-3d)

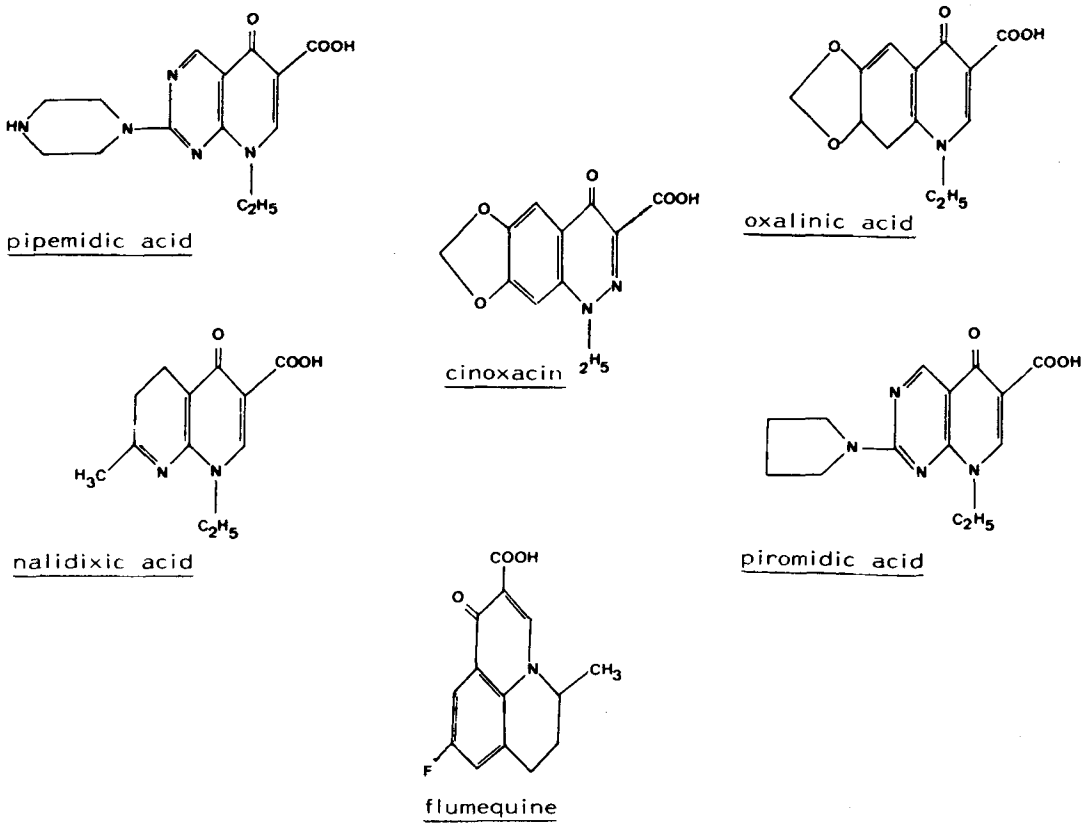

Fig. 1 : Comparative structural formulas of the 6 now corrently available quinolone derivatives.

pyrimidine-6 carboxylic acid] by Roger Bellon Laboratories, Neuilly-Paris, France, as 200 mg tablets of Pipram.

Selection of subjects

10 healthy volunteers wer used for this study (1 female, 9 males, mean age 29.6 ± 1.9 years, mean weight 65.5 ± 3.1 kg, mean body surface area 1.76 ± 0.04 m2). None of these subjects presented pathological changes either in renal function (blood nitrogen 25.5 ± 1.5 mg %, serum creatinin 1.1 ± 0.1 mg %, endogenous creatinin clearance 113 ml/min/1.73 m2), or in hepatic function (bilirubin 1.1 ± 0.1 mg %, SGOT and SGPT ranging between 12 and 20 U/ml). In all cases, informed consent was obtained before beginning the study.

Procedure

After oral administration of 500 mg Cinoxacin (as two capsules) to fasting subjects, serum concentrations were determined in blood samples taken at times 0.5 h, 1 h, 2 h, 4 h and 6 h.

Cinoxacin levels were also determined in urine collected during four 3-hour periods following administration of this drug (0-3 h, 3-6 h, 6-9 h, 9-12 h).

A similar procedure was applied one week later in the same group of subjects after ingestion of a single 400 mg dose of pipemidic ac (as two 200 mg tablets).

Assay technique

Cinoxacin assays were carried out following the technique of Briggs and Cokinos modified by Grisham (10). After chloroform extraction, fluorescence of the acidified supernatant was analyzed in an Aminco Bowman spectrofluorometer (excitation: 356 nm; emission: 432 nm). Standard curves were established using pooled human serum for determination of blood levels and a pH 7 0.1 M phosphate buffer for urinary levels.

Also pipemidic acid concentrations were determined spectrofluorometrically, using the technique recommended by Montay et al (18) (reading in an Aminco Bowman spectrofluorometer; excitation at 365 nm; emission at 450 nm).

Pharmacokinetic calculations

Serum concentrations curves of Cinoxacin and pipemidic acid exhibited an association of an elimination phase with an absorption phase; they were thus fitted to a Bateman function and analyzed using a one-compartment open model (5). Equation characterizing the absorption phase was established on the basis of the «residual values» method, the linear regression analysis for the elimination phase being based on the «least squares» method. Area under the serum concentration curves (AUC) were determined by application of the «trapezoidal rule» of Simpson and calculated using the formula: $AUC = \frac{Bo}{Ke} - \frac{Ao}{Ka}$ (where Ao and Bo = initial theoretical concentrations for the absorption and elimination process; Ka and Ke = absorption and overall elimination rate constants). The maximal concentrations, C_{max} (attained at time t_{max}) were calculated by introducing the value of t_{max} into the equation characterizing the curves for serum concentration (4,5) :

$$C = \frac{Bo \cdot Ka}{Ka - Ke} (e^{-Ke\,t} - e^{-Ka\,t}),$$

t_{max} being equal to :

$$t_{max} = \left(\ln \frac{Ao \cdot Ka}{Bo \cdot Ke}\right) \Big/ (Ka - Ke)$$

Cinoxacin and pipemidic acid absorption began after a period of time, t_0 (t_0 = «lag time»), the duration of which can be calculated applying the equation (4,5) :

$$t_0 = \left(\ln \frac{Ao}{Bo}\right) \Big/ (Ka - Ke)$$

Total clearance valuesm (Ct) were determined following the formula: $Ct = \frac{D}{AUC}$ (where D = administered dose), and renal clearances (Cr) using the formula: $Cr = \frac{U}{AUC}$ (where U = urinary elimination of the drug over the considered period).

Predictive calculations of maximal (C_{max}) and minimal (C_{min}) serum levels theoretically attained in the normal subject, on the one hand after n administrations of 500 mg doses of Cinoxacin or of 400 mg doses of pipemidic acid (C^n_{max} and C^n_{min}), and on the other hand at the «steady state» (after N drug administrations: C^∞_{max} and C^∞_{min}) were carried out using the following equations (4) :

$$C^n_{max} = C_{max} \frac{1 - e^{-n\,Ke\,\tau}}{1 - e^{-Ke\,\tau}}$$

$$C^n_{min} = C_{min} \frac{1 - e^{-n\,Ke\,\tau}}{1 - e^{-Ke\,\tau}}$$

$$C^\infty_{max} = C_{max} \frac{1}{1 - e^{-Ke\,\tau}}$$

$$C^\infty_{min} = C_{min} \frac{1}{1 - e^{-Ke\,\tau}}$$

(τ = time interval (in hours) between 2 consecutive doses of Cinoxacin or Pipemidic acid = dosage interval).

In order to obtain at the time of the first administration serum concentrations that are otherwise only attained at the steady state, an appropriate loading dose (LD) must be given. This loading dose can be calculated by applying the formula :

$$LD = D \frac{1}{1 - e^{-Ke}}$$

(where D = maintenance dose; in this case, 500 mg Cinoxacin or 400 mg pipemidic acid).

RESULTS

Pharmacokinetics of Cinoxacin

After a single oral dose of 500 mg of Cinoxacin, the following mean serum concentrations were found: 1.6 ± 0.3 µg/ml, 8.1 ± 1.5 µg/ml, 10.6 ± 1.5 µg/ml, 5.6 ± 1.3 µg/ml and 2.8 ± 1.5 µg/ml at 0.5, 1, 2, 4 and 6 hours, respectively (Table I).

Absorption began after a lag time, t_0, of 0.30 h and the absorption coefficient, Ka, was 2.7642 (h^{-1}), expressing a relatively brief absorption half-life, Ta½,

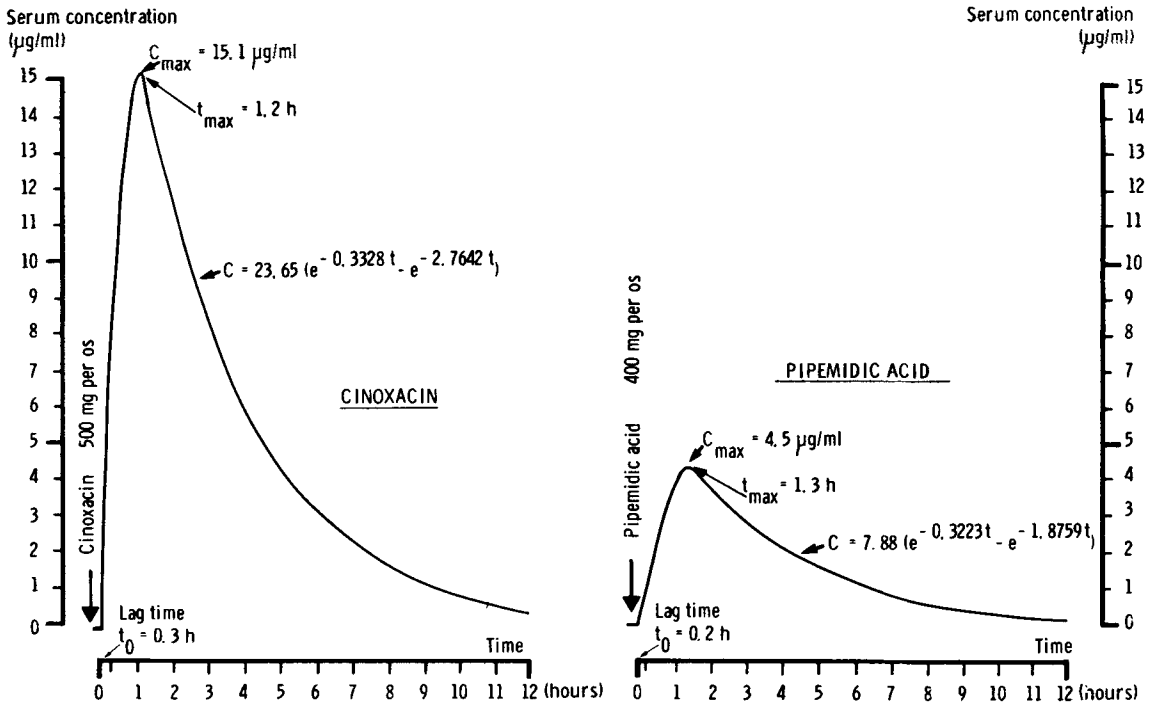

Fig. 2 : Theoretical serum concentration curves for Cinoxacin (500 mg per os - on the left) and pipemidic acid (400 mg per os - on the right), determined on the basis of the pharmacokinetic parameters established for the 10 studied subjects.

Table I : Mean serum concentrations determined after oral administration of a single 500 mg Cinoxacin and 400 mg pipemidic acid dose in the 10 normal subjects under study.

	Mean serum concentration (µg/ml)						
	0 h	0,5 h	1 h	2 h	4 h	6 h	12 h
After a single 500 mg oral dose of CINOXACIN	0	1.6 ± 0.3	8.1 ± 1.5	10.6 ± 1.5	5.6 ± 1.3	2.8 ± 1.5	0.4
After a single 400 mg oral dose of PIPEMIDIC ACID	0	1.3 ± 0.2	3.3 ± 0.3	3.4 ± 0.5	2.1 ± 0.5	0.9 ± 0.3	0.2

of 0.25 h. The overall elimination rate-constant, Ke, was 0.3328 (h^{-1}), corresponding to a biological half-life, t ½, of 2.08 h. Using the equation C (µg/ml) = 23.65 ($e^{-0.3328t} - e^{-2.7642t}$) characterizing the serum concentration curve, a maximal concentration (C_{max}) of 15.1 µg/ml reached at a time t_{max} of 1.18 h (70 min.) could be calculated (Figure 2).

Depending upon whether it was determined by measurement or by calculation, the area under the serum concentrations curve ($AUC_{0-\infty}$) was respectively 45.2 or 46.7 µg.h/ml. The apparent volume of distribution for Cinoxacin was 23.5 l/1.73 m2. Total clearance was 179 ml/min/1.73 m2, and renal clearance 159 ml/min/1.73 m2 (Table III).

Mean cumulative urinary recovery of Cinoxacin over the 3, 6, 9 and 12 hours following administration was respectively 229.4 ± 37.7, 370.1 ± 22.4, 412.7 ± ± 17.1 and 429.2 ± 15.7 mg (corresponding to 45.8%

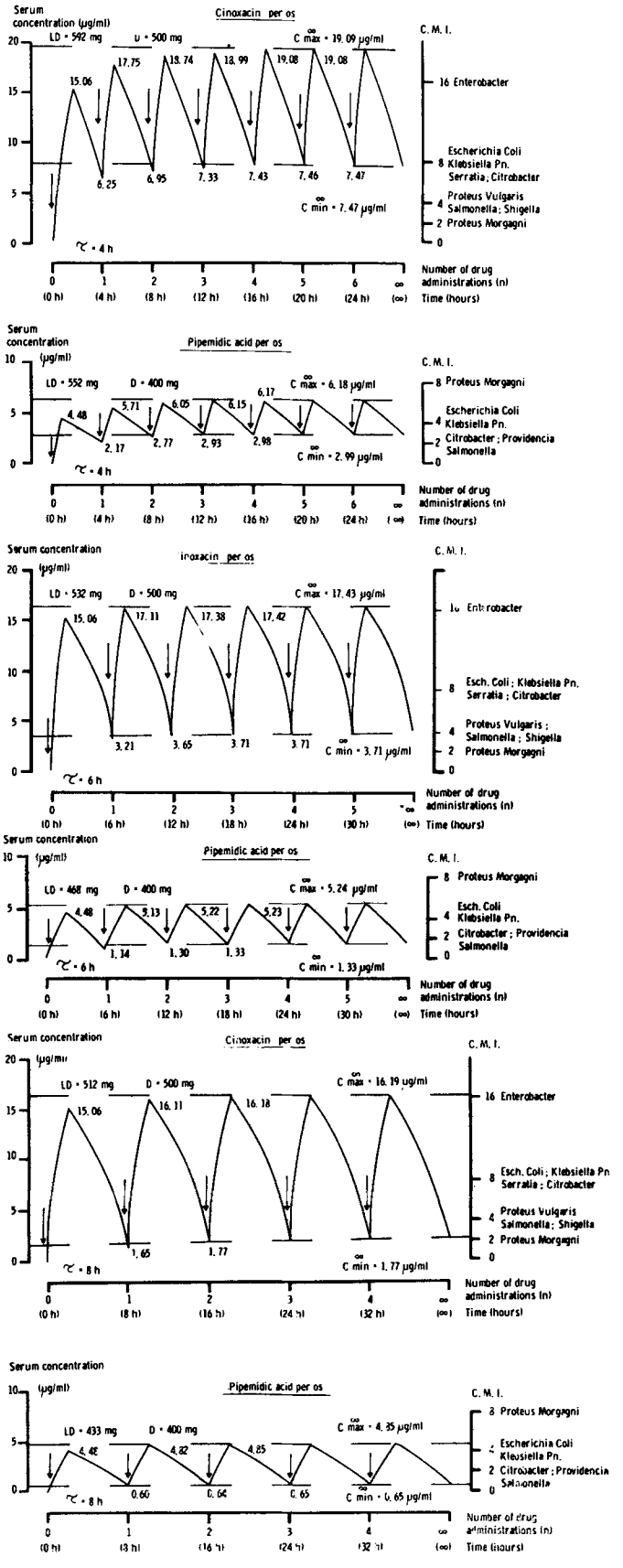

Fig. 3 : Comparative predictive determination of serum levels after repeated oral dosing with 500 mg Cinoxacin and 400 mg pipemidic acid. Calculations were carried out for dosage intervals of 4 h (above), 6 h (middle) and 8 h (below). Administration of a loading dose (LD) should allow achievement of «steady state» levels with the first dose.

74%, 82.5% and 86% of the ingested dose). Mean urinary concentrations over 0-3 h, 3-6 h and 9-12 h time intervals were 682 ± 166, 554 ± 115, 251 ± 73 and 90 ± 29 μg/ml respectively (Table II).

Values for C_{max} and C_{min}, theoretically attained after n doses, as well as at the «steady state» (after N doses) are given on Table IV and Figure 3; these were determined for repeated doses of 500 mg of Cinoxacin at 2, 3, 4, 6, 8 or 12 hours. Table IV also shows loading doses established for the various proposed dosages and which provide to reach the «steady state» levels from the first administration.

Pharmacokinetics of pipemidic acid

Mean serum concentration values determined after a single 400 mg dose of pipemidic acid are reported in Table I; these levels were of 1.3 ± 0.2 μg/ml, 3.4 ± 0.5 μg/ml, 2.1 ± 0.5 μg/ml and 0.9 ± 0.3 μg/ml (Table I) at 0.5, 1, 2, 4 and 6 hours respectively.

A lag time, t_0, of 0.20 h elapsed before the beginning of absorption by the gastro-intestinal tract; the half-absorption life, ta ½, was of 0.37 h and the absorption rate-constant, Ka, of 1.8759 (h^{-1}). The overall elimination rate-constant, Ke, was 0.3223 (h^{-1}), and the half-life, t ½, 2.15 h. The mean serum concentration curve was expressed by the equation: $C = 7.88\ (e^{-0.3223t} - e^{-0.8759t})$. A maximal concentration, C_{max}, of 4.48 μg/ml was theoretically attained at $t_{max} = 1.34$ h (Figure 2).

Measured and calculated values for the area under the serum concentration curve ($AUC_{0-\infty}$) were respectively 16.92 and 15.49 μg.h/ml. Volume of distribution was extremely high (60.1 l/1.73 m2), showing excellent diffusion throughout the body. Total clearance, Ct, was 386 ml/min/1.73 m^2 and renal clearance, Cr, 321 ml/min/1.73 m^2 (Table III).

Mean values for cumulative urinary recovery were respectively 124.8 ± 9.5, 254.9 ± 24.4, 307.9 ± ± 28.3 and 333.0 ± 29.6 mg (representing 31%, 64%, 77% and 83% of the ingested dose), 3, 6, 9 and 12 hours after administration. Mean urinary levels were 509 ± 90, 510 ± 96, 298 ± 74 and 131 ± 38 μg/ml over 0-3h, 3-6h, 6-9h and 9-12h time intervals (Table II).

Table IV and Figure 3 give calculated values for C_{max} and C_{min} in case of various dosage intervals (2, 3, 6, 8 or 12 hours). Loaging doses were also determined for the different dosage schedules.

DISCUSSION

Serum and urinary levels, as well as pharmacokinetic parameters of Cinoxacin determined in this study are in agreement with the data reported in the literature (1,2,3,6,7,13,15,20). For pipemidic acid however we have found a larger percentage of urinary recovery (83% over 24 h) than cited by Humbert et al (12) (63% over 24 h) or Soussy et al (22) (48.3% over 24 h).

Pharmacokinetic characteristics of Cinoxacin differ from those of pipemidic acid (Table III); gastro-intestinal absorption (ta ½ = 0.25 h) was faster than for that found with pipemidic acid (ta ½ = 0.37 h) and the volume of distribution was considerably smaller (23.5 l/1.73 m^2 versus 60.1 l/1.73 m^2).

Table II : Mean urinary concentrations and mean cumulative urinary recoveries determined after oral administration of a single 500 mg Cinoxacin and 400 mg pipemidic acid dose in the 10 normal subjects under study.

	Mean urinary concentration (μg/ml)				Mean cumulative urinary recoveries (mg)			
	0-3 h	3-6 h	6-9 h	9-12 h	0-3 h	0-6 h	0-9 h	0-12 h
After a single 500 mg oral dose of CINOXACIN	682 ± 166	554 ± 115	251 ± 73	90 ± 29	229 ± 38	370 ± 22	413 ± 17	429 ± 16
After a single 400 mg oral dose of PIPAMIDIC ACID	509 ± 90	510 ± 96	298 ± 74	131 ± 38	125 ± 10	255 ± 24	308 ± 28	333 ± 30

Table III : Comparison of the pharmacokinetic parameters for Cinoxacin (500 mg per os) and pipemidic acid (400 mg per os) in normal subjects under study (n = 10).

PHARMACOKINETIC PARAMETERS	CINOXACIN (500 mg)	PIPEMIDIC ACID (400 mg)
Initial theoretical concentration (absorption phase) Ao (µg/ml)	43.6	8.9
Initial theoretical concentration (elimination phase) Bo (µg/ml)	20.8	6.5
Absorption rate-constant $ka^{(h^{-1})}$	2.7642	1.8759
Overall elimination rate-constant $ke^{(h^{-1})}$	0.3328	0.3223
Absorption half-life ta ½ (h)	0.25	0.37
Biological half-life tb ½ (h)	2.08	2.15
Lag time t_0 (min.)	18	12
Maximal concentration C_{max} (µg/ml)	15.1	4.5
t_{max} (h)	1.18	1.34
Apparent Volume of Distribution AVD (litre/1.73 m2)	23.5	60.1
Area under the serum concentration curve $AUC_{0-\infty}$ (µg.h/ml)	45.19	16.92
Total clearance Ct (ml/min./1.73 m2)	179	386
Renal clearance Cr (ml/min./1.73 m2)	159	321
Urinary excretion U_{0-14h} (percentage of the administered dose)	86	83

Table IV : Maximal and minimal serum concentrations theoretically reached after repeated doses of 500 mg Cinoxacin and 400 mg pipemidic acid administered every 2, 3, 4, 5, 6, 8 or 12 hours. Aministration of a loading dose (LD) should allow attainment of «steady state» levels with the first dose.

Dosage		Loading Dose (LD) (mg)	Number of oral administration required to achieve steady state levels in the absence of loading dose	C_{max} (μg/ml)	C_{min} (μg/ml)
Cinoxacin	500 mg/2 h per os	826	11	28.9	22.0
Pipemidic acid	400 mg/2 h per os	842	12	9.4	8.3
Cinoxacin	500 mg/3 h per os	665	9	22.2	12.1
Pipemidic acid	400 mg/3 h per os	645	8	7.2	4.8
Cinoxacin	400 mg/4 h per os	592	8	19.1	7.5
Pipemidic acid	400 mg/4 h per os	552	6	6.2	3.0
Cinoxacin	500 mg/6 h per os	532	5	17.4	3.7
Pipemidic acid	400 mg/6 h per os	468	5	5.2	1.3
Cinoxacin	500 mg/8 h per os	512	4	16.2	1.8
Pipemidic acid	400 mg/8 h per os	433	3	4.9	0.6
Cinoxacin	500 mg/12 h per os	502	2	15.1	0.4
Pipemidic acid	400 mg/12 h per os	409	3	4.6	0.2

Serum levels were 3 to 4 times greater than for pipemidic acid, but no clear difference was observed in the urinary excretion (86 and 83% in 12 h).

Values reported in the literature indicate that at least 90% of organisms susceptible to these agents (essentially gram-negative bacteria and enterobacteriaceae) are inhibited by levels of less than 32 μg/ml Cinoxacin (9,11,14,16,23) and 12.5 μg/ml pipemidic acid (8,17). Administration of these two drugs at the dosages here used provides urinary concentrations well above these levels for the 12 hours following administration, at least in patients with normal renal function.

Serum levels of pipemidic acid, even when administered at short intervals (Table IV and Figure 3), are clearly insufficient for maintenance of adequate antibacterial activity in cases of generalized infection. On the other hand, the administration of 500 mg Cinoxacin every 6 hours (or preferably, every 4 hours) yields serum levels within the therapeutic

range (Table IV, Figure 3). These data would seem to indicate that Cinoxacin could also be used for the treatment of systemic infections by sensitive organisms, especially since, like other quinolone derivatives, it apparently induces neither the formation nor the transfer of plasmid-coded antibiotic resistance (19). These proposed therapeutic applications, however, are based on bacteriological and pharmacokinetic results and should obviously be confirmed in clinical trials.

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REFERENCES

1. Anderson K.E., Mardh P.A., Colleen S. (1978): Antibacterial activity and tissue distribution of Cinoxacin Curr Chemother *1*, 690-691.
2. Black H.R., Israel K.S., Farid K.Z., Nash J.F. (1978): Comparative pharmacology of Cinoxacin, nalidixic acid, oxolinic acid, nitrofurantoin and trimethoprim-sulfamethoxazole Curr Chemother *1*, 203-204.
3. Black H.R., Israel K.S., Wolen R.L., Brier G.L., Obermeyer B.D., Ziege E.A., Wolny J.D. (1979): Pharmacology of Cinoxacin in humans Antimicrob Agents Chemother *15*, 165-170.
4. Brogard J.M., Kopferschmitt J., Spach M.O., Lavillaureix J., Grudet D. (1979): Cefuroxime: pharmacokinetics in subjects with normal and impaired renal function; prediction of serum concentrations and dosage adjustments Drugs Exptl Clin. Res. *5*, 427-443.
5. Brogard J.M., Pinget M., Dorner M., Lavillaureix J. (1976): Etablissement du profil pharmacokinétique d'un antibiotique. Intérêt pratique et application à l'étude comparative des céphalosporines Bull Inst Pasteur *74*, 383-412.
6. Burt R.A.P., Morgan T., Payne J.R., Bonner R.M. (1977): Cinoxacin concentrations in plasma, urine and prostatic tissue after oral administration to man Br. J. Urology *49*, 147-152.
7. Colleen S., Andersson K.E., Mardh P.A. (1977): Studies on Cinoxacin. 3) Concentrations of Cinoxacin in serum, urine and tissues of urological patients J. Antimicrob Chemother *3*, p. 579-584.
8. De Lajudie P. (1974): L'acide pipémidique, nouvel antibactérien de synthèse J. Pharmacol. Clin. *1*, 155-171.
9. De Rosa F., Bianchi P., Enrico P., Vissani P.M. (1980): Comparison of in vitro activity of three antiseptic drugs of urinary tract (Cinoxacin, nalidixic and oxolinic acid) on 185 strains of gram-negative bacteria Drugs Exptl. Clin. Res. *6*, 21-26.
10. Eli Lilly Laboratories Investigators Manual (1976): Cinoxacin, compound 647 16 Indianapolis, Indiana.
11. Giamarellou H., Jackson G.G. (1975): Antibacterial activity of Cinoxacin in vitro Antimicrob Agents Chemother *7*, 688-692.
12. Humbert G., Fillastre J.P., Leroy A. (1976): Etude de l'élimination urinaire d'un nouvel antibactérien de synthèse, l'acide pipémidique, chez le sujet normal et l'insuffisant rénal Sem Hôp Paris, Thérapeutique, *52*, n° h.s., 32-38.
13. Israel K.S., Black H.R., Nelson R.L., Brunson M.K., Nash J.F., Brier G.L., Wolney J.D. (1978): Cinoxacin: pharmacokinetics and the effect of Probenecid J. Clin. Pharmacol. *18*, 491-499.
14. Jones R.N., Fuchs P.C. (1976): In vitro antimicrobial activity of Cinoxacin against 2968 clinical bacterial isolates Antimicrob Agents Chemother *10*, 146-149.
15. Maigaard S., Moller N.F., Welling P.G., Madsen P.O. (1979): Cinoxacin: pharmacokinetics and tolerance in patients with normal and impaired renal function Antimicrob Agents Chemother *16*, 411-416.
16. Mardh P.A., Coolleen S., Andersson K.E. (1977): Studies on Cinoxacin. I) In vitro activity of Cinoxacin, as compared to nalidixic acid, against urinary tract pathogens J. Antimicrob. Chemother. *3*, 411-416.
17. Monnier J., Bourse R., Suau Y. (1976): Etude bactériologique et pharmacocinétique d'un nouvel antibactérien urinaire, l'acide pipémidique Sem. Hôp. Paris, Thérapeutique *52*, n° h.s., 7-15.
18. Montay G., Vigouroux M., Roquet F., Reynier M. (1977): Dosage spectrofluorimétrique de l'acide pipémidique dans les liquides biologiques. Absorption digestive et élimination urinaire chez le rat, le lapin, le chien et l'homme Thérapie *32*, 553-561.
19. Ott J.L., Gordee R.S. (1980): Cinoxacin, a synthetic antibacterial agent that inhibitis transfer of R factors Curr Chemother Inf Dis *1*, 741-742. Proceedings of the 11th ICC and the 19th ICAAC, Ed. J.D. Nelson and G. Grassi, ASM, Washington (1980).
20. Rodriguez N., Madsen P.O., Welling P.G. (1979): Influence of Probenecid on serum levels and urinary excretion of Cinoxacin Antimicrob Agents Chemother *15*, 465-469.
21. Shimizu M., Nakamura S., Takase Y., Kurobe N. (1975): Pipemidic acid: absorption, distribution and excretion Antimicrob Agents Chemother *7*, 441-446.
22. Soussy C.J., Thibault M., Duval J. (1976): L'acide pipémidique, activité antibactérienne, comparaison avec l'acide nalidixique Sem Hôp Paris, Thérapeutique *22* n° h.s., 16-22.
23. Wick W.E.D., Preston W.A., White W.A., Gordee A.S. (1973): Compound 647 16, a new synthetic antibacterial agent Antimicrob Agents Chemother *4*, 415-420.