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Cephalexin: human studies of absorption and excretion of a new cephalosporin antibiotic

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1. Serum levels, half-lives and urine concentrations of cephalexin, an oral cephalosporin antibiotic which is unique in its absorption and excretion, are reported in human volunteers, fasting, non-fasting and non-fasting plus probenecid. Accumulation does not seem to occur.

2. Cephalexin clearance was 376 ml./min and the ratio of cephalexin/creatinine clearances was 2·6 in one volunteer.

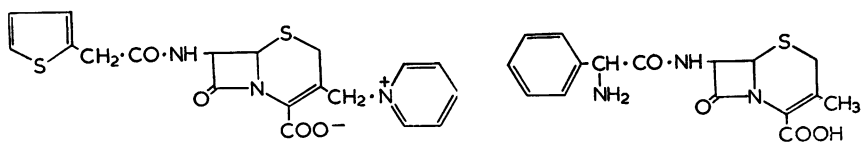
3. Cephalexin had no effect on the urinary excretion of leucocytes, red cells or protein.

4. The very high rate of absorption giving high serum levels and urine concentrations suggest cephalexin will be a useful antibiotic in susceptible bacterial infections in man.

Cephalexin (or cefalexin), 7-(D-α-amino-α-phenylacetamido)-3-methyl-3-cephem-4-carboxylic acid, is a semisynthetic derivative of cephalosporin C developed in the United Kingdom by Glaxo Research Ltd. It has the same cephalosporanic acid "nucleus" as cephaloridine, but differs in side chain substitutions (Fig. 1).

The antibacterial properties of cephalexin have already been reported (Wick, 1967; Muggleton, O'Callaghan, Foord, Kirby & Ryan, 1968; Perkins, Carlisle & Saslaw, 1968). Its spectrum of activity is similar to that of cephaloridine, although it is less active *in vitro*. The addition of human serum did not affect the minimum inhibitory concentration (m.i.c.) for the organisms (Wick, 1967).

Cephalexin differs from cephaloridine in being well absorbed following oral administration. In animal experiments, D. M. Ryan (personal communication) recovered 30–70% of an oral dose of cephalexin from the urine. Under similar experimental conditions, only 1–2% of orally administered cephaloridine could be recovered.



Cephaloridine Cephalexin

FIG. 1. Chemical comparison of cephalexin and cephaloridine.

Saslaw & Carlisle (1968) have reported the *in vivo* effect of oral cephalexin against experimental infections induced by penicillinase producing staphylococci in Macaca monkeys. Its efficacy was found to be similar to parenteral cephaloridine or cephalothin at the same dosage.

Daikos, Kontomichalou, Roussos & Papachristou (1968) reported clinical results with cephalexin in twenty patients. With an average daily dose of 3 g satisfactory responses were obtained in all the types of infections treated.

We report here the effects of probenecid and/or food on the serum levels and urinary recoveries in human volunteers following a 1 g dose of cephalexin compared with fasting values. The possibility of accumulation of the drug in the first 24 hr was investigated. The renal clearance of cephalexin and the effect of the antibiotic on urinary cellular and protein excretion in man is also reported.

Methods

Healthy, young adult human volunteers (for details see Table 1) were given cephalexin in 500 mg hard gelatine capsules according to the following schedule.

Experiment A

Six volunteers were given 1 g cephalexin by mouth following a 12 hr fast. Food and drink was withheld for a further 6 hr. Samples of venous blood at 1, 2, 4 and 6 hr and urine voided between 0–2, 2–4 and 4–6 hr after cephalexin were collected.

Experiment B

The same six volunteers were given 1 g cephalexin following a standard breakfast of fried egg and bacon, toast and marmalade and coffee or tea estimated to contain about 800 K calories. Samples of blood and urine were collected as in experiment A.

Experiment C

Probenecid 0·5 g was given every 6 hr to the same six volunteers for 24 hr. Simultaneously with the last dose, 1 g of cephalexin was administered. Other details were similar to experiment B.

Experiment D

Six volunteers were given 1 g cephalexin every 6 hr for five doses. Following the last dose, blood and urine samples were collected as in experiment B.

All blood samples were allowed to clot, then centrifuged and the serum stored at $-20°$ C. All urine samples, after measurement of volume, were stored without preservative at $-20°$ C. Assays were carried out in batches by agar diffusion using Sarcina lutea 400E. The limit of sensitivity varied slightly between batches from 0·3 μg/ml. to 0·6 μg/ml.

There was an interval of 1 week between each of experiments A to D.

Following the results of these experiments, the clearance of cephalexin and the effect of the drug on protein and cellular excretion were investigated on three healthy young adult human volunteers.

Experiment E

On three consecutive days urine voided between 9.0–10.0 a.m. and again 12 noon–1.0 p.m. from three volunteers was collected. The number of white blood cells and red blood cells were counted using a modified Fuchs-Rosenthal chamber, in urine centrifuged at 5,000 rev/min for 5 min. The results were expressed as an excretion rate of cells per hour. Salicylsulphonic acid was used to test for the presence of protein. This period was used for control excretion rates.

On day 4, following a "standard" breakfast, 1 g of cephalexin was taken, at 8.0 a.m. Venous blood was collected at 9.0 a.m. and 10.0 a.m. for the estimation of cephalexin and creatinine. Simultaneously, urine was collected between 9.0 and 10.0 a.m., the volume measured and aliquots taken for the estimation of cephalexin and creatinine. The urinary and plasma creatinine were measured using an Auto-analyser. The simultaneous clearance rates were calculated for creatinine and cephalexin. The urinary white cell and red cell excretion rates were also measured, as on control days, from 9.0 a.m.–10.0 a.m. and again from 12 noon–1.0 p.m.

Results

Serum levels

Detailed results of experiments A–D are given in Table 1.

The mean serum levels and ranges are plotted in Figs. 2A–D. Fasting (Fig. 2A), the mean peak serum level after 1 g cephalexin was 31·6 μg/ml. and was reached 1 hr after ingestion of the drug. All individuals showed peak levels at 1 hr (Table 1). At 6 hr cephalexin was just detectable. Following a meal (Fig. 2B), mean peak serum level was 20·9 μg/ml., but absorption was delayed, peak levels being reached at 2 hr (one volunteer, Gr, gave a peak level at 1 hr, Table 1). The serum levels showed a slower rate of decline when compared with the fasting values. Detectable levels were present at 6 hours. Probenecid caused an increase in the mean serum levels (Fig. 2C), giving a mean peak of 36·7 μg/ml. (an increase of 79% over the mean peak value achieved in experiment B). Individual increases in peak levels of up to 134% (volunteer Ph, Table 1) were recorded. Levels at 6 hr ranged from 4·5 to 9·7 μg/ml., with a mean of 7·1 μg/ml. Accumulation of the drug was negligible following five doses of 1 g at intervals of 6 hr as shown by the serum level curve (Fig. 2D).

The serum half-life of cephalexin (calculated by the method of least squares) ranged from 49·0 to 50·0 min in the fasting state, with a mean of 49·5 min. Food increased this to a mean of 76·5 min (range 46·0–92·0 min) and the addition of probenecid prolonged it to 107·1 min (range 88·0–133·0 min). The serum half-life following five doses of cephalexin was 58·3 min (range 50·0–80·0 min), although the results from five of the six volunteers ranged between 50·0 and 56·0 min; similar to the values obtained after a single dose.

Urinary concentrations and recoveries

The urinary concentration of cephalexin for each individual during each collection period in experiments A–D is shown diagrammatically in Figures 3A–D. The cumu-

lative percentage of dose excreted is also shown. All individuals when fasting (Fig. 3A) excreted at least 79·6% of the dose in 6 hr. The mean urinary recovery in the first 6 hr was 94·7% of the administered dose, with a range of 79·6–111·3%. Food generally reduced the concentration of cephalexin in each collection period (Fig. 3B), but the total amount excreted in the 6 hr was little changed—at least 79·7% of the dose (range 79·7–110·2%), with a mean of 95·7%.

Probenecid markedly reduced the urinary concentration and excretion in 6 hr (Fig. 3C). However, levels were usually >1,000 μg/ml. A mean (from five volunteers) of 73·7% was excreted in the first 6 hr. Individual amounts excreted ranged from 68·4 to 80·6%. Following the last of five doses of 1 g cephalexin given at intervals of 6 hr, urine concentrations (Fig. 3D) were not much different from fasting levels (Fig. 3A).

TABLE 1. *Individual details with serum and urine concentrations of cephalexin in experiments A, fasting; B, after standard meal; C, addition of probenecid; D, after five doses at intervals of 6 hr*

Volunteer	Sex	Age (yr)	Weight (kg)	Serum: Time after cephalexin (hr)	Serum: Conc. (μg./ml.) of cephalexin in experiments A	B	C	D	Urine: Time after cephalexin (hr)	Urine: Conc. (μg./ml.) of cephalexin in experiments A	B	C	D
Ha	F	30	54·2	1	26·7	24·3	39·6	30·9	0–2	7,190	5,885	835	5,355
				2	25·0	27·2	39·8	31·3	2–4	3,960	5,405	1,175	3,890
				4	3·3	8·9	18·9	5·2	4–6	170	1,230	1,855	2,085
				6	0·5	2·0	9·0	0·9					
Gr	M	26	70·0	1	32·2	26·3	39·3	37·1	0–2	7,790	6,985	2,855	9,225
				2	12·7	16·1	33·2	15·7	2–4	3,345	4,015	3,260	3,055
				4	1·1	2·5	11·4	1·4	4–6	715	825	1,170	970
				6	0·6	0·3	4·5	0·7					
Ph	M	29	57·3	1	35·6	14·6	45·0	27·8	0–2	5,280	3,175	2,475	10,800
				2	14·0	19·5	34·5	17·9	2–4	2,540	3,025	1,465	3,130
				4	2·2	7·3	17·0	4·6	4–6	590	615	710	1,160
				6	0·6	1·4	7·8	0·7					
Ea	M	28	73·5	1	32·7	12·3	16·5	12·0	0–2	6,430	3,015	1,880	3,545
				2	15·1	21·8	42·9	25·5	2–4	1,095	3,320	Lost	3,305
				4	2·5	4·3	13·7	7·6	4–6	4,395	1,175	1,140	1,260
				6	0·5	1·9	5·9	1·2					
Go	M	31	70·0	1	30·8	14·2	35·1		0–2	8,230	3,865	2,740	
				2	12·6	20·7	34·9	—	2–4	3,495	5,280	3,525	—
				4	1·6	7·9	12·8		4–6	735	1,075	1,300	
				6	0·5	1·1	5·9						
Cu	M	36	79·1	1	31·4	18·0	19·7		0–2	8,985	9,760	2,425	
				2	16·0	20·2	35·1	—	2–4	7,055	8,465	4,275	—
				4	2·8	6·7	17·8		4–6	2,080	1,855	1,980	
				6	0·5	1·3	9·7						
Hu	F	25	60·4	1				43·6	0–2				7,450
				2	—	—	—	32·3	2–4	—	—	—	515
				4				5·4	4–6				318
				6				1·3					
Ca	M	26	66·4	1				27·3	0–2				5,960
				2	—	—	—	34·1	2–4	—	—	—	4,760
				4				6·3	4–6				885
				6				0·7					

Clearance studies: experiment E

It is always difficult to measure clearance rates of drugs given orally because the serum level varies during the duration of the urine collection. For this reason we chose the situation which, from results of experiments A to D, seemed to give the most constant level—that is, 1 g cephalexin taken after a standard breakfast with

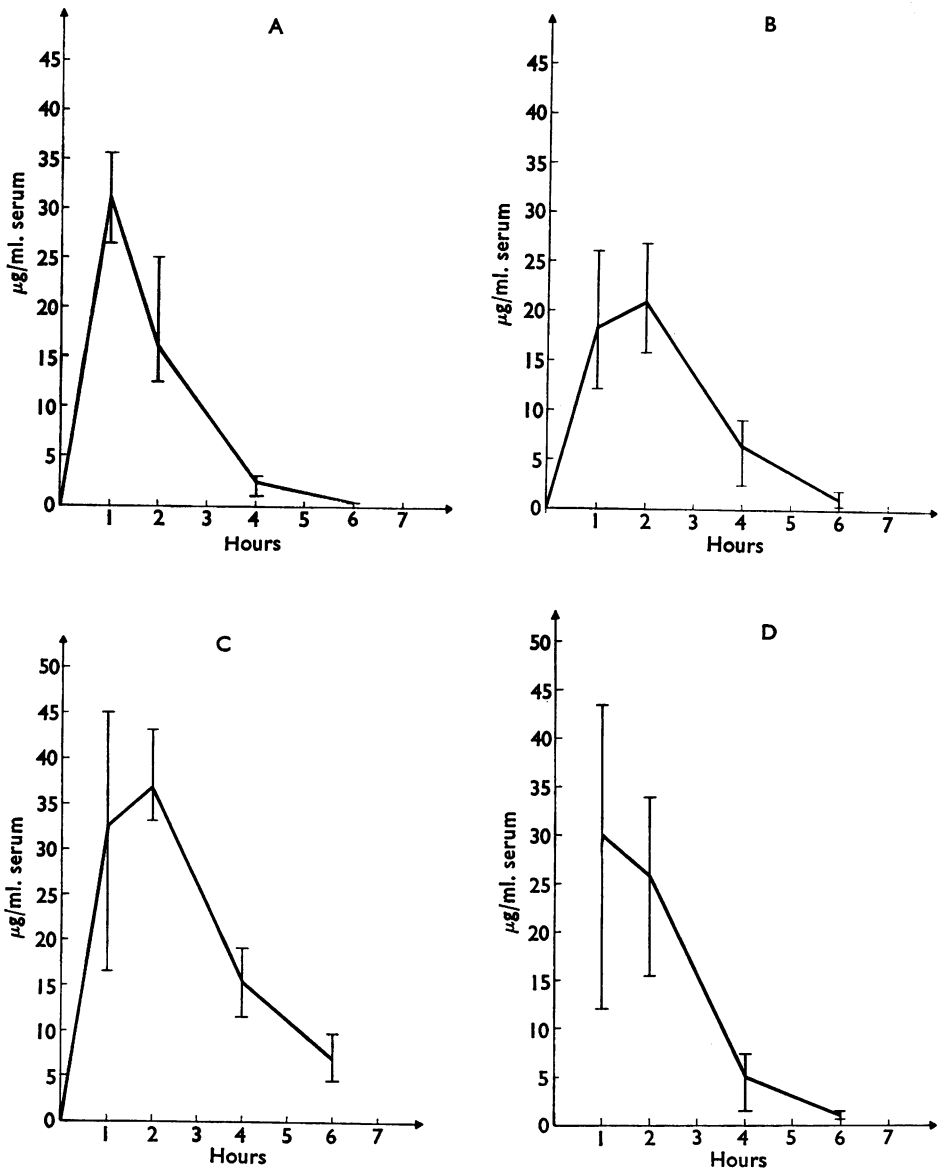


FIG. 2A–D. Serum levels of cephalexin. A, after 1 g oral dose taken before meals; B, after 1 g oral dose taken immediately after a meal; C, after 1 g oral dose taken with 0·5 g probenecid; D, after 1 g oral dose taken every 6 hr for 24 hr. All diagrams are average level and scatter in six volunteers.

blood samples collected 1 and 2 hr later (see Fig. 2B). Despite these precautions, however, of the three volunteers taking part in this clearance study only one was suitable to measure the clearance of cephalexin (volunteer Go), who maintained a serum level between 20·1 and 23·7 μg/ml. Corresponding levels for the other two volunteers were 37·3 μg/ml. at 1 hr and 15·6 μg/ml. at 2 hr in one; 38·9 μg/ml. and 13·1 μg/ml., respectively, in the other. All these levels and the corresponding urine concentrations were similar to those described in experiments A–D. The clearance of cephalexin was 376 ml./min in the one suitable individual, using a mean serum cephalexin value of 21·9 μg/ml., compared with a simultaneous creatinine clearance of 134 ml./min.

Table 2 shows the excretion rate per hour of urinary red cells and leucocytes in the three control periods and on the day cephalexin was given. There was no signi-

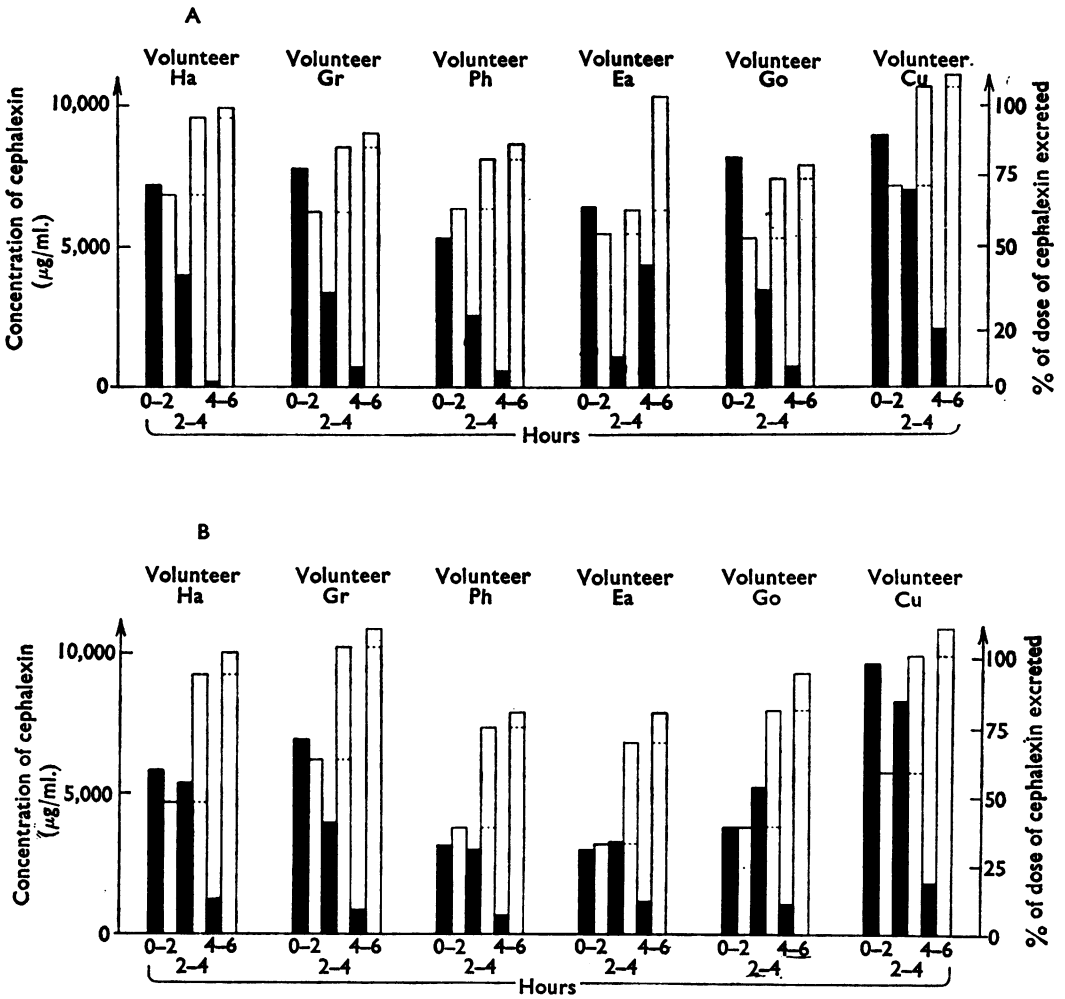


FIG. 3. Legend for A and B on page 744.

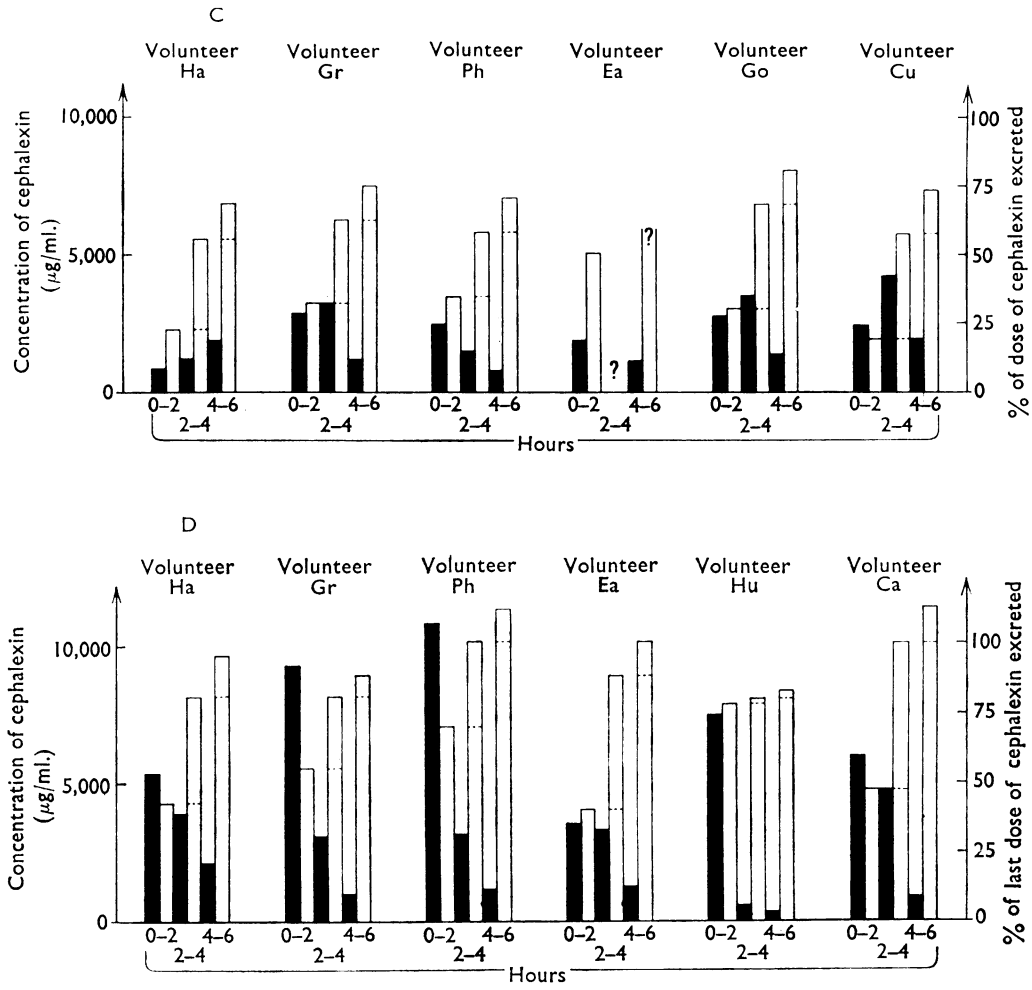


FIG. 3. Individual urine concentrations of cephalexin and cumulative percentage of dose excreted following 1 g oral dose in man—A, fasting; B, after a "standard" breakfast; C, with fifth dose of probenecid (0·5 g every 6 hr for five doses); D, following the last of five doses of 1 g cephalexin every 6 hr. ■, Concentration of cephalexin in urine of each volunteer during each 2 hr collection period. □, A-C, Cumulative percentage of dose of cephalexin excreted by each volunteer; □, D, amount of cephalexin excreted in each 2 hr collection period as percentage of last dose.

TABLE 2. *Effect of cephalexin on urinary cellular excretion—means and ranges (in parentheses)*

Volunteer	Before cephalexin: Leucocytes (per hr)	Before cephalexin: Red blood cells (per hr)	Before cephalexin: Protein	After cephalexin: Leucocytes (per hr)	After cephalexin: Red blood cells (per hr)	After cephalexin: Protein
Go	32,000 (nil–40,000)	16,000 (nil–40,000)	Nil	19,300 (14,000–25,600)	14,400 (4,700–26,200)	Nil
Ca	8,600 (nil–14,000)	8,600 (nil–16,000)	Nil	16,000 (3,000–23,000)	5,900 (nil–13,200)	Nil
Ta	3,300 (nil–10,000)	48,300 (5,000–100,000)	Nil	7,700 (0–18,000)	19,000 (5,600–36,000)	Nil

ficant difference in the urinary excretion rates following cephalexin. All results are within normal limits of cellular excretion for normal males. No protein, casts or crystals were found before or after cephalexin.

The drug was tolerated well by all volunteers taking part in these experiments.

Discussion

Griffith & Black (1968) reported serum and urine levels of cephalexin in both fasting humans and following a standard meal or probenecid. Our results are in close agreement with theirs, except that our volunteers were able to clear the antibiotic from the serum more quickly, although mean peak levels were similar. Perkins *et al.* (1968) have reported serum levels in normal volunteers following an overnight fast. The mean peak level following 1 g in their series was 25 μg/ml. (lower than in our series); however, 4 hr and 6 hr levels were similar. Consequently, the serum half life in fasting subjects in our series is less than it would be if it was calculated from data presented by these other investigators. The percentage absorption of cephalexin as measured by urinary recovery was not affected by food. This is in contrast to some other commonly used oral antibiotics. The absorption of benzyl penicillin is reduced when a dose is given closely related in time to a meal because of increased destruction by gastric acid (Weiss, Nadel, Eisenberg & Flippin, 1959). Likewise, in the case of the tetracyclines, the concomitant oral administration of calcium, magnesium or aluminium ions, either in the diet or for unrelated medicinal purposes, will adversely affect absorption due to the formation of insoluble complexes (Current Practice, 1968; Mull, 1966; Olson & Riley, 1966). Therapeutic levels are still achieved even under such conditions, however, by penicillin G and the tetracyclines. Our results with probenecid would suggest that this drug may be a useful adjuvant in clinical practice in selected instances.

Significant accumulation of the drug in persons with normal renal function did not occur after five 1 g doses given at intervals of 6 hr. This is confirmed both by comparison of the serum level curves (Fig. 2A with 2D) and the mean urine recovery of 99·3% in experiment D, which is similar to the recoveries following a single dose without probenecid. Accumulation would have been unexpected with a drug having the pharmacological qualities of cephalexin as shown in experiment A.

The peak serum levels of cephalexin are similar to those obtained with the same dose of cephaloridine given intramuscularly (Cohen, Romansky & Johnson, 1965; Currie, 1967; Dennis, Rasch & Hastings, 1965) and greater than that obtained with cephalothin (Naumann, 1967). The serum half life of cephaloridine is, of course, not dependent on food and is slightly longer than that of cephalexin, being 90 min (Kabins & Cohen, 1965; Naumann, 1967), but the serum half life of cephalothin is less, 40 min (Naumann, 1966). Probenecid has a much greater effect on the serum levels of cephalothin than of cephaloridine (Tuano, Brodie & Kirby, 1966; Kaplan, Reisberg & Weinstein, 1967).

The absorption of cephalexin is rapid and must take place from the upper gastrointestinal tract, giving peak levels at 1 hr and, even following food, at 2 hr. As nearly 100% is recovered unchanged in the urine the percentage of the dose absorbed is almost total.

For these reasons we may hope that the incidence of gastrointestinal side-effects due to alteration in bowel flora will be, at least, very low, and resistance patterns less liable to develop.

Following 1 g, urine concentrations reach very high levels (5,000–10,000 μg/ml.). so cephalexin should be a useful compound in the management of urinary infections.

The clearance of cephalexin obtained from one volunteer was 376 ml./min and the simultaneous creatinine clearance was 134 ml./min. This gives a ratio of 2·6 for cephalexin clearance/creatinine clearance and compares with 0·75 (Pryor, Joekes & Foord, 1967) to 0·9 (Tuano *et al.*, 1966) for cephaloridine, 1·8 for cephalothin (Tuano *et al.*, 1966) and 4–8 for penicillin G (Kunin, 1967). The result indicates that the antibiotic must be actively secreted by the tubules and the data from the experiments using probenecid support this view.

Despite the high urinary concentration the excretion of leucocytes and red cells did not change after the administration of the drug. In addition no casts, crystals or protein were found.

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