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THE EFFECT OF PROBENECID ON THE PHARMACOKINETICS AND DISTRIBUTION OF CEFOXITIN IN HEALTHY VOLUNTEERS

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1 Cefoxitin was given by acute intravenous injection to six healthy volunteers, in a crossover study to investigate the effects of concurrent probenecid administration.

2 Serum antibiotic concentrations were determined by microbiological assay. Cefoxitin concentrations were simultaneously determined in the fluid of blisters produced by topical cantharides. All antibiotic was accounted for in the urine.

3 Cefoxitin was administered by intravenous infusion, subsequent to a loading dose, to produce steady state levels in the region of 10 μg/ml, in one volunteer. The procedure was later repeated after prior administration of probenecid in the same subject.

4 Pharmacokinetic analyses indicated significant changes only in the parameters associated with renal excretion of drug. Clearance was reduced by half.

5 The absolute and relative amounts of antibiotic in the central and peripheral compartments were calculated for both modes of administration. In the acute study probenecid produced a small change in distribution away from the peripheral or tissue compartment, towards the central compartment.

6 There was no elevation of initial serum concentrations and sustained levels of antibiotic could be accounted for principally by retarded excretion produced by probenecid, with little contribution by alteration in the disposition of antibiotic.

7 The sustained serum levels of cefoxitin that resulted from its decreased excretion were also reflected in blister fluid. It was concluded that the sustained cefoxitin levels produced by probenecid resulted in similar raised levels in the peripheral or 'tissue' compartment, since the redistribution away from the peripheral compartment did not contribute materially to other changes in disposition of drug.

Introduction

Probenecid has been used for many years to increase the circulating levels of penicillin during therapy. It thus affords a reduction in the size or frequency of dosage, or may permit the use of effectice single-dose antibiotic therapy. The latter is accepted as appropriate therapy, particularly in the treatment of uncomplicated gonorrhoea.

Cefoxitin, a β-lactamase-stable cephalosporin (Birnbaum, Stapley, Miller, Wallick, Hendlin & Woodruff, 1978), has been successfully used in the treatment of abdominal sepsis (Geddes & Wilcox, 1978; Reeves, Bint, Holt & Stocks, 1978; Wilson, Leung & Williams, 1978). However, fairly high serum levels were required, the drug has a short half-life, and large doses were therefore used. To reduce the cost and inconvenience of relatively large doses we decided to investigate the effect of probenecid on the kinetics of cefoxitin since the former drug had already been reported to considerably extend the half-life of this drug (Goodwin, Rafter, Goldberg, Skeggs, Till & Martin, 1974). We were however concerned by theoretical reports that probenecid apparently restricted the distribution of penicillin-like drugs (Gibaldi & Schwartz, 1968; Gibaldi, Davidson, Plant & Schwartz, 1970), with the obvious implication that higher serum concentrations would not necessarily reflect a proportionate increase in higher concentrations at the site of infection. We therefore decided to undertake an appropriately detailed pharmacokinetic study of cefoxitin in human volunteers in order to examine this phenomenon. We also examined cefoxitin concentrations in the fluid of skin blisters in

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the hope of confirming, or otherwise, any theoretical findings of the effects of probenecid on the distribution of cefoxitin.

Methods

Volunteers

All six subjects, who gave their informed consent, were male members of the laboratory staff with a mean weight of 69.4 kg (64–82), a mean height of 1.74 m (1.70–1.83) and a mean age of 35.7 years (24–49). None had a history of renal or hepatic disease, nor were they receiving any drugs. None were deficient of G6-PD and could therefore take probenecid safely.

Protocol

(1) *Bolus intravenous injection* Fasted subjects arrived at the laboratory in the morning and were required to remain at rest during the first 90 min of the experiment. The intravenous dose of 2.05 g was dissolved in 10 ml of sterile water and given over 3 min between 09.00 and 09.30 h. Samples of venous blood were taken for assay before drug administration and subsequently at intervals of 15, 30, 45, 60, 90, 120, 180, 240 and 300 min. A sample of urine was taken before giving drug and collections were then made over the periods 0–2, 2–4, 4–6, 6–12, and 12–24 h. The procedure was carried out with and without prior administration of probenecid, with at least 7 days elasping between experiments. Probenecid was allocated to subjects on a randomised basis as described later.

(ii) *Continuous intravenous infusion* It was decided to study the pharmacokinetics of cefoxitin by infusion in the presence and absence of probenecid, in one (70 kg) subject who had participated in the acute study. A bolus loading dose of cefoxitin was followed by infusion at a steady rate in order to rapidly produce a constant serum level sustained over at least 3 h. The doses and rates were calculated from the results obtained from the bolus injection. The conditions and doses of probenecid were the same as those in the bolus injection study, with 2 weeks elapsing between the two infusions. Cefoxitin (2.05 g/l) in 0.9% saline was infused via an indwelling intravenous steel cannual using an IVAC pump. Without probenecid the bolus was 78 mg (38 ml) and the infusion rate 123 mg (60 ml) h^{-1}. With probenecid the bolus was 78 mg (38 ml) and the infusion rate 70 mg (34 ml) h^{-1}. Blood samples were drawn every 30 min via a heparinised intravenous cannula in the opposite arm. Serum assays were rapidly performed by a high pressure liquid chromatographic technique, to confirm the presence of steady-state conditions. Urine was collected hourly for the first 6 h, 2 hourly for 6 h, and finally a 12 h pooled sample was obtained. All samples were assayed by the HPLC method.

Drugs

Cefoxitin (Batch No. C-E935), used as the sodium salt, was administered in the bolus study in doses of 2.05 g (being the actual content of two nominal 1 g ampoules). It was obtained as a gift from Merck Sharp and Dohme, U.K. Probenecid (500 mg tablets) was given orally in individual doses of 500 mg at 21, 11 and 2 h before cefoxitin administration and at 6 and 12 h afterwards.

Blister technique

A blister was raised on the flexor surface of the forearm following the technique of Simon (1973). On the evening before the cefoxitin was administered, at 20.00 h, a piece of cantharides plaster 1 × 1 cm was strapped loosely on to the skin. This resulted in a good blister being present the next morning. The blister was covered with a spray-on plastic dressing and sampled at appropriate times by puncturing the skin with a fine needle. The ensuing drop of fluid was taken directly onto an antibiotic assay paper disc, saturating it, then blotting the excess in the normal fashion for assay.

Storage of samples

All serum and urine samples, and blister-fluid assay discs were stored at −20°C.

Assay methods

(i) *Microbiological technique* Cefoxitin was assayed in serum and urine using the large plate technique. Working standards for serum assays were prepared in pooled human serum, and for urine assays in pH 7.4 phosphate buffer. Serum samples were assayed undiluted. Urine samples were diluted as necessary in phosphate buffer. The agar was Penassay seed agar (Difco) and the indicator organism *B. subtilis* NCTC 10400. Doses were applied in triplicate to plates with 6 mm diameter blotting paper discs (Whatman Biochemicals Limited). The 95% confidence limits for the assay were 10–15%. Plates were read on an optical zone reader and the zone sizes converted to concentrations using the method of Bennett, Brodie, Benner & Kirby (1966).

(ii) *High Pressure Liquid Chromatography (HPLC)* Serum samples were deproteinized by adding an equal quantity of acetonitrile, mixing, and centrifugation. The supernatant was injected directly into

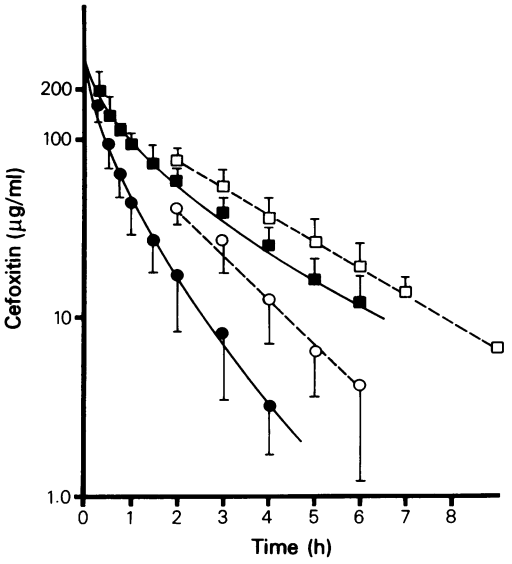

Figure 1 Mean serum and blister fluid levels of cefoxitin following an i.v. bolus of 2.05 g. ● and ■ represent serum levels in the absence and presence of probenecid respectively. ○ and □ represent blister fluid levels in the absence and presence of probenecid, respectively. Lines are fitted by least squares, and vertical bars indicate the s.d.

the mobile phase. Urine samples were centrifuged to remove particulate matter and diluted with water before injection. The apparatus used was as Waters Associates liquid chromatograph with a model 440 UV detector (254 nm) set at 0.005 AUFS. The analytical column (Microbondapak C_{18}) was protected by a guard column (C_{18} Corasil). The mobile phase was methanol:water:acetic acid 42:57:1 (flow rate 2 ml/min). The retention time of cefoxitin was 3.5 min and recovery from serum was 98–100%.

Pharmacokinetic analysis

Non-linear regression analysis of individual serum profiles obtained after a bolus injection of cefoxitin showed each to decay in a bi-exponential fashion. The curves were fitted with a high degree of correlation (r^2~0.999). All of the administered drug was accounted for in unchanged form in the urine. Accordingly, the pharmacokinetic parameters were derived on the basis of a two compartment open model with no metabolism occurring, and with excretion taking place from the central compartment, as described by the equation $C_p^t = Ae^{-\alpha t} + Be^{-\beta t}$ where C_p^t is the plasma concentration at time t, and A and B are the intercepts on the concentration axis, and α and β are the redistribution and plasma elimination rates respectively. The fraction of administered cefoxitin present in the peripheral and central compartments and the absolute quantities of drug present in each compartment after bolus introduction were derived by the methods described by Gibaldi & Perrier (1975). The corresponding fractions and quantities of cefoxitin in the two compartments during and after infusion were calculated by the methods described by Gibaldi (1969).

Results

Acute administration

Serum and blister fluid concentration-time profiles of cefoxitin are illustrated in Figure 1 and the urinary excretion profiles of unchanged cefoxitin are illustrated in Figure 2. It can readily be seen that probenecid markedly reduced the decay of serum cefoxitin concentration over the whole period of the investigation. The rate of excretion of unchanged cefoxitin in urine was correspondingly decreased. The recovery of unchanged cefoxitin in the urine amounted to 96–101% whether or not probenecid had been administered.

The mean results of pharmacokinetic analyses are shown in Table 1. It is seen that there is no other significant change introduced by prior probenecid administration apart from the very marked alterations in all the parameters associated with excretion. Thus the rate of plasma clearance was approximately halved by administration of probenecid and, correspondingly,

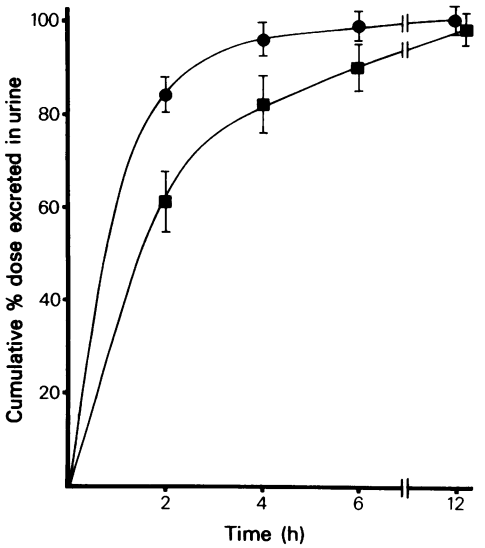

Figure 2 Cumulative urinary excretion of cefoxitin (mean ± s.d.) with (■) and without (●) probenecid expressed as percentage of administered dose.

Table 1 The effect of probenecid on cefoxitin kinetic constants (mean ± s.d.)

	Without probenecid	*With probenecid*	P
$T_{½}\alpha$ (h)	0.16 ± 0.02	0.18 ± 0.06	NS
$T_{½}\beta$ (h)	0.81 ± 0.07	1.53 ± 0.17	< 0.01
α (h^{-1})	4.80 ± 1.65	4.56 ± 2.36	NS
β (h^{-1})	0.86 ± 0.07	0.46 ± 0.05	< 0.01
A (μg/ml)	309 ± 123	183 ± 115	< 0.1
B (μg/ml)	102 ± 40.6	150 ± 108	NS
C^o_p (μg/ml)	410 ± 133	333 ± 120	NS
Area under curve	182 ± 41.8	371 ± 49	< 0.01
Apparent central volume (l)	5.64 ± 1.99	6.94 ± 2.28	NS
Apparent peripheral volume (l)	14.04 ± 3.21	12.63 ± 1.22	NS
Steady state volume (V_d ss) (l)	9.28 ± 1.98	11.49 ± 1.35	NS
Clearance (ml/min)	200 ± 40	96 ± 15	< 0.01
k_{10} (h^{-1})	2.28 ± 0.73	0.88 ± 0.21	< 0.01
k_{12} (h^{-1})	1.55 ± 0.83	1.91 ± 1.80	NS
k_{21} (h^{-1})	1.83 ± 0.46	2.24 ± 0.39	NS

the areas under the curve doubled. The particular parameters which might reflect gross changes in distribution, e.g, the serum half-life in the α phase and the apparent volumes of distribution, were not significantly changed.

Comparisons of the proportions of drug present in the two compartments are illustrated in Figure 3. The curves represent the calculated fractions of the drug present in each compartment following an i.v. bolus of 2.05 g. The data used for calculation were derived from the mean computer fitted profile (Figure 1). The ratios of drug in each compartment are listed in Table 2. It can be seen that after equilibration the proportion of drug in the peripheral compartment was slightly greater than that in the central compartment in the absence of probenecid. With concurrent administration of probenecid the proportion of antibiotic present in the peripheral compartment became slightly less in the post equilibration stage. By way of detailed comparison the actual quantity of drug in each compartment was calculated at a serum level of 10 μg/ml. This level was chosen since it represents a desirable therapeutic level. Without probenecid, at this serum level, i.e. 2.6 hr post-administration, the total amount of drug remaining in the body was 151 mg or 7.2% of the original bolus, of which 42% i.e. 63 mg, was present in the central compartment and 58%, i.e. 88 mg, was in the peripheral or 'tissue' compartment. Hence the partition between central and peripheral compartments was 0.73. Where probenecid was present the serum level had decreased to 10 μg/ml at 4.35 h. At this time, 151 mg drug remained of which 52% or 78 mg was in the central compartment and 48% of 72 mg was in the 'tissue' compartment. The partition ratio had therefore changed to 1.07.

The relationship between the mean serum concentrations and mean blister fluid concentrations of cefoxitin (Figure 1) showed that the higher serum concentrations that resulted when probenecid was co-administered paralleled those found in blister fluid. Four of the blister fluids were examined to determine their nature. Total protein values in four fluids were 54, 61, 50 and 55 g/l (normal value for serum 62–80 g/l). Electrophoresis showed a slight excess of β globulin in two cases, but never an excess

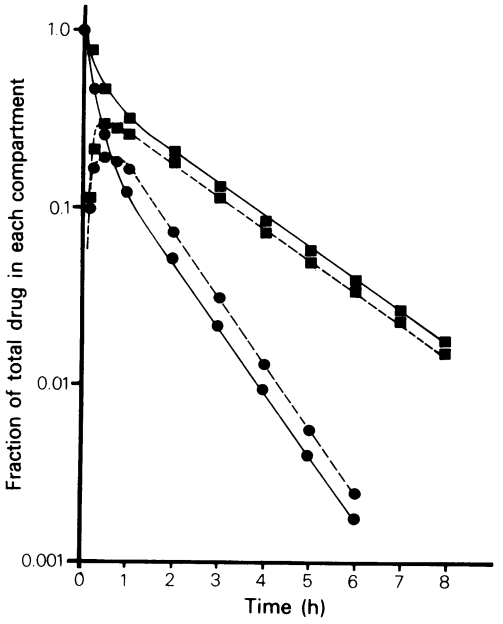

Figure 3 Calculated fraction of cefoxitin present in central (——) and peripheral or 'tissue' (– – –) compartments following an i.v. bolus of 2.05 g cefoxitin. ● and ■ represent absence and presence of probenecid respectively.

Table 2 Fraction of original bolus remaining in central (A1/A1°) and peripheral (A2/A1°) compartments, and fraction of total drug present in each compartment (f_c & f_p).

Time (h)	*Without probenecid* A1/A1°	A2/A1°	f_c	f_p	f_c/f_p	*With probenecid* A1/A1°	A2/A1°	f_c	f_p	f_c/f_p
0	1.0	0.0	1.0	0.0	1.0	1.0	0.0	1.0	0.0	1.0
0.25	0.48	0.17	0.733	0.267	2.74	0.63	0.21	0.748	0.252	2.97
0.5	0.27	0.20	0.572	0.428	1.34	0.46	0.28	0.623	0.377	1.65
0.75	0.18	0.18	0.491	0.509	0.96	0.37	0.28	0.564	0.436	1.29
1.0	0.13	0.16	0.453	0.547	0.83	0.31	0.27	0.538	0.462	1.16
2.0	0.051	0.069	0.424	0.576	0.74	0.20	0.19	0.517	0.483	1.07
2.6	0.030	0.042	0.423	0.577	0.73	0.154	0.145	0.516	0.484	1.07
3.0	0.022	0.030	0.423	0.577	0.73	0.130	0.120	0.516	0.484	1.07
4.0	0.0092	0.013	0.423	0.577	0.73	0.086	0.081	0.516	0.484	1.07
5.0	0.0039	0.005	0.423	0.577	0.73	0.057	0.053	0.516	0.484	1.07
6.0	0.0017	0.002	0.423	0.577	0.73	0.038	0.035	0.516	0.484	1.07
6.5						0.034	0.029	0.516	0.484	1.07
7.0						0.025	0.023	0.516	0.484	1.07
8.0						0.016	0.015	0.516	0.484	1.07
9.0						0.011	0.010	0.516	0.484	1.07

of albumin. All cell counts were in the region of 10,000/mm³, mostly as polymorphonuclear leucocytes. These data indicated that the blister contents corresponded to an inflammatory type of fluid.

Steady state infusion

In the single volunteer given cefoxitin by constant infusion the final steady state serum concentrations were designed to be 10 μg/ml, so that direct comparison could be made with the acute administration experiment. With probenecid a mean value of 9.8 μg/ml was achieved after 2 h and subsequently maintained for 3 h and, without probenecid, after 1 h a mean value 8.3 μg/ml was achieved and maintained for 3 h (Figure 4). The calculated quantities of drug present in each compartment are plotted (Figure 4) showing the effect of probenecid on the distribution of cefoxitin under true steady state infusion conditions. Under these circumstances the proportion of drug in the central compartment was slightly larger than that in the tissue compartment regardless of whether probenecid was present or not. The ratio of central to peripheral amounts was 1.18. When the infusion was stopped the relative greater proportion in the central compartment very rapidly decreased to values approximating those in an acute administration.

Discussion

It is generally accepted that probenecid reduces the rate of excretion of penicillin-like compounds by competing for the site of active transport in the renal tubule (Weinstein, 1965). A similar effect is seen with other weak acids but not with basic drugs such as gentamycin (Bergan, Weslie & Brodwall, 1972). More recently the concept has arisen that the elevated and more sustained levels that result from co-administration of probenecid and penicillin-like antibiotics cannot wholly be accounted for by renal mechanisms (Gibaldi & Schwartz, 1968; Gibaldi *et*

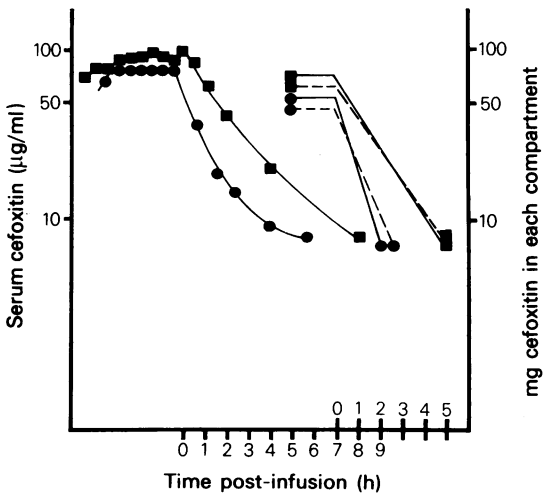

Figure 4 Infusion and post infusion serum levels of cefoxitin and calculated amount of drug present in central and tissue compartments. Left-hand curves, ● and ■ represent serum drug levels without and with probenecid respectively. Infusion data are listed in text. Right-hand curves represent the quantity of drug (mg) present in —— central compartment and - - - peripheral or 'tissue' compartment. ● and ■ represent without and with probenecid respectively.

al., 1969). The main basis for the conclusion was that the volume of distribution appeared to be significantly altered with prior probenecid administration. However, volumes of distribution do not necessarily have any practical or physiological basis and erroneous methods have been used in their evaluation (Riegelman, Loo & Rowland, 1968). Furthermore, all the antibiotics studied were metabolised to varying extents.

It had been suggested that probenecid produced a significant redistribution, away from the peripheral or tissue compartment. This concept is important from a therapeutic point of view since it implies that there is the possibility that probenecid might reduce tissue concentrations, despite a higher plasma concentration. The concept has not been considered for steady state or infusion conditions. Very recently it was noted that probenecid raised the serum levels of orally administered cephradine and cefaclor, in addition to retarding their excretion (Welling, Dean, Selen, Kendall & Wise, 1979).

The current study is of special value since, unlike other reports on this problem, there is a complete absence of either biliary excretion or hepatic or renal metabolism. Cefoxitin thus provides a more direct probe for evaluating the problem.

The kinetic parameters listed in Table 1 show that there appeared to be no significant change produced by probenecid except on the expected values associated with excretion. The mean clearance rate of 200 ml/min without probenecid is consistent with active secretion in the renal tubule (in comparison with inulin clearance) and this is reduced to half in the presence of probenecid. There was very close agreement of clearance values whether calculated for acute loading or for continuous infusion. The halving of the clearance rate by probenecid could thus account for the doubling of the area under the curve.

Nevertheless, the study was taken further to consider two other factors. The distribution of cefoxitin between the two kinetic compartments was calculated in order to provide data that might show variations with time of the partition of the drug between the two compartments. The ratio of the varying quantity of drug in each compartment following an i.v. bolus administration (as shown in Table 2) indicates a small alteration in disposition in that probenecid appeared to decrease the proportion of drug in the peripheral compartment. However, in terms of the magnitude by which probenecid sustained the circulating levels of antibiotic, this small change in distribution does not appear to be of therapeutic significance.

The study was extended to the different situation where drug was infused to produce a constant serum level, or steady-state condition. Since the actual results corresponded closely to a predicted level of 10 μg/ml this provided additional confirmation of the absence of significant changes in redistribution and the reliability of the theoretical considerations. The relative amounts of drug distributed between the two compartments at steady-state infusion conditions are different than those during the pseudo-equilibrium that results after the distribution phase has disappeared following an acute administration, primarily because the two compartment system 'collapses' into a one compartment system at true steady-state conditions (Gibaldi, 1969). Thus there can be no alpha phase until the infusion is stopped. As far as administration of cefoxitin by infusion is concerned the therapeutic implications are also clear. By prior administration of probenecid it is possible to reduce the quantity of cefoxitin infused by approximately half and still produce an equivalent plasma level of 10 μg/ml without decreasing the 'tissue' concentration. Unlike that in an acute administration the amount of drug in the peripheral or 'tissue' compartment is slightly greater than that in the central compartment whether or not probenecid has been used. The concentrations of drug in various tissues will obviously vary since the peripheral compartment represents a kinetic average of all those tissues and organs that are less easily perfused than the central compartment. But it can be assumed that a proportionate increase in all these concentrations will result from an overall increase in the serum concentration.

From a scientific point of view the shift away from the peripheral compartment as predicted by Gibaldi *et al.* (1970) has been demonstrated, but the effects of this are very small when compared to the consequences of reduced renal excretion. The examination of the cefoxitin content of the blister fluids might be considered to represent one means, albeit imperfect, of investigating such changes in the peripheral compartment.

From a therapeutic point of view, probenecid had no practical effect on the tissue distribution of cefoxitin in healthy subjects, and that the sustained serum concentrations were principally the result of diminished renal clearance. This occurs whether the antibiotic is administered acutely, as multiple injections, or by infusion and can explain the improved clinical success seen when these two drugs are combined.

Reprint requests should be addressed to Dr D.P. Thornhill.

References

BENNETT, J.V., BRODIE, J.L., BENNER, E.J. & KIRBY, W.M.M. (1966). Simplified, accurate method for antibiotic assay of clinical specimens. *Appl. Microbiol.*, **14**, 170–177.

BERGAN, T., WESLIE, L. & BRODWALL, E.K. (1972). Influence of probenecid on gentamicin pharmacokinetics. *Acta med. scand.*, **191**, 221–224.

BIRNBAUM, J., STAPLEY, E.O., MILLER, A.K., WALLICK, H., HENDLIN, D. & WOODRUFF, H.B. (1978). Cefoxitin, a semisynthetic cephamycin: a microbiological overview. *J. Antimicrob. Chemother.*, **4**, (Suppl. B), 15–32.

GEDDES, A.M. & WILCOX, R.M.L. (1978). Cefoxitin in abdominal sepsis. *J. Antimicrob. Chemother.*, **4** (Suppl. B), 151–153.

GIBALDI, M. (1969). Effect of mode of administration on drug distribution in a two-compartment open system. *J. pharm. Sci.*, **58**, 327–331.

GIBALDI, M., DAVIDSON, D., PLAUT, M.E. & SCHWARTZ, M.A. (1970). Modification of penicillin distribution and elimination by probenecid. *Int. J. clin. Pharmac.*, **3**, 182–189.

GIBALDI, M. & PERRIER, D. (1975). *Pharmacokinetics*, pp. 45–89. New York: Marcel Dekker.

GIBALDI, M. & SCHWARTZ, M.A. (1968). Apparent effect of probenecid on the distribution of penicillins in man. *Clin. Pharmac. Ther.*, **9**, 345–349.

GOODWIN, C.S., RAFTER, E.B., GOLDBERG, A.D., SKEGGS, H., TILL, A.G. & MARTIN, C.M. (1974). Effect of rate of infusion and probenecid on serum levels, renal excretion and tolerance of intravenous doses of cefoxitin in humans: comparison with cephalothin. *Antimicrobial Agents Chemother.*, **6**, 338–346.

REEVES, D.S., BINT, A.J., HOLT, H.A. & STOCKS, P.J. (1978). Cefoxitin sodium: a clinical and pharmacological study. *J. Antimicrob. Chemother.*, **4**, (Suppl. B), 155–160.

RIEGELMAN, S., LOO, J. & ROWLAND, M. (1968). Concept of a volume of distribution and possible errors in evaluation of this parameter. *J. pharm. Sci.*, **57**, 128–133.

RODRIGUEZ, N., MADSEN, P.O. & WELLING, P.G. (1979). Influence of probenecid on serum levels and urinary excretion of cinoxacin. *Antimicrobial Agents Chemother.*, **15**, 465–469.

SIMON, C., MALERCZYK, V., BRAHMSTAEDT, E. & TOELLER, W. (1973). Cefazolin, ein neues Breitspektrum-Antibiotikum. *Deutsche Med. Wochenschrift*, **98**, 2448–51.

SPECTOR, R. & LORENZO, A.V. (1974). Inhibition of penicillin transport from the cerebrospinal fluid after intracisternal inoculation of bacteria. *J. clin. Invest.*, **54**, 316–325.

WEINSTEIN, L. (1965). Penicillin. In *The pharmacological basis of therapeutics*, eds. Goodman, L.S. & Gilman, A. pp. 1193–1229. 3rd ed. New York: Macmillan.

WELLING, P.G., DEAN S., SELEN, A., KENDALL, M.J. & WISE, R. (1979). Probenecid: an unexplained effect on cephalosporin pharmacology. *Br. J. clin. Pharmac.*, **8**, 491–495.

WILSON, P., LEUNG, T. & WILLIAMS, J.D. (1978). Antibacterial activity, pharmacokinetics and efficacy of cefoxitin in patients with abdominal sepsis and other infections. *J. Antimicrob. Chemother.*, **4**, (Suppl. B), 127–141.

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