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Pharmacokinetics of Bacampicillin and Bacmecillinam in Plasma and Peripheral Lymph

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Summary

The pharmacokinetics of tablets containing equimolar amounts of bacampicillin and bacmecillinam totalling 500 mg were studied in healthy volunteers. Bacampicillin and bacmecillinam are prodrugs which hydrolyse completely upon absorption to give ampicillin and mecillinam respectively. The concentrations of ampicillin and mecillinam were determined in serum, peripheral lymph and urine. Both substances were found to invade lymph more slowly than serum and also to remain in the former somewhat longer. There were also longer lag time values for lymph than for serum, lasting 0.7 hours for both compounds after the first dose and 0.5 hours after the 7th dose. The elimination half-life was around one hour for both antibiotics and sites, the individual values usually longer for lymph than for serum. After 7 doses, the levels were of the same order as after one dose. The peak concentrations in lymph were approximately half of those in serum and appeared somewhat later than in serum. The mean (± SD) curve peaks in lymph for ampicillin were 2.3 ± 0.7 and 2.1 ± 0.4 μg/ml after the first and 7th doses. The corresponding values for mecillinam were 1.6 ± 0.6 and 1.5 ± 0.2 μg/ml. For ampicillin, the areas under the serum curves were 40–50 per cent higher than under the lymph curves, whereas the areas were smaller, although similar, for mecillinam in both types of specimens. The ratio of ampicillin to mecillinam was close to the optimal for antibacterial *in vitro* synergistic activity in serum, lymph, and urine. Penetration into the lymph was satisfactory. This is significant, since lymph levels reflect concentrations obtainable in unmanipulated tissues, which may become infected. Consequently, the design of the fixed combination of equimolecular quantities bacampicillin and bacmecillinam seems suitable from a pharmacokinetic point of view.

Mecillinam is a new semisynthetic beta-lactam antibiotic with an *in vitro* spectrum covering *Enterobacteriaceae* and a few other Gram-negative, rod-shaped bacteria (27). The activity of mecillinam against Gram-positive microbes is low. The mechanism of action is specific binding to penicillin binding protein (PBP) number 2 (26), which is an enzyme participating in the synthesis of cell wall peptidoglycan. No other PBP species is inhibited by mecillinam at usual *in vivo* levels, although some binding to other species may occur with much higher mecillinam concentrations (24). This is in contrast to ampicillin or cephalosporins which also bind to other PBP species having enzyme functions, although their binding to these is less than that of mecillinam to PBP-2. Consequently, mecillinam acts synergistically with other beta-lactam antibiotics (13, 18, 23).

A synergistic action may permit a reduction in dose with retained activity and a widening of the spectrum. Simultaneously, although this may not apply when two compounds with at least partial immunological cross reactions, reduction in dose may in general result in fewer adverse effects, as shown for the combination sulfadiazine + trimethoprim compared to sulfamethoxazole + trimethoprim for which a higher dose is required (23). The mutation rate to resistance against mecillinam is high, 10^{-5} (24, 27). When mecillinam is combined with ampicillin, there is less emergence of resistance *in vitro* than observed with either mecillinam alone or with mecillinam + cloxacillin (24). The precise long term effect of resistance to a beta-lactam combination is, however, unknown; beta-lactamase production is one resistance mechanism that would encompass both components. Reduced development of resistance is another reason for choosing ampicillin. Accordingly, investigations on a pharmaceutical composition with a fixed ratio of beta-lactam antibiotics is in progress.

In this combination, ampicillin has been chosen as partner for mecillinam because it allows oral dosage and is active against *Haemophilus influenzae* and streptococci, including enterococci, in addition to its activity against enterobacteria.

In this study, we have investigated the pharmacokinetics of a composition containing the 1′-ethoxycarbonyloxyethyl esters of ampicillin and mecillinam; it consists of their 1-carboxy esters which give improved oral absorption. The tablets contained equimolar amounts of the components; this reflects the optimal ratio of *in vitro* synergy. To study the levels and ratios of the components in the body in relation to their ratio in the composition, serum, peripheral lymph, and urine have been monitored after both acute and chronic dosage. The lymph was sampled to yield better insight into the approximate conditions extracellularly at potential sites of infection.

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Material and Methods

Subjects

Five healthy 20–25 (mean 21.5) years old male volunteers participated in the study. Blood and urine were collected from two more subjects, but lymph flow through the collection system was too low to allow sampling, so their results are not included. The subjects were examined clinically and normal values obtained in the following clinical chemical tests: blood urea nitrogen (BUN), serum creatinine, alkaline phosphatase, bilirubin, lactic dehydrogenase, alanine aminotransferase (ALAT = SGPT), aspartate aminotransferase (ASAT = SGOT), thymol, erythrocyte sedimentation rate (ESR), haemoglobin, chloride, phosphorous, potassium, sodium, leucocyte count, serum electrophoresis, and albumin concentration. None of the subjects had previously had hypersensitive reactions to penicillins and they did not have antibenzylpenicillin IgE as evidenced by the *Rast* technique (antigen disc from Pharmacia AB, Sweden; done at Astra Läkemedel AB, Sweden). The volunteers were thoroughly instructed of the nature and form of the study, gave written consent, and were insured against possible mishaps.

Drug

The combination (preparation code name A 2382) was given as 250 mg tablets containing equimolar amounts of 128 mg of the 1′-ethoxycarbonyloxyethyl ester of ampicillin (bacampicillin) and 122 mg of the 1′-ethoxycarbonylethyl ester of mecillinam (bacmecillinam). Both substances are rapidly hydrolysed upon absorption (2, 3), the former corresponding to 89 mg ampicillin and the latter to 83 mg mecillinam.

Dissolution in artificial stomach juice (USP IXX) was in the range 66-72 per cent after 10 minutes and 96-100 per cent after 20 minutes.

Dosage

Two tablets of A 2382, i.e. 500 mg, were given 8-hourly for 3 days. The first and the 7th doses, which were those studied, were given after overnight fasting for at least 8 hours. The tablets were swallowed with a glass of water, and solid foods allowed only after 2 hours. Carbonated soft drink was allowed ad libitum to enhance lymph flow.

Sampling

The subjects were ambulatory during the study. Serum was sampled at 0, 30, 45, 60, and 90 minutes as well as 2, 3, 5, 7, and 8 hours after drug administration. Lymph was sampled at intervals indicated in the individual curves of Figure 1 and referred in time to the middle of the collection interval. In some instances, less samples were obtained than planned due to insufficient lymph flow. Urine was collected during the periods 0–1.5; 1.5–3; 3–5; and 5–8 hours. Lymph from a superficial lymph vessel on the leg was collected continuously through catheters into test tubes fixed to the leg as described by *Engeset* et al. (12). Both legs were cannulated except in subjects nos. 1 and 3 (Figure 1), and the mean simultaneous concentration for the two legs used. The tubes contained all lymph escaping from the catheter during the preceeding interval. To avoid disturbance from acute reactions, the pharmacokinetic studies started only on the third day after cannulation had been performed.

The samples were frozen to -196°C (liquid N_2) with sufficient quantities of standards in normal pooled human serum and *Sørensen's* phosphate buffer of pH 6.5 to last for all assays. There was no detectable reduction in antibiotic activity in either liquid milieu at this temperature during 7 months.

Assay

The penicillins were assayed microbiologically with strains resistant to one of the antibiotics and sensitive to the other, *Micrococcus luteus* ATCC 9341 for ampicillin and *Klebsiella pneumoniae* No. 44/75 for mecillinam. No synergy was obtained with either strain (*L. Magni,* personal communication, 1978). The strains had been selected and obtained from *L. Magni,* Astra Läkemedel AB, Södertälje,

Fig. 1a

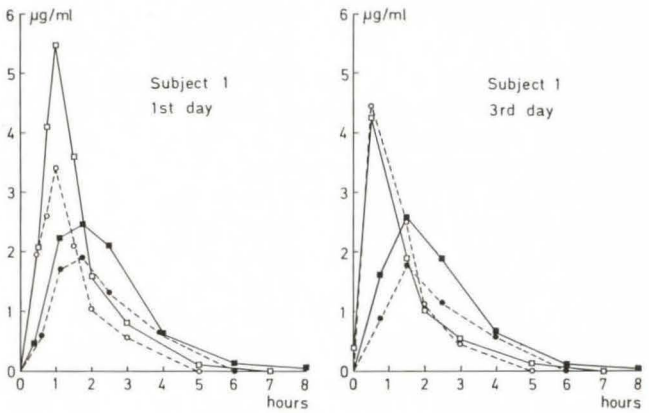

Fig. 1b

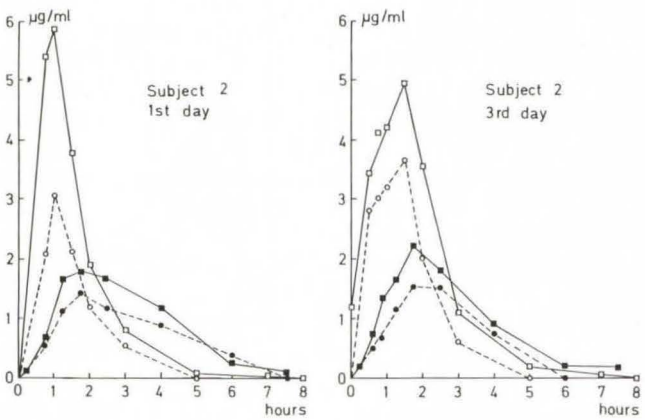

Fig. 1c

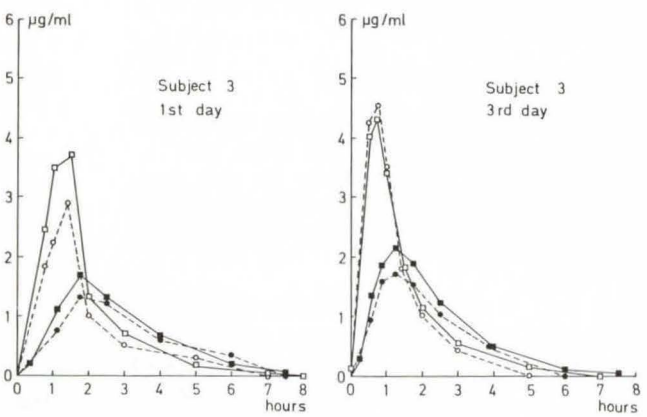

Fig. 1a–e Concentrations in individual healthy subjects of ampicillin and mecillinam in serum and lymph after the first and seventh dose of 500 mg tablets containing bacampicillin and bacmecillinam in an equimolar combination

ampicillin —— { □ serum ■ lymph

mecillinam ------- { ○ serum ● lymph

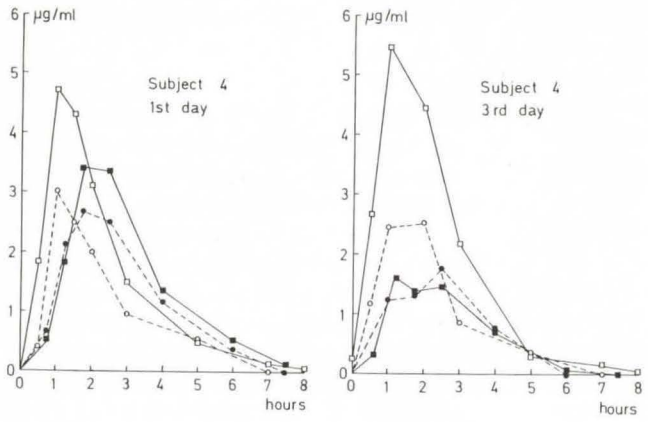

Fig. 1d

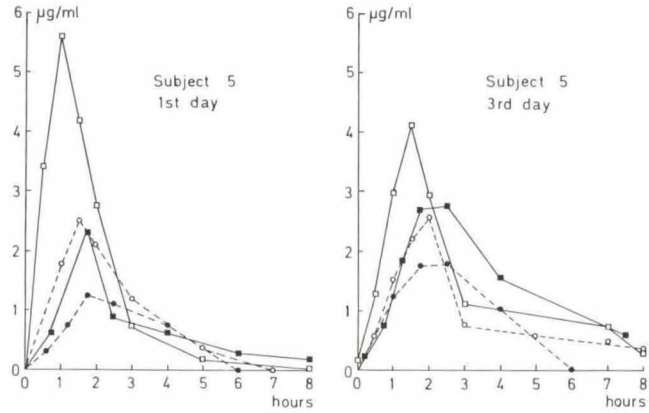

Fig. 1e

Sweden. The agar diffusion method (5) with agar wells was used. The lower limits of sensitivity were 0.02 µg/ml for ampicillin and 0.3 µg/ml for mecillinam.

Pharmacokinetic evaluation

The pharmacokinetic properties were determined according to the first order, one-compartment open model by the data program AUTOAN/NONLIN of *Wagner/Sedman* and *Metzler* (29). The following terminology is used:

k_A = constant of invasion (hour^{-1}) of drug into serum or lymph,

k_E = constant of elimination (hour^{-1}) of drug into serum or lymph,

$t^1/_2$ = half-life (hour) of drug in serum or lymph; $t^1/_2 = 1\,n2/k_E$,

c_0 = hybrid intercept (µg/ml) to time $t = 0$, $c_0 = F \cdot k_E$,

lag = lag time (hour) before appearance of drug in serum or lymph as estimated from curve fitting (AUTOAN/NONLIN),

F = area under the serum of lymph curve till infinity (µg·hour/ml) according to the trapezoidal rule. Final portion of the curve has been estimated as $F'' = c_p^n/k_E$, when the final sample contains a detectable antibiotic concentration, c_p^m.

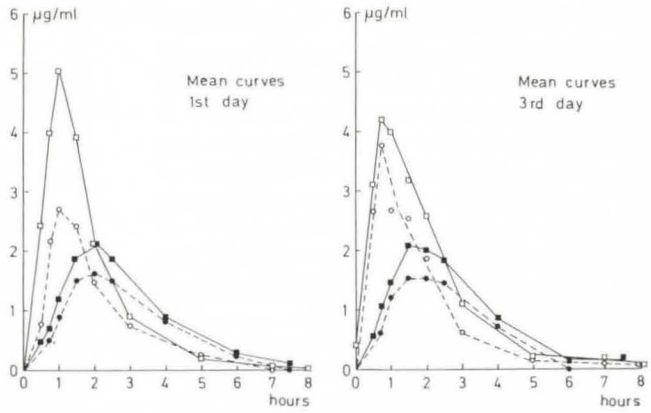

Fig. 2 Mean concentrations of ampicillin and mecillinam in 5 healthy volunteers after the first and seventh dose containing 500 mg tablets of bacampicillin and bacmecillinam in an equimolar combination

ampicillin —— { □ serum ■ lymph

mecillinam ------- { ○ serum ● lymph

Results

Serum and lymph concentrations

The individual concentrations of ampicillin and mecillinam are shown in Figure 1, and mean levels in Figure 2. For all subjects, the ampicillin peaks in serum, and consequently in lymph, are above those of mecillinam after the first dose. After the 7th dose, the mean serum curves of ampicillin and mecillinam are more similar. The central and peripheral levels of both antibiotics are similar after the first and last dose. This is particularly true for lymph in which the levels of the two antibiotics were quite similar throughout the observation period on both days. Accordingly, the mean rations of ampicillin : mecillinam in serum are between 2:1 and 1:1, being closer to the latter on the third day. By comparison, in lymph the ratios are closer to 1:1 on both days (Figure 3). The means and variances of the mean curves are indicated in the Tables 1–2.

One point of significance is the observation that the lymph peaks are lower and occur later than those in serum, and that the antibiotic levels are maintained longer in lymph than in serum.

Urinary recovery

The urinary recovery of active drugs is shown in Figure 4. The total recovery of ampicillin was 74 per cent on the first and 66 per cent on the 3rd day. The respective figures for mecillinam were 70 and 64 per cent.

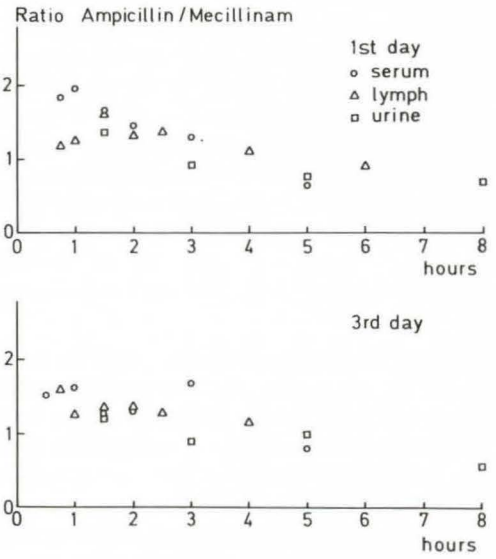

Fig. 3 Ratio of ampicillin : mecillinam concentrations in serum, peripheral lymph and urine after first and seventh dose containing 500 mg tablets of bacampicillin and bacmecillinam in an equimolar combination

The ratio of the components fluctuated around 1:1 in all samples (Figure 3).

Pharmacokinetic characteristics

The pharmacokinetic characteristics of ampicillin and mecillinam in serum and lymph are shown in Tables 3–4.

Table 1 Serum concentrations (μg/ml) of ampicillin and mecillinam after one and seven doses (i.e. on the third day) of 500 mg tablets containing bacampicillin and bacmecillinam in equimolar amounts

	Sampling time (hour)								
Antibiotic, dose no.	0.5	0.75	1.0	1.5	2.0	3.0	5.0	7.0	8.0
Ampicillin, 1st day	2.42 ± 0.85	3.98 ± 1.47	5.02 ± 0.95	3.90 ± 0.30	2.12 ± 0.76	0.90 ± 0.33	0.19 ± 0.16	0.06 ± 0.05	0.02 ± 0.03
Ampicillin, 3rd day	3.11 ± 1.20	4.21 ± 0.12	4.00 ± 1.09	3.18 ± 1.58	2.57 ± 1.47	1.10 ± 0.66	0.18 ± 0.07	0.19 ± 0.31	0.06 ± 0.12
Mecillinam, 1st day	1.15 ± 1.06	2.16 ± 0.38	2.69 ± 0.67	2.41 ± 0.33	1.46 ± 0.53	0.74 ± 0.30	0.24 ± 0.23	< 0.3	< 0.3
Mecillinam, 3rd day	2.64 ± 1.76	3.77 ± 1.09	2.66 ± 0.88	2.53 ± 0.79	1.84 ± 0.74	0.61 ± 0.18	0.46 ± 0.15	0.10	0.07

Table 2 Lymph concentrations (μg/ml) of ampicillin and mecillinam after one and seven doses (i.e. on the third day) of 500 mg tablets containing bacampicillin and bacmecillinam in equimolar amounts

	Sampling time (hour)								
Antibiotic, dose no.	0.5	0.75	1.0	1.5	2.0	2.5	4.0	6.0	7.5
Ampicillin, 1st day	0.47 ± 0.19	0.70 ± 0.26	1.19 ± 0.40	2.32 ± 0.69	2.13 ± 0.75	1.86 ± 0.94	0.90 ± 0.34	0.29 ± 0.14	0.10 ± 0.05
Ampicillin, 3rd day	0.56 ± 0.23	1.07 ± 0.51	1.46 ± 0.47	2.07 ± 0.40	2.01 ± 0.51	1.83 ± 0.58	0.86 ± 0.42	0.13 ± 0.05	0.18 ± 0.25
Mecillinam, 1st day	< 0.3	0.46 ± 0.32	0.88 ± 0.39	1.50 ± 0.59	1.62 ± 0.59	1.49 ± 0.59	0.81 ± 0.22	0.22 ± 0.20	< 0.3
Mecillinam, 3rd day	< 0.3	0.54 ± 0.54	1.21 ± 0.30	1.52 ± 0.20	1.51 ± 0.16	1.45 ± 0.35	0.72 ± 0.20	< 0.3	< 0.3

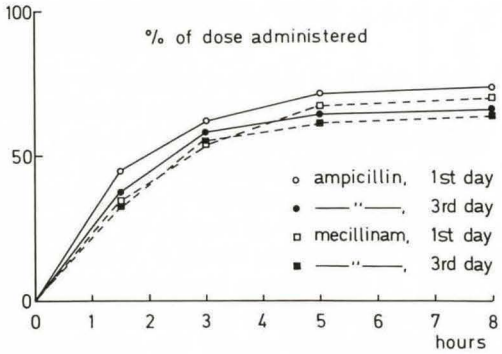

Fig. 4 Cumulative urinary excretion in five healthy subjects of active ampicillin and mecillinam in per cent of doses given after 500 mg tablets containing bacampicillin and bacmecillinam in an equimolar combination

The lag time before obtaining appreciable levels for both antibiotics is longer in lymph than in serum. In line with the fact that moderate, but measurable levels are present at the time the 7th dose is given, the apparent lag time is lower for both serum and lymph on the 3rd day.

The invasion into serum of both substances proceeds faster than into lymph. The mean values for serum are higher on the first day, but there is considerable difference between the subjects; the difference between days is not significant. The lymph invasion velocities are the same for both doses.

Elimination half-life is of the same order for both compounds and body fluids. There is a (non-significant) trend towards longer half-life for lymph.

The area under the curve in serum is significantly higher for ampicillin than for mecillinam. The ampicillin curve has 1.39 the area of the mecillinam curve after the first and 1.48 after the 7th dose. The ampicillin serum curves have a mean area which on the first day is 1.21 times higher than the lymph curves and 1.41 higher after the 7th dose. For mecillinam, the area under the serum and lymph curves were more similar.

Discussion

When developing a pharmaceutical preparation consisting of a fixed combination of two synergistically acting antibiotics, it is essential that the relative amounts of the two components is such that the ratio of the active drugs within various body sites is close to the optimum found for synergy *in vitro*. In the case of the sulfamethoxazole + trimethoprim combination, the proportion of the drugs in the tablets differs from that which is obtained in body fluids (14, 20). The ratio of the components *in vivo*, therefore, is widely different from that which is optimal for synergy *in vitro*.

Nearly all pharmacokinetic studies on antibiotics have been based on serum and urine samples. In our study, we have additionally studied peripheral lymph. As peripheral lymph is formed directly from the extracellular fluid (cfr. reviews on the lymph system in general [10, 11, 16] and renal lymph [9, 18]), the drug levels observed therein directly reflect those obtainable extravascularly at sites which may become infected. Only few human lymph studies have been published (1, 3, 4, 15, 17).

Most of these have studied central lymph from the thoracic duct. About 30–50 per cent of this lymph is derived from the liver with discontinuous blood capillaries and a higher proportion of leakage of proteins than is the case for most other tissues. This is in contrast to the peripheral lymph which we have followed through cannulation of a lymph vessel in the leg. This contains drainage from subcutaneous tissue and muscular fascia of the leg, both of which have continuous capillaries. The composition of this lymph is identical to the interstitial tissue fluid within the drainage area (11).

We consider it important that the ratio of ampicillin to mecillinam in all instances has been below 2:1, and during the latter 1/2 to 2/3 of the dosage interval has been close to 1:1. This is within the limits usually obtained as optimal for synergy in strains belonging to the *Enterobacteriaceae* and close to the

Table 3 Pharmacokinetic characteristics of ampicillin and mecillinam in serum after one and seven doses (i.e. on the third day) of 500 mg tablets containing bacampicillin and bacmecillinam in equimolar amounts

Antibiotic, dose no.	k_A* ($hour^{-1}$)	k_E ($hour^{-1}$)	t 1/2 (hour)	c_o ($\mu g/ml$)	lag (hour)	AUC ($\mu g \cdot hour/ml$)
Ampicillin, 1st day	4.937 ± 3.887	1.014 ± 0.178	0.86 ± 0.30	8.05 ± 1.16	0.48 ± 0.14	8.18 ± 2.03
Ampicillin, 3rd day	2.547 ± 2.424	0.881 ± 0.223	1.12 ± 0.60	8.45 ± 3.67	0	10.21 ± 3.09
Mecillinam, 1st day	7.080 ± 6.280	0.733 ± 0.239	1.17 ± 0.66	4.00 ± 0.50	0.57 ± 0.20	5.90 ± 1.90
Mecillinam, 3rd day	3.349 ± 2.604	0.937 ± 0.401	1.00 ± 0.56	6.17 ± 2.14	0.23 ± 0.10	6.88 ± 0.96

* Abbreviations explained in Materials and Methods.

Table 4 Pharmacokinetic characteristics of ampicillin and mecillinam in peripheral lymph after one and seven doses (i.e. on the third day) of 500 mg tablets containing bacampicillin and bacmecillinam in equimolar amounts

Antibiotic, dose no.	k_A* ($hour^{-1}$)	k_E ($hour^{-1}$)	t 1/2 (hour)	c_o ($\mu g/ml$)	lag (hour)	AUC ($\mu g \cdot hour/ml$)
Ampicillin, 1st day	1.637 ± 1.433	1.715 ± 0.225	1.04 ± 0.30	4.91 ± 2.13	0.72 ± 0.32	6.76 ± 2.13
Ampicillin, 3rd day	2.101 ± 1.891	0.612 ± 0.126	1.18 ± 0.25	4.25 ± 1.15	0.45 ± 0.16	7.20 ± 2.51
Mecillinam, 1th day	2.274 ± 1.209	0.437 ± 0.172	1.79 ± 0.68	2.77 ± 1.58	0.73 ± 0.26	6.11 ± 1.26
Mecillinam, 3rd day	2.373 ± 2.248	0.626 ± 0.182	1.18 ± 0.32	3.35 ± 0.83	0.54 ± 0.14	5.46 ± 1.19

* Abbreviations explained in Materials and Methods.

optimal ratio for synergy which *in vitro* is around 1:1 (13, 19, 24).

The concentrations obtained in lymph reach the minimum inhibitory concentrations (MIC) of each antibiotic alone for 70–90 per cent of the enterobacteria, depending upon species (20, 24, 27). When ampicillin and mecillinam are present in combination, the levels reached in lymph cover 90–95 per cent of the enterobacterial isolates (13, 19, 24). The ampicillin alone is sufficient to inhibit *H. influenzae,* and streptococci including enterococci.

In all subjects, the peak concentrations of the drugs occurred 0.5–1 hours earlier in serum than in lymph. It is also important to note that there is a relatively longer duration of antibiotic levels in the peripheral lymph than in serum. It might be questioned whether this were due to a lag in lymph sampling. Accordingly, lymph samples were referred to the mid-point of their collection intervals. The time it takes for a molecule to pass through the capillary wall into the extracellular fluid and hence to the collecting vessel for the lymph (10) and catheter is unknown.

The finding that the area under the curves for ampicillin were relatively higher than for mecillinam in serum compared to peripheral lymph may indicate better penetrability into tissues for mecillinam than for ampicillin. The fact that the recovery in urine was similar for the two compounds is consistent with this supposition.

The longer duration of the antibiotic levels in peripheral lymph and the finding that peripheral concentrations are above those in serum during the latter 1/2–2/3 of the dosage interval have also been found in other studies on penicillin in lymph (21), on aminoglycosides in perilymph of the inner ear (22, 29), and in tissue cages for a number of substances with a short half-life (5, 8). The non-protein bound levels in plasma and lymph follow a parallel course if the half-life is long (1) or the drug is infused continuously (7, 27).

In conclusion, the composition of the combination tablet consisting of equimolar amounts of bacampicillin and bacmecillinam give relative concentrations within the body which correspond to the optimum for synergy *in vitro* and appears suitable from a pharmacokinetic point of view.

References

1. *Anderson, K.E., H. Dencker, P.-A. Mårdh, M. Åkerlund:* Relationships between the concentrations of doxycycline in serum and in thoracic duct lymph after oral and intravenous administration in man. Chemotherapy 22 (1976) 277–285
2. *Bergan, T.:* Penicillins. Antibiotics and Chemotherapy 25 (1978) 1–122
3. *Bergan, T.:* Pharmacokinetic comparison of oral bacampicillin and parenteral ampicillin. Antimicrobial Agents and Chemotherapy. 13 (1978) 971–974
4. *Bergan, T., E. Engeset, E.B. Christophersen:* Gentamicin concentration in human lymph. Pp. 619–623 in Daikos, G.K. (ed.): Progress in Chemotherapy. Hellenic Society for Chemotherapy. Athens 1974
5. *Bergan, T., B. Øydvin:* Microbial assay of josamycin. Acta Pathologica et Microbiologica Scandinavica Sect. B 80 (1972) 101–106
6. *Bergan, T., I. Versland:* The mini-pig as a model for penetration of penicillins. Scandinavian Journal of Infectious Diseases, Suppl. 14 (1978) 135–142
7. *Broe, M.E. De:* Antibiotics in renal lymph. Archives of International Pharmacodynamics. 201 (1973) 193–194
8. *Chisholm, G.D., J.S. Calnan, P.M. Waterworth:* Antibacterial agents in renal lymph. Pp. 194–211 in O'Grady, F., W. Brumfitt (eds.): Urinary Tract Infection. Oxford University Press. London 1968
9. *Chisholm, G.D., C.B. Smith, P.M. Waterworth, J.A. Calnan:* Factors influencing the distribution of antibacterial agents in interstitial tissue fluid: molecular size and protein binding. Infection 4 (1976), Suppl. 2, 123–125
10. *Cockett, A.T.K., A.P. Roberts, R. Moore:* Significance of antibacterial levels in the renal lymph during treatment for pyelonephritis. Journal of Urology 95 (1966) 164–168
11. *Courtice, F.C.:* Lymph and plasma proteins: barriers to their movement throughout the extracellular fluid. Lymphology 4 (1971), 9–17
12. *Engeset, A., B. Hager, A. Nesheim, A. Kolbenstvedt:* Studies on human peripheral lymph. I. Sampling method. Lymphology 6 (1973) 1–5
13. *Grunberg, E., R. Cleeland, G. Beskid, W.F. DeLorenzo: In vivo* synergy between 6β-amidinopenicillanic acid derivatives and other antibiotics. Antimicrobial Agents and Chemotherapy 9 (1976) 589–594
14. *Hansen, I.:* The combination trimethoprim-sulphamethoxazole. Antibiotics and Chemotherapy 25 (1978) 217–232

15. *Hejzlar, M., V. Bartos, L. Král, V. Brzek:* Ampicillin levels in the blood serum and thoracic duct lymph in man. Pp. 153–154 in Hejzlar, M., M. Semonský, S. Masák: Advances in Antimicrobial and Antineoplastic Chemotherapy. Urban & Schwarzenberg. München 1972
16. *Levine, R.R., T.J. deMarco, C.M. Dizon:* The lymphatic system: its role in the absorption and distribution of drugs. Pp. 79–107 in Proceedings of the Fourth International Congress on Pharmacology. Schwabe & Co. Basel 1969
17. *Lithander, A., B.O.A. Werner, L.O. Forsgren:* Passage of benzylpenicillin and ampicillin into the thoracic duct lymph after intravenous injection in man. Antimicrobial Agents and Chemotherapy 1968 (1969) 366–372
18. *Mayerson, H.S.:* The lymphatic system with particular reference to the kidney. Surgery, Gynecology & Obstetrics 116 (1963) 259–272
19. *Neu, H.C.:* Synergy of mecillinam, a beta-amidinopenicillanic acid derivative, combined with beta-lactam antibiotics. Antimicrobial Agents and Chemotherapy 10 (1976) 535–542
20. *Rieder, J., D.E. Schwartz, M. Fernex, T. Bergan, E.K. Brodwall, A. Blumberg, P. Cottier, W. Scheitlin:* Pharmacokinetics of the antibacterial combination sulfamethoxazole plus trimethoprim in patients with normal or impaired kidney function. Antibiotics and Chemotherapy 18 (1974) 148–198
21. *Schachter, R.J.:* Fate and distribution of penicillin in the body. I. Circulation of penicillin in the lymph. Proceedings of the Society of Experimental Biology and Medicine 68 (1948) 29–34
22. *Scheer, M., K. Bartmann:* Concentrations of aminoglycosides in serum and perilymph of guinea-pigs. Pp. 503–506 in Hejzlar, M., M. Semonský, S. Masák: Advances in Antimicrobial and Antineoplastic Chemotherapy. Urban & Schwarzenberg. München 1972
23. *Skjerven, O., T. Bergan:* Double blind comparison of sulfonamide-trimethoprim combinations in acute uncomplicated urinary tract infections. Infection. In press
24. *Sjöberg, B., P. Bamberg, B. Ekström, U. Forsgren, L. Magni, B.G. Pring:* Synergistic action *in vitro* between amidinopenicillanic acids and penicillins or cephalosporins. Current Chemotherapy (1978) 432–434
25. *Spratt, B.G.:* Distinct penicillin binding proteins involved in the division, elongation, and shape of *Escherichia coli* K 12. Proc. Nat. Acad. Sci. USA 72: 2999–3003
26. *Spratt, B.G.:* Properties of the penicillin-binding proteins of *Escherichia coli* K 12. European Journal of Biochemistry 71 (1977) 341–352
27. *Tybring, L.:* Mecillinam (FL 1060), a 6β-amidinopenicillanic acid derivative: *in vitro* evaluation. Antimicrobial Agents and Chemotherapy. 8 (1975) 266–270
28. *Verwey, W.F., H.R. Williams:* Relationships between the concentrations of various penicillins in plasma and peripheral lymph. Antimicrobial Agents and Chemotherapy 1962 (1963) 476–483
29. *Wagner, J.G.:* Fundamentals of Pharmacokinetics. Drug Intelligence. Hamilton, Ill., 1975
30. *Wagner, W.-H.:* Investigations on the transport of streptomycin to the perilymph. Pp. 601–602 in Daikos, G.K.: Progress in Chemotherapy. Vol. I. Antibacterial Chemotherapy. Hellenic Society for Chemotherapy. Athens 1974

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