FACTORS INFLUENCING THE ABSORPTION AND DISPOSITION OF MECILLINAM AND PIVMECILLINAM IN MAN

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- 1 In a pharmacokinetic study in six volunteers peak serum mecillinam concentrations were proportional to the oral dose of pivmecillinam at two dose levels of 200 and 400 mg.
- 2 Effects of bed rest, probenecid and a 6 day course of treatment with pivmecillinam on serum mecillinam concentrations after an oral dose of pivmecillinam (two 200 mg capsules) have been investigated.
- 3 Resting subjects had lower peak serum levels and a decreased rate of clearance than moderately active subjects, changes which are similar to those previously reported for benzylpenicillin.
- 4 Pretreatment with probenecid produced significantly higher serum mecillinam levels, a longer serum antibiotic half-life and a decreased rate of drug clearance which suggests that mecillinam is actively excreted by kidney tubules.
- 5 Plasma mecillinam level profiles obtained after the first dose of a 6 day treatment period were not significantly different from corresponding values after the first dose on the seventh day which indicates that each dose of mecillinam is eliminated in healthy young adults before succeeding doses are taken.

Introduction

Mecillinam is a new β -lactam antibiotic related to the penicillins but different in the following three respects:

- (i) Structurally the compounds are substituted at a 6-amidino instead of a 6-amino group (Lund & Tybring, 1972),
- (ii) they are more active against gram negative than against gram positive organisms, being about ten times more active against *Escherichia coli* than ampicillin (Greenwood, Linton Brooks, Gargan & O'Grady, 1974), and
- (iii) although producing protoplast forms by interfering with bacterial cell wall synthesis, they do so by mechanisms which are different from the actions of penicillin. Mecillinam does not inhibit murein transpeptidase or endopeptidase nor D-alanine carboxypeptidase (Park & Burman, 1973).

Pivmecillinam and mecillinam are the oral and

parenteral forms respectively of this new amidino penicillin which have been found to be effective in the treatment of urinary tract infections (Wise, Reeves, Symonds & Wilkinson, 1976) and enteric fever (Limson, 1973). Since the parent compound mecillinam is not absorbed from the gastrointestinal tract, studies on absorption have been carried out with the pivaloyl ester which is efficiently absorbed. This ester has no antibacterial activity but is rapidly hydrolysed to the active form, mecillinam, in the body. Earlier studies carried out in Denmark on ambulant factory workers (Roholt, Nielsen & Kristensen, 1966), showed higher blood levels than those obtained in resting volunteers in England (Williams, Andrews, Mitchard & Kendall, 1976). We have, therefore, investigated in more detail the factors which might modify the blood levels of this drug and have looked specifically at the effects of dose, probenecid administration, chronic treatment and physical activity.

Methods

Studies were carried out in six healthy medical students aged between 20 and 25 years whose biochemical profiles were within the normal range for the Queen Elizabeth Hospital, Birmingham (Bold & Wilding, 1975), and who were not taking other drugs. Permission for this study was first obtained from the Queen Elizabeth Hospital Medical Research Ethical Committee. Subsequently details of the study were explained to each volunteer and informed consent obtained.

Subjects were admitted to a hospital side ward and the studies were commenced at between 09.00 h and 09 h 30 min on the same day of consecutive weeks. A plastic intravenous cannula was inserted into a forearm vein and connected to a three way tap through which normal saline was slowly infused to keep the cannula patent. The bladder was emptied and a blood sample (5 ml) taken immediately before the drug was given. Blood was sampled at 15, 30, 45 and 60 min and then at 1.5, 2, 2.5, 3, 4 and 6 hours. In each case a 2 ml sample was discarded before collecting the sample for analysis. A 6 h urine was collected for analysis.

Serum and urine samples were assayed in triplicate for mecillinam by the agar cup plate method using the Leo HA² *Escherichia coli* as test organism. The method, which has been described in more detail elsewhere (Williams, Andrews, Mitchard & Kendall, 1976), has an accuracy of better than $\pm 20\%$ at the 95% confidence limit. Mecillinam hydrochloride dihydrate was used as a reference standard but the results are expressed as $\mu\text{g/ml}$ of anhydrous mecillinam/ml serum or as per cent of the administered dose.

Antibiotic studies

In each study capsules containing pivmecillinam hydrochloride (200 mg) were taken by mouth. The study was undertaken in five parts. In the first study each subject was given one capsule. Subsequently on four occasions at intervals of 1 week the subjects were given two capsules. On the first of these the subjects were lying in bed. On the next day the subjects started a 6 day course of two capsules four times daily for 6 days. They were then readmitted on the seventh day, given two capsules and the study was repeated as for the previous week. On the third occasion the subjects were ambulant and samples were taken from a cannula which was kept patent by intermittent injections of heparinized saline. The subjects were again supine for the final study and two 500 mg tablets of probenecid were given by mouth 30 min before the pivmecillinam capsules.

Figure 1 Peak serum mecillinam concentrations in six subjects after 200 and 400 mg as capsules of pivmecillinam hydrochloride.

The data were analysed both by using the computer programme described by Engberg-Pedersen (1974) which is based on an empirical polynomial expression and by the more conventional terminal-regression analysis of the logarithm of serum drug concentration/time plot.

Results

The individual peak serum mecillinam concentrations obtained after one and after two 200 mg capsules of pivmecillinam hydrochloride are shown in Figure 1. The mean values were 1.43 and 2.5 $\mu\text{g/ml}$ respectively. The effects of (a) bed rest and moderate activity, (b) a 6 day treatment period of pivmecillinam (400 mg four times daily) and (c) probenecid (1 g) taken 30 min before the antibiotic on the mean serum mecillinam concentrations in the six subjects after two 200 mg capsules of pivmecillinam are shown in Figures 2, 3 and 4 respectively. The serum concentration values, and absorption and disposition characteristics for these studies are presented in Tables 1 and 2 respectively. The mean ($\pm$ s.d.) serum half-life after the single 200 mg capsule was 1.2 (± 0.25) h, the apparent first order elimination rate constant was 0.63 (± 0.09) $\mu\text{g ml}^{-1}\text{h}$ and the AUC was 3.0

Figure 2 Mean serum mecillinam concentrations obtained from six subjects after pivmecillinam hydrochloride (2 x 200 mg capsules) taken (a) supine in bed, or (b) whilst ambulant.

Figure 3 Mean serum mecillinam concentrations obtained from six subjects after 2 x 200 mg capsules taken (a) before and (b) after a 6 day course of pivmecillinam (400 mg, four times daily).

Table 1 Mean serum mecillinam concentrations ($\pm$ s.d.) obtained in six subjects under different conditions of treatment after a single oral dose of 2 x 200 mg capsules of pivmecillinam hydrochloride.

Treatment condition	Serum mecillinam concentrations ($\mu\text{g anhydrous mecillinam/ml}$)											
	Time (h)											
Supine	0.25	0.5	0.75	1.0	1.5	2.0	2.5	3.0	4.0	6.0		
	< 0.1	0.88 (0.49)	1.47 (0.61)	2.25 (0.89)	2.4 (0.51)	2.29 (0.62)	1.79 (0.29)	1.5 (0.28)	0.64 (0.14)	< 0.1		
After pivmecillinam (400 mg) for 6 days	0.28 (0.15)	1.34 (0.36)	2.12 (0.66)	2.5 (0.75)	2.85 (0.69)	2.4 (0.44)	1.71 (0.32)	0.38 (1.24)	0.53 (0.21)	< 0.1		
After probenecid (2 x 500 mg tablets)	0.45 (0.72)	1.3 (0.59)	2.64 (0.64)	3.22 (0.62)	3.81 (0.82)	3.58 (0.84)	3.25 (0.77)	2.59 (0.48)	1.5 (0.29)	0.36 (0.31)		
Ambulant	0.31 (0.22)	1.77 (0.66)	2.71 (0.83)	3.36 (1.03)	3.1 (0.33)	2.62 (0.49)	1.7 (0.35)	1.25 (0.33)	0.5 (0.19)	< 0.1		

Table 2 Mean ($\pm$ s.e. mean) absorption and disposition characteristics of mecillinam in six volunteers after pivmecillinam hydrochloride (2 x 200 mg capsules)

	Peak serum concentration ($\mu\text{g/ml}$)	Peak time (h)	$T_{1/2}^1$ (h)	AUC ² ($\mu\text{g h ml}^{-1}$)	6 h urine (% dose)	Elimination rate constant ($\mu\text{g ml}^{-1} \text{ h}^{-1}$)	Linear* regression coefficient
Supine	2.5 (0.24)	1.7 (0.17)	1.2 (0.21)	6.2 (0.34)	25 (2.0)	0.61 (0.15)	0.98 (0.006)
After pivmecillinam (400 mg) for 6 days	2.7 (0.27)	1.5 (0.18)	1.1 (0.17)	6.3 (0.26)	25 (2.2)	0.65 (0.18)	0.99 (0.002)
After probenecid (2 x 500 mg tablets)	3.8 (0.39)	1.7 (0.18)	1.5 (0.27)	11.5 (0.84)	19 (3.7)	0.50 (0.12)	0.98 (0.12)
Ambulant	3.1 (0.36)	1.3 (0.18)	1.1 (0.12)	7.0 (0.26)	23 (4.3)	0.65 (0.10)	0.99 (0.003)

* Linear regression coefficient is calculated for the terminal regression of a plot of logarithm of plasma concentration against time.

¹ $T_{1/2}$ is the serum mecillinam half-life determined by regression analysis.² AUC is the area under the serum mecillinam concentration/time curve. **Figure 4** Mean serum mecillinam concentrations obtained from six subjects after pivmecillinam hydrochloride (2 x 200 mg capsules) taken (a) alone and (b) after probenecid (1 g).

(± 0.4) $\mu\text{g h ml}^{-1}$. Unfortunately figures are not available for the % of dose recovered in a 6 h urine after a single capsule.

Discussion

The data obtained in this study expand our earlier work. Pivmecillinam is efficiently absorbed from the capsule formulation of the hydrochloride, producing peak mecillinam concentrations at about 1.5 hours. Both peak serum concentrations and amount of drug absorbed, as indicated by AUC, were proportional to oral doses of 200 and 400 mg.

The benzylpenicillin data of Schmidt & Roholt (1966) was subsequently analysed by Levy (1967) who determined that in bedridden patients the volume of distribution of benzylpenicillin as well as the % excreted in urine was increased, whereas the rate constant for metabolism was decreased. The trend of results obtained in our own studies was similar to those reported for benzylpenicillin. The serum mecillinam levels were significantly ($P < 0.05$) higher during the first 2 h in ambulant volunteers (Figure 2) and the % of antibiotic excreted in the urine and its rate of elimination by supine subjects were slightly less than when the subjects were ambulant although these differences did not reach statistical significance.

The small differences in the curves before and after a course of treatment shown in Figure 3 and

Table 1 were not statistically significant, from which it can be concluded that the mecillinam does not accumulate in young people during treatment. However, preliminary studies at present being carried out in this department suggest that serum levels are raised for longer periods of time in the elderly. This observation may be related to the preliminary observations of Wise *et al.* (1976) who found a raised 6 h serum mecillinam level in some patients with poor renal function.

It appears from the study of Roholt *et al.* (1965) in which probenecid was shown to increase serum mecillinam levels that mecillinam is actively excreted by the renal tubules. The results obtained in this study (Figure 4 and Table 1) confirm this observation. Both the peak serum concentration and the serum half-life were significantly increased, and the apparent first order elimination rate constant and the percentage excreted in urine decreased ($P < 0.02$) after probenecid.

The half-lives of just over 1 h quoted in Table 1 were determined graphically. These values are the same as those previously obtained by us (Williams *et al.*, 1976) from studies in which an intramuscular injection and an oral solution were used; the values also agree well with those of 1.2 h after parenteral and 1.0-1.4 h after oral administration which were obtained by Roholt *et al.* (1975). Slightly longer half-lives of 1.5-2.0 h were obtained by Wise *et al.* (1976) from studies in patients who received two 200 mg capsules of pivmecillinam.

In our earlier paper dealing with the pharmacology of mecillinam (Williams *et al.*, 1976) we discussed reasons why our serum mecillinam values were lower than those of Roholt and co-workers (1975). In the meantime Wise *et al.* (1976) have

published results from a patient study in which they obtained a mean peak serum mecillinam concentration of 3.9 $\mu\text{g/ml}$ after an oral 400 mg capsule dose of pivmecillinam. This value is higher than our own of 2.5 $\mu\text{g/ml}$ but lower than the 5.0 $\mu\text{g/ml}$ of the Roholt group although as the study by Wise *et al.* (1976) was in patients their range of peak serum levels was predictably large being from 1.3-6.4 $\mu\text{g/ml}$. It is therefore apparent that different laboratories report considerably different plasma mecillinam concentrations after similar doses. However, in spite of scrupulous attention to practical detail and extensive collaboration between the laboratories, which included an exchange of personnel, it has not yet been possible to explain these differences.

In conclusion it is perhaps worth emphasizing that there is only a superficial similarity between the pivmecillinam/mecillinam pair of antibiotics and pivampicillin and ampicillin. Oral ampicillin is a therapeutically effective antibiotic in spite of its poor absorption. Conversion to the pivaloyl ester improves absorption efficiency and leads to higher serum ampicillin levels from equivalent doses (Jordan, de Maine & Kirby, 1970). On the other hand mecillinam is so poorly absorbed from the gastrointestinal tract that when given orally it is ineffective in the treatment of systemic or urinary tract infections. Pivmecillinam on the other hand is well absorbed and is an effective therapeutic agent.

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