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Mecillinam serum levels following intravenous injection: a comparison with pivmecillinam

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Serum mecillinam concentrations have been obtained in 6 volunteers after intravenous injection of 200 mg mecillinam and two 200 mg tablets containing pivmecillinam hydrochloride. Initial concentrations were between 6 and 9 mg/l and peak concentrations of about 2·0 mg/l occurred at 1 to 1·5 h after the tablets. Analysis of the intravenous data shows the concentration/time curve to be biphasic and similar to that previously reported for penicillin G. The biexponential curves describing the data have been calculated using nonlin. Comparison of the areas under the serum mecillinam concentration/time curves suggests a bioavailability of 65 to 70% for the tablets. However, the two preparations contain therapeutically equivalent amounts of antibiotic, as two 200 mg tablets of pivmecillinam contain 30% more mecillinam than the 200 mg injection.

Introduction

The present study was carried out to assess the pharmacokinetics of a new intravenous preparation of mecillinam and to study the bioavailability of new 200 mg tablets of pivmecillinam. It is anticipated that these preparations will soon be in clinical use. It was therefore considered important to determine the availability of mecillinam from these preparations and to compare the serum antibiotic level data with those obtained from preparations previously studied (Roholt, Nielsen & Christensen, 1975; Williams, Andrews, Mitchard & Kendall, 1976; Andrews, Kendall & Mitchard, 1976).

Methods

Six male volunteers aged between 21 and 26 years who were not taking other drugs, participated in this study which was approved by the Research Ethical Committee. Each volunteer was fit and had normal serum biochemistry and normal haematology (values were within the normal range for the Queen Elizabeth Hospital: Bold & Wilding, 1976).

The subjects who fasted overnight were admitted to a hospital side ward where they remained supine for the duration of the study. These commenced between 9 and 9.30 a.m.

on the same day of consecutive weeks. Blood samples were collected from a plastic cannula inserted in a forearm vein through which normal saline was slowly infused. Basal blood and urine samples were taken prior to the study immediately before the antibiotic was given. Blood samples were collected at 0·25, 0·5, 0·75, 1·0, 1·5, 2·0, 2·5, 3·0, 4·0 and 5·0 h and an additional 10-min sample was collected during the i.v. study. In each case care was taken to ensure that the blood was not contaminated by saline and serum was separated as quickly as possible after the samples were collected. Urine was collected for a 6-h period, the volume and pH were recorded and a 25-ml aliquot reserved for analysis. All samples were immediately cooled to below 0°C and were assayed for mecillinam on the same day.

Mecillinam preparations

A new parenteral preparation of mecillinam and a new tablet formulation of pivmecillinam both supplied by Leo Laboratories were investigated in this study.

The injectable form of mecillinam consists of 200 mg of anhydrous mecillinam powder contained in a rubber sealed vial: the powder was dissolved in 2 ml of sterile water just before use.

The tablets each contained 200 mg of pivmecillinam hydrochloride. Two of these tablets, which is equivalent to 273 mg of mecillinam, were given to each subject. The order of treatments was ıandomized and the second treatment was given one week after the first.

Assay methods

A microbiological method was used to assay both urine and serum sample for mecillinam. Determinations were made in triplicate using the agar cup plate method and the Leo HA[2] *Escherichia coli* as test organism. Although mecillinam hydrochloride dihydrate was used as reference standard, the results are expressed in terms of anhydrous mecillinam. Details of the method have been described elsewhere (Williams *et al.*, 1976; Andrews *et al.*, 1976).

Data analysis

The data were analysed using the nonlin computer programme.

Results

The mean serum mecillinam concentrations obtained in 6 volunteers after intravenous mecillinam and tablets of pivmecillinam are shown in Figure 1. The initial serum levels

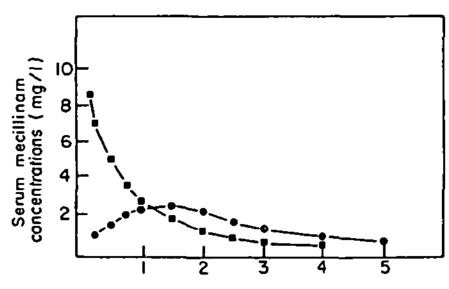

Figure 1. Mean serum mecillinam concentration time curve expressed as anhydrous mecillinam after an intravenous injection of 200 mg mecillinam (■) and two tablets each containing 200 mg of pivmecillinam hydrochloride (●).

after the injection exceeded 6·5 mg/l (actual values ranged from 5·7 to 9·0) whilst the peak of mean serum concentrations after two tablets was 1·90 mg/l (the range of actual peak concentrations was 1·7 to 2·7).

Peak serum concentrations after the tablets occurred at just over 1 h in four of the subjects. In the remaining two subjects the peak concentrations were delayed until between 2 and 2·5 h.

Regression analysis of the intravenous data established that the serum mecillinam concentration/time curves were biphasic. The expression $C_p = 12{\cdot}9e^{-0{\cdot}1t} + 4{\cdot}8e^{-0{\cdot}01t}$ in which C_p is the serum mecillinam concentration was calculated from the data of one individual (subject 6). The computer drawn curve corresponding to this equation together with the actual data points for this subject are presented in Figure 2.

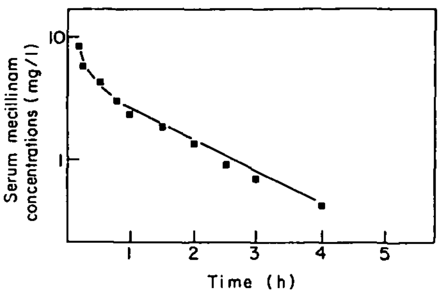

Figure 2. Serum mecillinam concentrations (■) obtained in subject 6 after an intravenous injection of 200 mg mecillinam and a computer drawn curve described by the equation:

$$C_p = 12{\cdot}9e^{-0{\cdot}1t} + 4{\cdot}8e^{-0{\cdot}01t}.$$

The mean β phase half-life values ($t_{\frac{1}{2}}$) were 0·814 (±0·16) and 1·06 (±0·2) h for the i.v. and oral data respectively. However, the difference between these values was not significant and a comparison of the oral and intravenous data obtained in the same individual as shown in Figure 3 clearly shows that the clearance of mecillinam is similar

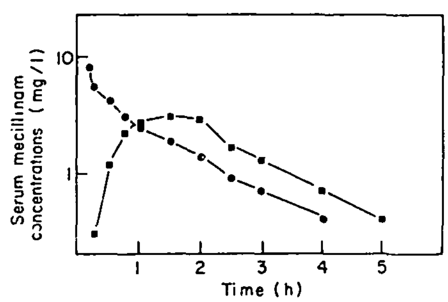

Figure 3. Semi-logarithmic plot of the serum mecillinam concentrations expressed as anhydrous mecillinam obtained in subject 6 after an intravenous injection of 200 mg mecillinam (●) and two tablets each containing 200 mg of pivmecillinam hydrochloride (■).

in the two situations. Details of the biexponential equation values for each subject are listed in Table I. The mean volume of distribution for the central compartment calculated from the extrapolated intravenous data was 8·7 (±1·04) l. Values for the half-lives, areas under the serum concentration/time curve (AUC) and bioavailability of the tablet preparation are shown in Table II. The per cent bioavailability has been calculated after reducing the oral AUC by 200/273 to correct for the small difference in amount of mecillinam equivalent given by the two routes.

Table I. Values for the biexponential serum equation $C_p = Ae^{-\alpha t} + Be^{-\beta t}$ calculated from the intravenous serum data

Subject	A	α	B	β
1	12·75	0·044	3·12	0·011
2	6·94	0·036	2·13	0·007
3	7·40	0·048	3·48	0·012
4	7·63	0·034	3·82	0·011
5	4·92	0·039	4·94	0·011
6	12·95	0·105	4·83	0·010
Mean	8·76	0·051	3·72	0·010
S.D.	3·3	0·026	1·06	0·002

Table II. Some availability and disposition characteristics of mecillinam

	AUC (mg l^{-1} h)	$t_{\frac{1}{2}}$ (h)	Bioavailability (%)
i.v.	322·6	0·814	—
S.D.	15·7	0·16	
Oral	289·8	1·06	66
S.D.	26·4	0·2	4·3

Discussion

The data presented in this paper are similar to those obtained by us in earlier studies with mecillinam (Andrews, Kendall & Mitchard, 1975; Williams *et al.*, 1976; Andrews *et al.*, 1976). A comparison of the intravenous and oral serum mecillinam data presented in Figure 1 shows that the initially high serum levels after i.v. administration drop rapidly to about 2·0 mg/l within 1 h and to 0·8 mg/l at 2 h; levels therefore exceed 1 mg/l for nearly 2 h. Serum levels rise more slowly after oral administration. Serum mecillinam concentrations rise to 1 mg/l in 15 min. and remain above this level for about 3·5 h. However, under the conditions of this study peak concentrations after the tablet, although never less than 1·6 mg/l were never greater than 2·8 mg/l. Although the peak value for the mean mecillinam serum concentrations after the two tablets was 1·90 mg/ml, only one subject had a peak serum concentration of less than this value. The remaining five subjects all had peak concentrations greater than 1·9 mg/l, their mean peak value being 2·33 (±0·27) mg/l. It is a common observation that the peak value of a mean serum antibiotic concentration/time curve is not representative of the actual peak concentrations, yet it is a fact which is not generally appreciated. Mean serum drug concentration curves are calculated from data obtained in a number of subjects at specific time intervals. Only very rarely does a peak concentration occur at exactly the same time during a study in all subjects. Therefore, the peak mean value is normally unrelated to the actual mean of peak concentrations.

The serum mecillinam concentrations obtained in this study after two 200 mg pivmecillinam tablets are very similar to those obtained in our earlier studies with 2×200 mg capsules of pivmecillinam (Andrews *et al.*, 1975; 1976). The mean of peak serum concentrations were similar (2·23±0·3 and 2·61±0·6 mg/l for tablets and capsules respectively) and the peak of the mean serum mecillinam concentration curves both occurred at about 1·5 h. However, although the initial serum mecillinam concentrations obtained by us in this study after intravenous administration were similar to those reported by Roholt *et al.* (1975) the peak serum mecillinam concentrations after an oral dose are still only about one half of those obtained by the Danish group. There are two factors which may contribute to this difference. The average age of the subjects used in our studies is about 23 years whereas the workers in Denmark use subjects who are considerably older. Preliminary studies by ourselves and other groups (unpublished observations) indicate that the clearance of mecillinam is related to the efficiency of renal function, for the half-life of mecillinam is longer in older persons (we hope to be able to report the results of this study in this journal in the near future). The second factor of importance relates to the conditions of the study. The subjects in our studies are always supine whereas the subjects in Denmark are employees of Leo Laboratories and go about their normal duties during the course of the study. It is now well established (Schmidt & Roholt, 1966; Levy, 1976; Andrews *et al.*, 1976) that activity after administration of an antibiotic produces higher serum levels than are obtained in supine subjects. Therefore the combination of these two factors probably accounts for the lower serum mecillinam levels reported by us after oral administration.

In an earlier paper (Andrews *et al.*, 1975) it was suggested that pivmecillinam capsules were well absorbed because an 80% bioavailability was calculated with respect to an intramuscular dose. However, it was argued that this figure was probably an over-estimate and that probably more than 20% of the antibiotic was lost by some process of presystemic extraction. The present study confirms this by comparing the systemic availability of mecillinam after two 200 mg tablets of pivmecillinam with that of 200 mg mecillinam after intravenous administration; about 30% of an oral dose of pivmecillinam fails to reach the systemic circulation as mecillinam. However, the suggested oral dose of pivmecillinam is 400 mg. This contains 36·5% more mecillinam than the 200 mg parenteral dose and as can be seen from the AUC data presented in Table II, the oral dose is therapeutically equivalent to the intravenous preparation.

In the same paper we presented absorption and disposition characteristics of mecillinam. The half-life values which are similar to those reported in this study were assumed to provide a measure of drug clearance which we felt to be justified because anlaysis of the serum mecillinam concentration/time curves after an intramuscular injection and an oral dose of pivmecillinam appeared to be described by a one compartment model. However, as shown in Figure 2 and Table I the intravenous data clearly establishes the serum mecillinam concentration/time curve to be biphasic. The initial alpha phase was not observed in the earlier reported oral studies as it is only apparent during the initial 60 min of the intravenous study. It is therefore largely concealed during the absorption phase in the other studies.

In 1969 Plaut, O'Connell, Pabico & Davidson, administered Penicillin G to supine patients and obtained a biphasic serum penicillin concentration/time curve showing an initially rapid fall-off or α phase which persisted for 60 min and was followed by a slower β phase with a half-life of 24 min. It would therefore appear that the β phase half-life of mecillinam is about twice that of penicillin but that the distribution processes are probably similar.

Acknowledgement

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