The tubular excretion of benzylpenicillin in patients with cystic fibrosis

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- 1 The tubular excretion of benzylpenicillin (BP) was investigated in six volunteers with cystic fibrosis.
- 2 The volunteers received a continuous infusion of BP at increasing infusion rates in order to maintain constant plasma concentrations at three different levels. Blood and urine samples were taken every 30 min. Sufficient urinary flow was ensured by a saline infusion (500 ml h^{-1}).
- 3 The renal clearance of BP was calculated for the non-protein bound fraction of the drug.
- 4 Tubular clearance and tubular excretion rate were estimated from the renal clearance of the antibiotic minus the glomerular filtration rate; the latter was considered to be equal to creatinine clearance.
- 5 The data were analysed according to a Scatchard plot and values for ECu_{50} and maximal tubular excretion rate were calculated. The mean value of ECu_{50} was $89 \pm 24 \text{ (mg l}^{-1} \pm \text{s.d.)}$ and that for the maximal tubular excretion rate was $2603 \pm 714 \text{ (mg h}^{-1} \pm \text{s.d.)}$. The latter value was significantly less than that found in a previous study of healthy volunteers, but the ECu_{50} was similar.
- 6 It is concluded that the tubular excretory capacity for BP is decreased in patients with cystic fibrosis in direct relation to their low body weight.

Keywords cystic fibrosis benzylpenicillin tubular excretion

Introduction

Several authors have reported a relatively high renal clearance of β -lactam antibiotics in patients with cystic fibrosis (Bergan & Michalsen, 1979; Jusko *et al.*, 1974, 1975; Guggenbichler & Kienel, 1979; Yaffe *et al.*, 1977; Spino *et al.*, 1984). Various explanations have been offered including an increased tubular excretion. Since tubular excretion of β -lactam antibiotics is a saturable process (Bins & Mattie, 1988), characterized by a maximal rate of excretion and the concentration at which half of that maximal rate is reached (ECu_{50}), a study with benzylpenicillin was performed to establish whether the values of either of these two parameters differed in

patients with cystic fibrosis from those found earlier for healthy volunteers (Bins & Mattie, 1988).

Methods

The patients studied were all under treatment for respiratory complaints at the Sophia Paediatric Hospital, Rotterdam. The nature and possible risks of the investigation were explained to the patients and their parents. Parents and children gave their consent to the study and a Review Committee of the hospital approved the protocol.

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Throughout the experiment routine supportive therapy (i.e. administration of nebulized mucolytic and bronchodilatory agents and physiotherapy), as well as pancreatic enzyme treatment was continued.

The experimental procedure is described in detail elsewhere (Bins & Mattie, 1988). In brief, three steady-state plasma concentrations (low, high and very high) were achieved by a combination of bolus intravenous injection plus 2.5 h i.v. infusion. Saline was administered intravenously throughout the whole procedure at a rate of 500 ml h⁻¹. This ensured a high urinary flow, thus keeping the urinary penicillin concentration and, thereby, tubular reabsorption as low as possible. Every half hour urine was collected and a blood sample was taken from an intravenous catheter in the arm opposite to the one used for drug administration. The first half hour of each period was regarded as an equilibration interval. The creatinine and antibiotic contents of samples taken beyond this time were measured. The limit of assay for creatinine in plasma was > 20 µmol l⁻¹ with a coefficient of variation of 5–10%. The limit of the microbiological assay of benzylpenicillin was 0.032 mg l⁻¹ with a coefficient of variation of 5–10%. One sample from each subject was used to measure the plasma binding of penicillin by equilibrium dialysis. The mean creatinine clearance calculated for each 2.5 h period was considered to be equal to the glomerular clearance of unbound penicillin. The renal elimination rate of penicillin was calculated over each half-hour interval. The tubular excretion rate (R_{tub}) was obtained by subtracting the rate of unbound penicillin excretion by glomerular filtration from the total elimination rate. The rate of tubular excretion was described as a function of the unbound serum drug concentration (C_u), the maximal tubular excretion rate ($R_{\text{tub,max}}$) and

the free concentration at which half this maximal rate was reached (ECu_{50}), as follows:

$$R_{\text{tub}} = R_{\text{tub,max}} \cdot C_u / (C_u + ECu_{50})$$

$R_{\text{tub,max}}$ and ECu_{50} were estimated by regression analysis of the transformation of this equation according to Scatchard: $R_{\text{tub}}/C_u = R_{\text{tub,max}}/ECu_{50} - R_{\text{tub}}/ECu_{50}$ (Bins & Mattie, 1988). The results were subjected to analysis of covariance or multiple regression analysis, where appropriate.

Results

Patients

Six patients (3F, 3M), ranging in age from 11 to 21 years, participated in the study. They all suffered from a severe form of cystic fibrosis, as documented in Table 1.

Plasma drug concentrations

Low, high and very high therapeutic plasma concentrations of penicillin were reached in all patients (Table 2). The concentrations were

Table 2 Mean unbound plasma concentrations of benzylpenicillin in patients with cystic fibrosis during three successive infusion periods

Patient	Concentration (mg l ⁻¹)		
	Period 1	Period 2	Period 3
JV	5.7	19.9	143.7
KB	5.8	30.0	176.2
MT	5.1	29.6	144.0
RD	6.4	59.1	272.9
EV	4.2	28.8	190.0
LV	3.5	23.1	124.6
Mean	5.1	31.8	175.2

Table 1 Characteristics of patients with cystic fibrosis

Patient	Sex	Age (years)	Height (cm)	Na (mEq l ⁻¹)	TA (%)	FEV ₁ (%)	RV _{bb} (%)
JV	M	21	156	108	20	47	48
KB	M	14	183	135	57	19	73
MT	F	16	153	128	41	20	68
RD	M	16	153	98	27	54	45
EV	F	11	140	112	52	49	59
LV	F	14	165	94	43	47	57
average		15	158	113	40	39	58
(s.d.)		(3.3)	(15)	(16)	(14)	(16)	(11)

Na: Sodium content perspiration test

TA: 'Trapped air' (= volume which does not take part in ventilation) as percentage of the total lung capacity (TLC_{bb}).

FEV₁: Expiratory one-second-value as percentage of TLC_{bb}.

RV_{bb}: Residual volume as percentage of TLC_{bb}.

Table 3 Serum protein binding of benzylpenicillin in patients with cystic fibrosis

Patient	% bound
JV	37.8
KB	32.3
MT	36.8
RD	35.6
EV	34.0
LV	41.4
Mean	36.3
s.d.	3.2

reasonably constant at the three different levels. The plasma protein binding of benzylpenicillin was not concentration-dependent in the range of concentrations reached in this study (Table 3). The binding values were significantly lower ($P < 0.05$) than those found for six healthy volunteers, i.e. $53 \pm 7.7\%$ (Bins & Mattie, 1988).

Tubular excretion

The values calculated for $R_{\text{tub,max}}$ and ECu_{50} are shown in Table 4. Analysis of covariance of the regression lines in the Scatchard plot showed that the variation between the individual slopes was not significant and that the common slope was significantly different from zero ($P < 0.001$). From this common slope an ECu_{50} of 96 mg l^{-1} was calculated. This value was in good agree-

ment with the mean value calculated from individual estimates and did not differ from the value found for six healthy volunteers, although the latter were older ($26 \pm 3 \text{ years} \pm \text{s.d.}$) and heavier ($79 \pm 10 \text{ kg} \pm \text{s.d.}$) (Bins & Mattie, 1988).

Despite the high fluid load there was still considerable fluctuation in urinary flow during the experiment. Therefore, multiple regression analysis of the tubular clearance was performed according to Scatchard using the results obtained for patients and for healthy volunteers, and using the reciprocal value of the urinary flow as an additional independent variable. For this purpose the observations from our earlier study of healthy volunteers were used (Bins & Mattie, 1988). It was shown that diuresis had no significant influence on clearance. There was a significant variance between individuals in both groups ($P < 0.0001$); moreover the difference between patients and healthy volunteers was highly significant ($P < 0.001$). The regression of clearance on excretion rate did not differ significantly between patients and healthy volunteers. Using the common value of ECu_{50} (93 mg l^{-1}) the $R_{\text{tub,max}}$ was calculated for each individual. The values found are shown in Figure 1 in relation to bodyweight. It can be seen that the significantly lower maximal tubular excretion rate found for patients ($P < 0.05$) is related to a significantly lower body weight ($P < 0.001$). When the results were expressed as maximal tubular excretion rate per kg bodyweight the values for patients and healthy volunteers were similar: 70.0 ± 17.2 and $70.8 \pm 32.7 \text{ (mg h}^{-1} \text{ kg}^{-1} \pm \text{s.d.)}$, respectively.

Table 4 Characteristics of the tubular excretion of benzylpenicillin in patients with cystic fibrosis compared with healthy volunteers

Patient	Weight (kg)	ECu_{50} (mg l^{-1})	$R_{\text{tub,max}}$ (mg h^{-1})
JV	33	119	2552
KB	52	65	2336
MT	37	93	2822
RD	36	103	1930
EV	27	55	2074
LV	43	97	3905
Mean	38	89	2603
s.d.	8.6	24	714
Volunteers (Bins & Mattie, 1988)			
Mean	79	93	5535
s.d.	10	41	2633

Maximal tubular excretion capacity ($R_{\text{tub,max}}$) and free plasma concentration at which half of $R_{\text{tub,max}}$ was reached (ECu_{50}) were calculated from Scatchard plots

Figure 1 Relationship between bodyweight and maximum tubular transport of benzylpenicillin in healthy volunteers (○) and patients with cystic fibrosis (●).

Discussion

The results show that the tubular clearance of benzylpenicillin in patients with cystic fibrosis is less than in healthy volunteers. However, our patients were on the average younger than the healthy volunteers and they weighed much less. Furthermore, their creatinine clearance values were lower and proportional to their excretory capacity for benzylpenicillin. The difference between patients and healthy volunteers lies in a lower excretory capacity ($R_{\text{tub,max}}$) and not in a different affinity of the transport system for benzylpenicillin, as represented by the EC_{50} value. Other authors have reported an increased renal clearance of β -lactam antibiotics in patients with cystic fibrosis (Bergan & Michalsen, 1979; Jusko *et al.*, 1974, 1975; Guggenbichler & Kienel, 1979; Yaffe *et al.*, 1977; Spino *et al.*, 1984). The cause of the discrepancy between these findings and our results is not clear. It is unlikely that benzylpenicillin would behave much differently in this respect from other β -lactam antibiotics. The most important differ-

ence between previous studies and ours appears to be that we ensured maximal diuresis, thus minimizing the effects of a difference in reabsorption between patients and healthy volunteers. In addition, other authors did not take account of differences in protein binding. This could be of considerable significance, as in the case of dicloxacillin (Jusko *et al.*, 1975; Guggenbichler & Kienel, 1979). Finally, the results of other authors are often obscured by presenting the data only as normalized values of clearance per kg bodyweight (Sörgel *et al.*, 1987; De Groot & Smith, 1987).

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