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Original Article

Cefsulodin for the treatment of *Pseudomonas* infections – a study comparing cefsulodin and ticarcillin

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The efficacy of cefsulodin against infections caused by *Pseudomonas aeruginosa* was investigated first in an open trial and then in a controlled comparative study in which ticarcillin was used. The first trial consisted of 16 patients with proven *Pseudomonas aeruginosa* infections, 9 of whom also received an aminoglycoside. In the second trial 28 such patients were evaluated (14 on cefsulodin 1 g 4 times daily and 14 on ticarcillin 5 g 4 times daily); all patients also received an aminoglycoside. The results of the two trials were similar in that 75% of the patients of the first trial and 86% of the second group exhibited an excellent or good response to cefsulodin. For the ticarcillin group a similar response was noted. In the first trial the sensitivity of *P. aeruginosa* did not change markedly, whereas one strain of the cefsulodin group became resistant in the second trial. Pharmacokinetic data were in agreement with those reported in the literature. Side effects were rare. Neth J Med 1989; 34:233–242.

Key words: *Pseudomonas aeruginosa*; Cefsulodin; Ticarcillin; Clinical trial; Aminoglycoside

Introduction

Cefsulodin is a cephalosporin antibiotic with distinctive in vitro and in vivo activity against *Pseudomonas aeruginosa* [1,2]. Theoretically, this antibiotic has several advantages over other antibiotics with anti-*Pseudomonas* activity. First of all, it acts selectively against *P. aeruginosa*. Although this makes cefsulodin unsuitable for empirical therapy in serious infections, it is to be preferred in proven *Pseudo-*

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monas infections because all other anti-*Pseudomonas* drugs have a broader spectrum of antimicrobial activity. Secondly, compared to ticarcillin, the sodium load of cefsulodin therapy is negligible and the latter drug does not adversely affect platelet function. In order to investigate the efficacy of cefsulodin against infections caused by *P. aeruginosa*, an open trial among patients with severe *Pseudomonas* infections and then a controlled comparative study using ticarcillin were carried out. The aim of the latter part of the study was to establish whether cefsulodin is at least as efficacious as ticarcillin for the treatment of *P. aeruginosa* infections.

Materials and Methods

Patients

Twenty-two patients with suspected or proven infections caused by *P. aeruginosa* entered the first non-comparative trial after giving informed consent; only those who had not undergone previous anti-*Pseudomonas* treatment were eligible. This trial was part of an early multicentre trial of cefsulodin (Clinical report, Ciba-Geigy). The drug was given at a dosage of 1 g 4 times daily i.v.

In the second trial 28 patients with proven *Pseudomonas* infections were randomized to receive either cefsulodin (dosage: 1 g 4 times daily i.v.) or ticarcillin (dosage: 5 g 4 times daily i.v.), both in combination with tobramycin or netilmicin (dosage: 2 mg/kg 3 times daily and 3 mg/kg 3 times daily, respectively, adjusted for renal impairment if necessary). The latter drug was given to patients with preexisting substantial renal insufficiency or deafness. The dose of cefsulodin was adjusted to marked renal insufficiency in only four patients (two in the first and two in the second trial). Only those patients who had not received prior anti-*Pseudomonas* therapy, were included in this study, after having given informed consent; moreover the *P. aeruginosa* had to be sensitive to at least one of the beta-lactam antibiotics.

Sensitivity testing

In vitro sensitivity was tested by inoculation of a 1 : 1000 dilution of an 18-h culture on Isosensitest agar in a two-fold dilution series. Sensitivity was defined by an MIC for cefsulodin $\leqq 16$ mg/l and for ticarcillin $\leqq 128$ mg/l.

Evaluation of efficacy

Clinical criteria. At the end of treatment the clinical response was scored as excellent (cure), good (significant improvement), fair (some improvement) or poor (no improvement).

Bacteriological criteria. The bacteriological response was scored as elimination of the pathogen, reduction of the number of pathogens, no quantitative or qualitative change, or replacement by a different pathogen.

TABLE 1

Patient characteristics: open trial.

Age (yr)	Sex	Infectious condition	Medical history
58	M	Wound infection	Renal transplant/ surgery of ureter
76	F	Cystitis	–
43	M	Ecthyma gangrenosum	Non-Hodgkin's lymphoma
52	F	Pleural empyema	Bronchial carcinoma, lobectomy
56	M	Cholangitis	After cholecystectomy
49	M	Septicaemia + sinusitis	Hairy cell leukaemia
36	M	Pneumonia	Cystic fibrosis + bronchiectasis
54	M	Infected neoplastic skin lesions	Hodgkin's disease
78	M	Urinary tract infection	–
82	F	Urinary tract infection	–
31	M	Preputial infection with chills	Acute myeloid leukaemia
61	M	Prostatitis	–
20	F	Bronchopneumonia	Cystic fibrosis
59	M	Lung abscess	–
21	M	Bronchopneumonia	Cystic fibrosis
20	F	Bronchopneumonia	Cystic fibrosis

* Patient died, due to infection.

Cefsulodin with (+) or without (–) aminoglycoside	Response	
	clinical	bacteriological
–	Good	Replacement (*S. epidermidis*)
–	Good	Elimination
+	Good	Elimination
–	Fair	No change
+	Good	Replacement (*K. pneumoniae*)
+	Good	Elimination
+	Poor	Replacement (*P. mirabilis*)
–	Poor *	No change
–	Excellent	Elimination
–	Good	Elimination
+	Excellent	Elimination
–	Good	Elimination
+	Good	Replacement (*Pseudomonas* sp. + *H. influenzae*)
+	Good	Elimination
+	Poor	Elimination
+	Good	Elimination

TABLE 2a

Results of treatment with cefsulodin: comparative trial.

Age (yr)	Sex	Infectious condition	Medical history	Aminoglycoside (T = tobramycin N = netilmicin)	Response	
					clinical	bacteriological
48	M	Pulmonary infiltrate	Tonsillar carcinoma, resection lymph nodes	T	Excellent	Reduced
55	F	Pneumonia	Diabetes mellitus; myasthenic syndrome	T	Good	Resistant
20	M	Abscess in axilla	Non-Hodgkin's lymphoma	T	Excellent	No follow-up
66	M	Otitis media	Diabetes mellitus, cerebral vascular disease	N	Poor	No follow-up
69	M	Urinary tract infection + lower resp. tract inf.	Cardiac & renal insufficiency; peptic ulcer	T	Good	Reduced
70	M	Perichondritis	–	N	Good	Elimination
75	M	Pneumonia	Postoperative (bifurcation prosthesis); chronic respiratory disease	T	Good	Elimination
67	M	Colonization by *Pseudomonas*	Non-Hodgkin's lymphoma; granulocytopenia (granulocyte count $< 0.5 \times 10^9/l$)	T	Good	Elimination
62	M	Septicaemia	Ileus; chronic lymphocytic leukaemia	T	Good	Elimination
73	M	Bronchopneumonia	Postoperative (aortic valve prosthesis); pulmonary emphysema	T	Fair	Elimination
74	M	Urinary tract infection	Total hip replacement; diabetes	T	Good	Replacement (*Candida*)
64	F	Respiratory tract inf.	Bronchiectasis; lobectomy ($1\frac{1}{2}$ yr)	T	Good	Elimination
67	M	Chronic external otitis	Angina pectoris	N	Excellent	Elimination
56	M	Septicaemia	Leukopenia (recent chemotherapy); (granulocyte count $< 1.0 \times 10^9/l$) thoracotomy	T	Good	No follow-up

TABLE 2b

Results of treatment with ticarcillin: comparative trial.

Age (yr)	Sex	Infectious condition	Medical history	Aminoglycoside (T = tobramycin N = netilmycin)	Response	
					clinical	bacteriological
43	M	Perichondritis (left ear)	Schizophrenia	T	Excellent	No follow-up
84	F	Pyelonephritis/septicaemia	Cerebrovascular accident	T	Good	Elimination
71	M	Pneumonia	Acute lymphocytic leukaemia, diabetes mellitus	T	Good	Reduced
36	M	Urinary tract infection	Hip prosthesis, renal transplant (5 yr)	N	Good	Elimination
36	M	Pneumonia	Allogenic bone marrow transplantation	T	Poor	No follow-up
50	F	Perichondritis/ external otitis	Agranulocytosis; recurrent external otitis, perichondritis	N	Excellent	Elimination
76	F	Pyelonephritis/septicaemia	Diabetes mellitus; renal insufficiency	N	Excellent	Replacement (*Enterococcus*)
80	M	Cholangitis/bacteraemia	Pancreatic carcinoma	T	Good	Elimination
71	M	Pleural empyema	Lobectomy; diabetes mellitus	T	Poor	No change
67	M	Urinary tract infection	Surgery for subdural haematoma & empyema; impaired micturition	T	Good	Replacement (*K. pneumoniae*)
68	M	Bronchopneumonia	Respiratory insufficiency, chronic bronchitis; diabetes mellitus, sick sinus syndrome, cardiac failure	T	Good	Elimination
84	M	External otitis	Chronic bronchitis	N	Good	Elimination
67	M	Respiratory tract infection	Bronchiectasis	T	Good	Elimination
24	M	Septicaemia	Allogenic bone marrow transplantation	T	Good	Replacement (*S. epidermidis*)

Pharmacokinetics

In the first study blood samples were taken on one of the first few days of treatment with cefsulodin at 0, 1, 2, 3, 4, and 6 h and, if possible, 1 week later. Blood was collected in heparinized tubes and centrifuged; plasma was stored at −70 °C until the assay. Cefsulodin concentrations were determined microbiologically by agar diffusion, using a *P. aeruginosa* strain (10701) as test organism. The exponential elimination rate constant was calculated from the plasma concentrations by the least-squares method. The concentration at zero time was calculated by extrapolation. The apparent volume of distribution was calculated by dividing the dose by the concentration at zero time. Total plasma clearance was calculated as the product of the volume of distribution and the elimination rate constant.

Results

First study

Of the 22 patients that entered the study, two were excluded because *P. aeruginosa* was not the cause of the infection. The MIC of cefsulodin was 2 to 4 mg/l in the majority of patients, but in a few patients it was 8 or 16 mg/l. The efficacy could not be evaluated in four cases because of early death due to unrelated causes [3] and discontinuation of treatment because of side effects [1]. The diagnoses of the remaining 16 patients are given in Table 1.

Of these 16 patients, seven received only cefsulodin and nine were on combination therapy (cefsulodin plus tobramycin, in most cases). The clinical response was excellent in two, good in ten, fair in one and poor in three cases. One of the poor responders died (due to the *P. aeruginosa* infection). There was no difference in response between patients receiving cefsulodin alone and those on combination therapy (efficacy rate 5/7 and 7/9, respectively).

As for the bacteriological response, the pathogen was eliminated in 10 of 16 patients. Of the remaining six patients, two exhibited no change, while four had a different pathogen (*Klebsiella pneumoniae, Proteus mirabilis, Staphylococcus epidermidis* and *Pseudomonas* sp. together with *Haemophilus influenzae*) that had replaced the *Pseudomonas aeruginosa*. The sensitivity of *P. aeruginosa* did not decrease markedly during cefsulodin treatment in any of our patients. There was no relation between initial MIC and response.

Second study

Of the 28 patients, 14 were treated with cefsulodin and 14 with ticarcillin. Eleven in the cefsulodin group and ten in the ticarcillin group received combination therapy with tobramycin, the remainder were treated with netilmicin (see Materials and Methods). Patient characteristics are presented in Tables 2a and b. The two groups were similar as far as sex, age and underlying illness were concerned. In practically all patients the MIC for cefsulodin was 2 or 4 mg/l and that for ticarcillin 8 or

16 mg/l. For the cefsulodin group the clinical response was excellent in three, good in nine, fair in one and poor in one case. For the ticarcillin group the clinical results were similar: excellent in three, good in nine and poor in two cases; one of the poor responders, however, died of other causes during therapy. The bacteriological response in the cefsulodin-treated group was elimination of the pathogen in seven patients and reduction of the number of micro-organisms in two patients. In one case the *Pseudomonas* became resistant (MIC more than 64 mg/l); moreover a second micro-organism (*Proteus inconstans*) was cultured from this patient's sputum. In a second case *Candida albicans* was cultured from urine after irradication of the *Pseudomonas*. No bacteriological follow-up was available for three patients. In the ticarcillin group *P. aeruginosa* was also eliminated in seven, decreased in one and unchanged in one case. In three patients *Pseudomonas* was replaced by a different micro-organism: *Klebsiella pneumoniae, Enterococcus* and *Staphylococcus epidermidis*. Bacteriological follow-up was not performed in two cases. Again there was no relation between initial MIC and response.

Side effects

Side effects were rare. One patient on cefsulodin developed thrombophlebitis at the site of the infusion catheter and another developed thrombocytopenia. In the latter case cefsulodin-dependent antibodies against platelets could be detected by the method of Claas et al. [3]. Both side effects were seen in the first study.

Pharmacokinetics

Using the data on 13 patients we were able to calculate the pharmacokinetic parameters for cefsulodin; in six cases, the plasma concentrations were measured on the first day of treatment and on the eighth day. Pertinent data are given in Table 3. In patients 1 and 14 the dose was adjusted to 600 and 750 mg 4 times daily, respectively. In all patients maximal concentrations ranged between 20 and 50 mg/l – except in patient 1, in whom maximal concentrations between 70 and 160 mg/l occurred – and through concentrations of about 4 to 10 mg/l, without unwanted effects. The calculated plasma clearance correlated closely with the creatinine clearance, as calculated from body weight and plasma creatinine according to the method of Siersbaek-Nielsen [4] (Fig. 1). It can be seen that for all practical purposes cefsulodin plasma clearance may be regarded as being equal to creatinine clearance. The mean half life, as calculated from the mean elimination rate constant, was 2 h. There was no consistent change in pharmacokinetic parameters between the first day and one week later.

Discussion

The overall results of an open and a comparative trial on the treatment of *P. aeruginosa* infections with cefsulodin were remarkably similar. An excellent or good response was observed in at least 75% of the patients. In this respect our data corroborate those published earlier [5–7].

TABLE 3

Pharmacokinetic parameters of cefsulodin in 13 patients.

Patient number	Volume of distribution (l)	Volume per kg bodyweight (l/kg)	Elimination rate constant (h^{-1})	Cefsulodin clearance (ml/min)	Creatinine clearance (ml/min)	$T_{1/2}$ (h)
1	15.7 *	0.37 *	0.104 *	26.9 *	17.4 *	6.66 *
2	15.7	0.26	0.195	50.9	59.7	3.55
5	27.0 *	0.57 *	0.268 *	104.5 *	94.0	2.59 *
6	25.3	0.39	0.557	243.9	86.2	1.25
7	21.2 *	0.35 *	0.436 *	153.8 *	137.5 *	1.59 *
11	22.6 *	0.43 *	0.301 *	113.0 *	128.9 *	2.30 *
14	18.9 *	0.35 *	0.270 *	83.9 *	36.9 *	2.57 *
16	18.3 *	0.27 *	0.305 *	92.9 *	65.8 *	2.27 *
18	47.0	0.82	0.279	218.1	69.8	2.49
19	16.6	0.43	0.591	163.1	106.5	1.17
20	20.9 *	0.34 *	0.318 *	109.5 *	107.7 *	2.18 *
21	19.3	0.34	0.373	120.1	153.1	1.86
22	11.6	0.27	0.568	109.4	96.0	1.22
mean	21.6	0.40	0.351	122.3	89.2	1.97 **
SD	(8.7)	(0.15)	(0.149)	(61)	(39.2)	

* Mean of values on two occasions.

** Calculated from mean elimination rate constant.

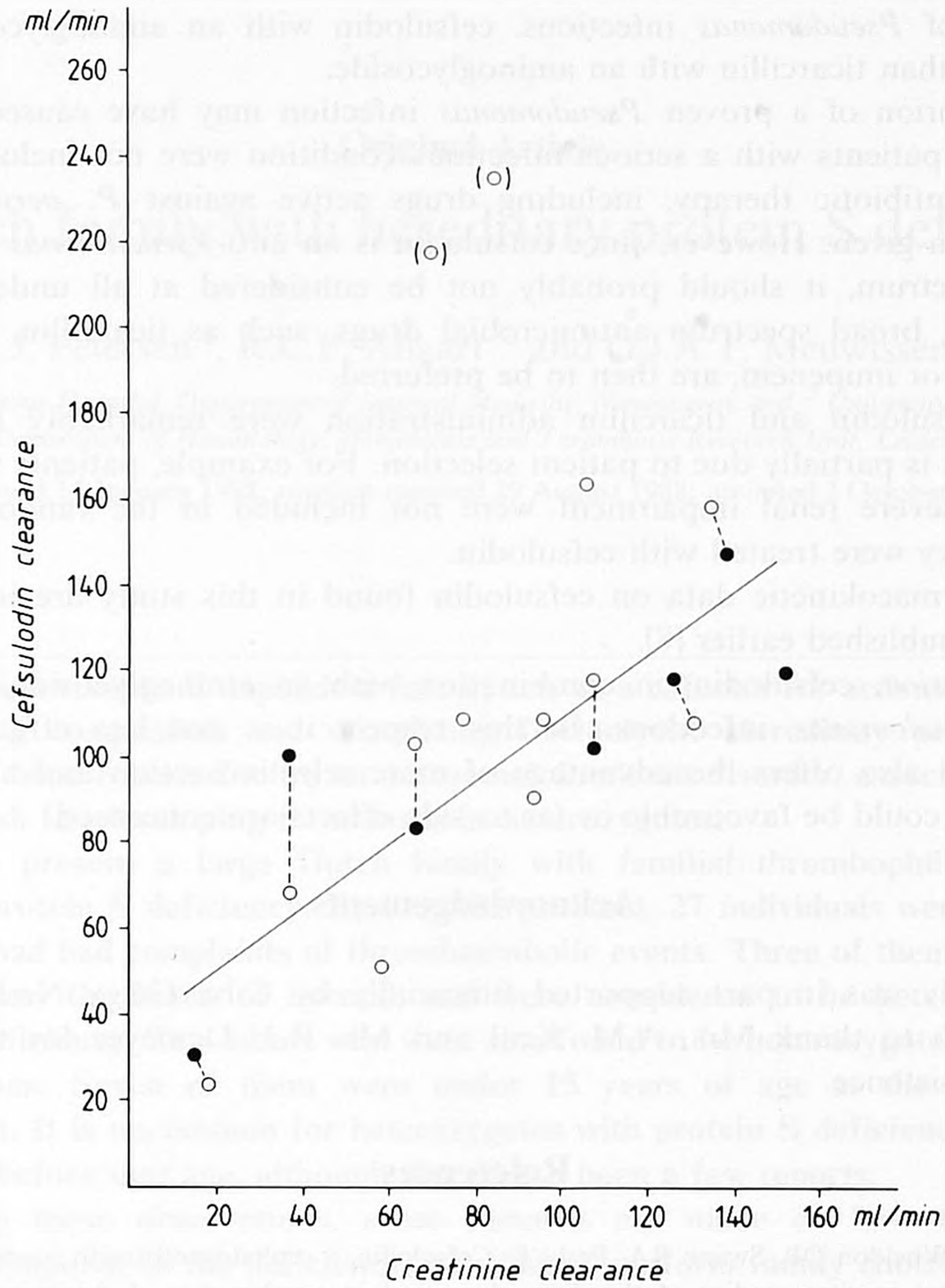

Fig. 1. Relation between total plasma clearance of cefsulodin and creatinine clearance in patients treated for *Pseudomonas* infections. Open and closed symbols represent initial assessment and assessment 1 wk later, respectively. Symbols in parentheses were not used for calculation of the regression line.

The majority of patients in the present study took the beta-lactam drugs in combination with aminoglycosides. There were two reasons for this approach: namely to increase efficacy, whether by an additive or synergistic effect, and (possibly even more important) to prevent or at least delay emergence of resistance to the beta-lactam antibiotic. Our study does not clearly demonstrate an increased efficacy as a result of the addition of aminoglycosides. Interestingly, combination with aminoglycosides could not prevent the emergence of resistance in one patient; in this case the micro-organism became resistant to cefsulodin as well as ticarcillin.

Due to the strict inclusion criteria, i.e. only patients with proven *Pseudomonas* infections who had not been treated previously with anti-*Pseudomonas* drugs, the study was limited in size. Nevertheless, there were no indications that, for the

treatment of *Pseudomonas* infections, cefsulodin with an aminoglycoside is less efficacious than ticarcillin with an aminoglycoside.

The criterion of a proven *Pseudomonas* infection may have caused some bias since some patients with a serious infectious condition were not included because empirical antibiotic therapy, including drugs active against *P. aeruginosa*, had already been given. However, since cefsulodin is an anti-*Pseudomonas* drug with a narrow spectrum, it should probably not be considered at all under these circumstances; broad spectrum antimicrobial drugs, such as ticarcillin, piperacillin, ceftazidime or imipenem, are then to be preferred.

Both cefsulodin and ticarcillin administration were remarkably free of side effects. This is partially due to patient selection. For example, patients with cardiac failure or severe renal impairment were not included in the randomized trial, although they were treated with cefsulodin.

The pharmacokinetic data on cefsulodin found in this study are in agreement with those published earlier [8].

In conclusion, cefsulodin, in combination with an aminoglycoside, is effective against *Pseudomonas* infections. In this respect it is not less efficacious than ticarcillin; it also offers the advantage of more selective action and a lower total dose, which could be favourable as far as side effects are concerned.

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References

1 Slack MPE, Wheldon DB, Swann RA, Perks E. Cefsulodin, a cephalosporin with specific antipseudomonal activity: in-vitro studies of the drug alone and in combination. J Antimicrob Chemother 1979;5:687–691.

2 Ruf KB. Monaspor® (Cefsulodin). Clinical and pharmacological profile of a unique antibiotic, highly effective against *Pseudomonas aeruginosa*. In: Pharmanual. A comprehensive guide to the therapeutic use of cefsulodin. Basel, München, Paris, London, New York, Sydney: Karger, 1980.

3 Claas FMJ, Van der Meer JWM, Langerak J. Immunological effect of cotrimoxazol on platelets. Br Med J 1979;2:298.

4 Siersbaek-Nielsen K, Mølholm Hansen J, Kampmann J, Kristensen M. Rapid evaluation of creatinine clearance. Lancet 1971;i:1133–1134.

5 Giamarellou H, Koumaditis A, Dispariki K, Xefteri H, Daikos GK. Therapeutic effectiveness and pharmacokinetics of cefsulodin in multi-resistant *Pseudomonas aeruginosa* infections. Drug Exp Clin Res 1981;7:219–226.

6 Ahrens T. Treatment of *Pseudomonas* infections with cefsulodin: results of a multicenter clinical trial in Europe. In: Periti P, Grassi GG, eds. Current chemotherapy and immunotherapy. Proceedings of the 12th International Congress of Chemotherapy, Florence, Italy: 19–24 July 1981;528–529.

7 Møller NE, Koch C, Vesterhauge S, Jensen K. Treatment of pulmonary *Pseudomonas aeruginosa* infection in cystic fibrosis with cefsulodin. Scand J Infect Dis 1982;14:207–211.

8 Vischer W, Gerardin A, Humbert G, Lecaillon JB, Schöller JP, Theobald W. Pharmacokinetics of cefsulodin after single and chronic intravenous administration to humans. In: Periti P, and Grassi GG, eds. Current chemotherapy and immunotherapy. Proceedings of the 12th International Congress of Chemotherapy, Florence, Italy: 19–24 July 1981;524–525.