THE USE OF CEFOTAXIME IN PNEUMOLOGY

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SUMMARY

The clinical efficacy of cefotaxime in lower respiratory tract infections has been studied. Thirty-three patients suffering from pneumonia, bronchiectasies, exacerbations of chronic bronchitis, lung abscesses and pleural empyema sustained by Gram-positive or Gram-negative organisms susceptible to cefotaxime, have been treated with the antibiotic at the doses of 1-2 g every 8-12 h by i.m. or i.v. route for 5-12 days. Cure was achieved in 84,3 % of patients, improvement in 9,3 %, no modification in 6,5 %. Responsive patients showed a very rapid improvement of the clinical status (2-4 days). The prompt action of cefotaxime is probably to be attributed to its high intrinsic antibacterial activity and to the effective concentrations reached in bronchial and lung tissue as well as in bronchial secretions.

RESUMO

O uso da Cefotaxima em Pneumologia

A fim de avaliar a eficácia da Cefotaxima nas infecções do tracto respiratório inferior foram estudados trinta e três doentes com pneumonia, bronquiectasias, exacerbação de bronquite crónica, abcesso pulmonar e empiema pleural causados por organismos Gram positivos ou Gram negativos sensíveis à Cefotaxima, os quais se submeteram a terapêutica com este antibiótico nas doses de 1-2 g cada 8-12 h. administrado pela via i.m. ou i.v. durante 5-12 dias. Em 84,3 % dos casos houve cura total enquanto que 9,3 % dos doentes melhoraram e 6,5 % não sofreram alteração do seu estado. Os doentes que responderam favoravelmente fizeram-no num curto espaço de tempo (2-4 dias). A rápida acção da Cefotaxima fica provavelmente a dever-se à sua grande actividade antibacteriana intrinseca e às elevadas concentrações atingidas quer nos tecidos pulmonares e brônquicos quer nas secreções brônquicas.

Cefotaxime (HR 756) is a semisynthetic derivative of cephalosporin endowed with a very high intrinsic antibacterial activity against Gram-positive and Gram-negative bacteria and a remarkable resistence to beta-lactamases. It is the most active compound against Enterobacteriaceae and beta-lactamase-producing Neisseria gonorrhoeae and Haemophilus influenzae.[1, 2, 3, 4, 5, 6, 7]

Because of these activities it is of great interest to test its activity in the treatment of bronchopulmonary infection.

EXPERIENCES AT OUR INSTITUTION

Penetration of the cefotaxime in lung tissue and bronchial secretions

Before performing the clinical trial, the pharmacokinetic behaviour of cefotaxime at the level of respiratory apparatus was studied.[8]

In fact the presence of adequate concentrations of antibiotic at the site of infection is considered necessary to achieve a therapeutic result. Hence, there is a growing interest in the pharmacokinetics of antibacterial drugs. A number of studies have been devoted to the determination of the antibiotic concentrations that can be achieved in bronchial secretions, on the assumption that efficient penetration in this area is important to obtain therapeutic results in bronchial infections or at least to accelerate them. Therefore, in pharmacokinetic studies of any new antibiotic the determination of penetration in bronchial secretions is considered useful in gaining a more complete profile of the antibiotic's behavior.

In the study performed in our Clinic the concentrations that cefotaxime can reach in bronchial secretions, sputum, and pulmonary and bronchial tissues after administration by intravenous and intramuscular routes were determined.

The study was performed in 30 patients (22 males, 8 females) with bronchopulmonary infections admitted to the Intensive Care Unit or to the Clinic of Respiratory Diseases. Antibiotic assays were carried out contemporaneously in serum and in bronchial secretion obtained through an inserted tracheal cannula or by fiberoptic bronchoscopy. In 12 patients the antibiotic content was measured in sputum. Patients were treated either with 2 g intravenously (as a bolus injection) or with 1 g intramuscularly every 8 h. In six patients who underwent pulmonary surgery for lung cancer, a single dose of 2 g of cefotaxime was injected before operation to make possible to obtain specimens of bronchial and pulmonary tissue 1 h after administration.

Some of the results obtained in this study are shown in Table 1. After administration of 2 g intravenously, very high serum levels were achieved the peak being at 15 min. with mean values of 266.6 μg/ml. After intramuscular injection of 1 g, the peak was reached after 30 min. to 1 h. Peaks in bronchial secretions were usually obtained 1-2 h after intramuscular administration they were usually reached after 2 to 4 h. The bronchial secretion/serum ratios showed a tendency to increase with time, that is they were higher when serum concentrations were at the lowest levels (from 0.01 to 0.02 at 30 min. to 0.25 to 0.53 at 8 h). Cefotaxime concentrations in bronchial secretions have a trend to increase with the time and to accumulate after repeated administrations. Higher and more constant levels seem to be

Received: July 7, 1982

TABLE 1 **Concentrations of cefotaxime in serum and bronchial secretions after administration by i.v. or i.m. route**

Treatment	Specimen	Concentration (μg/ml) mean values ± S.D.					
		30'	1H	2H	4H	6H	8H
2 g i.v.	Serum	137 ± 61.3	105 ± 50.5	48 ± 26.8	22.5 ± 9	3.19 ± 2.1	0.68 ± 0.4
	Bronchial Secr.	1.52 ± 1.4	2.96 ± 1.65	1.60 ± 0.7	0.94 ± 0.40	0.48 ± 0.34	0.17 ± 0.28
1 g i.m.	Serum	33.9 ± 11.3	26.9 ± 8.3	17.5 ± 3.9	8.2 ± 3.1	3.3 ± 8.6	1.2 ± 0.4
	Bronchial Secr.	0.28 ± 0.26	0.74 ± 0.38	1.58 ± 1.37	1.52 ± 0.97	0.80 ± 0.44	0.37 ± 0.37
1 g i.m. every 8 h (0)	Serum	31.8 ± 8.7	27.6 ± 6.5	17.2 ± 4.2	7.6 ± 2.2	3.2 ± 1	0.79 ± 0.4
	Bronchial Secr.	0.58 ± 0.41	0.96 ± 0.38	2.46 ± 0.94	2.30 ± 0.99	0.86 ± 0.48	0.42 ± 0.28

(°) Assay performed after the fourth administration

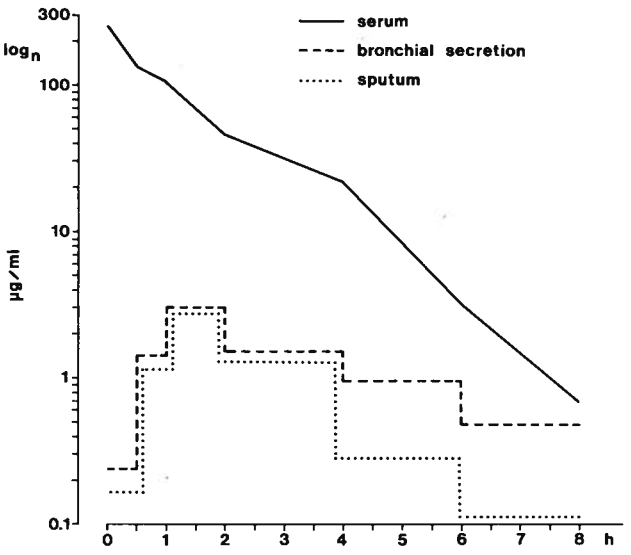

Figura 1: HR 756: concentrations in serum, bronchial secretion and sputum.

reached by repeated intramuscular administration, as it can be seen by the data obtained after four intramuscular doses of 1 g (Table 1).

From the results obtained in these experiences the conclusion can be drawn that the levels of cefotaxime in bronchial secretion represent, as do those of all other cephalosporins, only a small percentage of the concentrations in serum. However they are in the range of concentrations active on the common respiratory pathogens as well as on many Enterobacteriaceae, Providencia, Serratia, and, to a certain extent, on Pseudomonas aeruginosa organisms. Due to the high intrinsic antibacterial activity of cefotaxime, peak concentrations achieved in bronchial secretions were manyfold higher than the MIC (approximately 5 to 20 fold higher) for the susceptible strains, and even the trough levels were superior to the MIC (Fig. 1).

In bronchial and lung tissues the contents of antibiotic is very high, many fold higher than in bronchial secretions. Usually the concentrations are a little more elevated in bronchial than in pulmonary tissue; a mean value 7.6 μg/g versus 5.3 μg/g.

In conclusion these data show that cefotaxime diffuse very well in bronchial and lung tissue and reaches effective concentrations also in bronchial secretions. They allow to expect a good therapeutic efficacy of cefotaxime in respiratory infections.

Clinical experiences

33 patients (16 males and 17 females), of age ranging between 19 and 78 years, with normal renal function entered in our study. One of them was not evaluable since he left the hospital before the completion of therapy. The schedules of treatment were the following ones:

1 g every 12 h i.m.: 10 patients
1 g every 8 h i.m.: 4 patients
2 g every 12 h i.v.: 12 patients
2 g every 8 h i.v.: 7 patients

The different dosages and schedules of treatment were chosen according to the disease. The period of treatment ranged between 5 and 12 days. The patients were suffering from pneumonia, bronchiectasies, exacerbations of chronic bronchitis, lung abscesses, pleural empyema. The concomitant pathology was mainly lung cancer, followed, by pneumoconiosis, tuberculosis, asthma (Table 2).

The causative pathogens were isolated and identified, by the use of common microbiological methods[9] from bronchial aspirates, except in three cases in which they were obtained from sputum (Table 3). The susceptibility to antibiotics of the isolated microrganisms was determined by

TABLE 2 **Clinical diagnosis in patients treated with cefotaxime**

Diagnosis	N. of cases	Concomitant pathology	N. of cases
Pneumonia	12	Lung Cancer	6
		Pneumo-coniosis	1
		Tbc	2
Bronchiectasies (exacerbations)	6		
Chronic Bronchitis (exacerbations)	7	Asthma	2
Lung Abscess	5		
Pleural Empyema	2	Lung Cancer	1

TABLE 3 **Bacteriological results in patients treated with cefotaxime**

Organisms Isolated from Bronchial Aspirates	N. of Strains	Elimi-nation	Persis-tence	Superin-fection
Staph. Aureus Pen-Sens (°)	4	4		
Staph. Aureus Pen-Res (°°)	5	4	1	
Str. Pneumoniae	9	8	1	
Strept. Beta-Haemol (Group A)	2	2		
Strept. Viridans (°)	1	1		
H. Influenzae	2	2		
Klebsiella Pn.	6	5		1
Proteus Mirabilis	1	1		
Proteus Vulgaris	1	1		
Pseudomonas Aer.	2		2	
Total	33	28 (84.8%)	4 (12.1%)	1 (3.1%)

(°) Staph. Aur. + Strept, Viridans isolated from sputum of one case.
(°°) 1 Strain from sputum.

Kirby-Bauer technique.[10] If the causative organism was resistant to cefotaxime, the patient was withdrawn from the study.

All patients were submitted to standard laboratory tests to monitor haemotological parameters and hepatic and renal functions and clinical chemistry as well as to bacteriological examination of sputum before the tratment, after five day treatment and 24 hours after the end of treatment.

The evaluation of the efficacy of therapy was based on the following parameters: improvement of the clinical status, χ-ray modification, decrease of volume of sputum, modification of its characteristics, bacteriological results.

The results that we obtained will be briefly summarized here: (Table 3) the microrganisms isolated were all susceptible to cefotaxime and in their majority (about 85%) were very rapidly eliminated, usually within 2-4 days. At the end of treatment one strain of Staphylococcus aureus and one of pneumococcus were not eradicated, but the patients were markedly improved and needed no further antibiotic treatment.

In one case of exacerbation of bronchiectasies due to Klebsiella there was a superinfection due to Proteus vulgaris that required a treatment with aminoglycoside associated to other antibiotics.

Finally the two infections due to Pseudomonas aeruginosa susceptible to cefotaxime were not eliminated and required the addition of tobramycin to be eradicated. These observations confirm that cefotaxime can be active on Pseudomonas aeruginosa in vitro, but usually it is not in position to have a good therapeutic effect when used in clinical infections due to this species.

The clinical efficacy of cefotaxime is documented by the high percentage of patients cured (84%). It is worth of attention the rapidity by which cure is reached.

In responsive patients signs of improvement, that is reduction or disappearance of fever, reduction of sputum volume and decrease of its purulence, were often obtained in 2-4 days. The overall clinical results are shown in Table 4.

TABLE 4 **Cefotaxime in Bronchopulmonary Infections: Evaluation of Therapeutic Results**

	N. of Patients	N. of Patients		
	N. of Patients	Cured	Improved	Unchanged
Pneumonia	12	11	1	
Bronchiectasies (Exacerbations)	6	4	1	1
Chronic Bronchitis (Exacerbations)	7	7		
Lung Abscess	5	4		1
Pleural Empyema	2	1	1	
Total	32	27 (84.3%)	3 (9.3%)	2 (6.5%)

No signs of renal or liver impairment were observed (Table 5). In conclusion cefotaxime, in our experience, showed to be highly effective in the treatment of respiratory infections, sustained both by Gram-positive and Gram-negative species. Moreover it was very well tolerated.

TABLE 5 **Some Laboratory data in Patients Treated with Cofotaxime**

	Bun	Creatininemia	SGPT
Before Treatment	29.2 ± 13.6	1.01 ± 0.09	12.15 ± 6.4
After Treatment	32.4 ± 18.6	1.13 ± 0.11	14.04 ± 5.3

Similar satisfactory results in the treatment of different infections of the lower respiratory tract have been reported also by other Authors.[11, 12, 13, 14, 15]

One of the most striking features of the clinical effects of cefotaxime has been, in our study, the rapidity of its action, allowing a clear improvement of the clinical situation in many cases within 2-4 days.

The reason of its prompt action is probably to be attributed to many factors. On one hand cefotaxime is endowed with high intrinsic antibacterial activity, due probably to a very high affinity for target proteins (penicillin Binding Proteins) of bacteria [16] and with a good resistance to beta-lactamases destruction, that allow it, for instance, to be active also on ampicillin-resistant H. influenzae.[7] On the other hand it reaches very high concentrations in bronchial and lung tissues, that are many-fold higher the MIC of susceptible organisms.

Also the levels in bronchial secretions, even if low with respect to serum concentration, as it happens with all beta lactamase antibiotics, range in limits within which susceptible strains can be eliminated.

The combination of these favourable characteristics in antimicrobial activity and in pharmacokinetic behaviour can account for the therapeutic effectiveness of cefotaxime.

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