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Penetration of Cefotaxime and Desacetylcefotaxime into Brain Abscesses in Humans

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Since clinical trials comparing the efficacies of different antibiotic regimens for treatment of brain abscesses are difficult to perform, the choice of antibiotics must rely on the antibacterial spectrum and the ability of the drug to penetrate into the abscess fluid. The aim of this investigation was to study the ability of cefotaxime and its active metabolite desacetylcefotaxime to penetrate into brain abscesses. Eight patients were given 3 g of cefotaxime intravenously every 8 h. Abscess fluid samples, obtained at surgery at various times after dosing, and blood samples were analyzed for their concentrations of cefotaxime and desacetylcefotaxime by using a newly developed microbiological assay. The brain abscess concentrations of cefotaxime and desacetylcefotaxime were 1.9 ± 1.7 and 4.0 ± 2.2 mg/liter, respectively. Simultaneous concentrations in plasma were 2.0 ± 1.0 and 3.9 ± 1.8 mg/liter, respectively. With increasing time following cefotaxime dosing there was a significant increase in the abscess:plasma concentration ratio of desacetylcefotaxime. Since both cefotaxime and desacetylcefotaxime penetrate well into the brain abscess, reaching concentrations above the MIC for probable bacteria except gram-negative anaerobes, it is concluded that cefotaxime in combination with metronidazole may be used as an alternative in the treatment of brain abscesses.

Brain abscesses are often caused by gram-positive bacteria such as streptococci, staphylococci, and anaerobic cocci. Less often the causative agent may be a gram-negative rod such as *Escherichia coli* or a *Klebsiella* or *Bacteroides* species. Frequently a mixed flora is found (1, 8, 14, 22).

Antibiotic treatment has often to be initiated before surgery and before the etiology of the brain abscess is known. It is therefore of importance that empiric antibiotic treatment be effective against possible etiological agents.

Since brain abscess is an uncommon disease, it is unlikely that clinical trials comparing the efficacies of different antibiotics for treatment of brain abscesses will comprise sufficient numbers of patients to obtain a reasonable statistical evaluation of differences between regimens. The choice of antibiotics must therefore rely on the antibacterial spectrum and the ability of the drug to penetrate into the abscess fluid (7, 11, 29).

For many years, penicillin G in combination with chloramphenicol has been regarded as the empiric standard therapy (5, 7, 11). Recently, the efficacies of different antibiotic regimens in the treatment of brain abscesses were reviewed, and it was stated that chlorampenicol was not an efficacious therapy and that cefotaxime plus metronidazole might be an alternative for the treatment of brain abscess (5).

Cefotaxime, one member of the broad-spectrum cephalosporins, has a suitable antibacterial spectrum covering most bacteria causing brain abscesses. Cefotaxime undergoes desacetylation in the liver by nonmicrosomal pathways to desacetylcefotaxime (6, 28). Although this metabolite is less active than cefotaxime, its antibacterial spectrum and activity are comparable to those of the expanded-spectrum cephalosporins, and synergy between the metabolite and the parent compound is common (23).

The aim of this study was to investigate the ability of cefotaxime and desacetylcefotaxime to penetrate into human brain abscess fluid. Since desacetylcefotaxime has lost one polar acetyl group and therefore should be less hydrophilic than its parent compound, it was hypothesized that desacetylcefotaxime might penetrate better into the abscess fluid than cefotaxime.

MATERIALS AND METHODS

Subjects. Eight patients (five males and three females), with an average age of 46 ± 18 years, with brain abscesses were entered into the study. The diagnosis was suspected from clinical symptoms and signs and from the results of computerized tomographic scanning and was confirmed at surgery. The mean body weight and surface area of the patients were 69.9 ± 18.8 kg and 1.81 ± 0.30 m^2, respectively. Serum creatinine concentration was 77.1 ± 24.4 μmol/liter. The patients had no history of renal or hepatic disease or allergy to β-lactam antibiotics. Predisposing diseases, suspected routes of entry, location of the abscesses, and antibiotic treatment prior to the start of the cefotaxime therapy are shown in Table 1. All patients were given corticosteroids to reduce brain edema.

Informed consent was obtained from the patients or next of kin. The study protocol was approved by the Ethics Committee of the Medical Faculty, Uppsala University.

Study protocol. When the clinical diagnosis of brain abscess had been made, a loading dose of cefotaxime (4 g) was given as an intravenous bolus injection followed by 3 g intravenously every 8 h. All patients also received 0.5 g of metronidazole intravenously every 8 h. Cefotaxime and metronidazole were not given simultaneously. Immediately before the cefotaxime dose preceding the operation, a venous blood sample was taken for trough concentrations of cefotaxime and desacetylcefotaxime in serum. Further blood samples were obtained at 1, 2, 4, 6, and 8 h after the dose and at the same time as the abscess sample was obtained. After centrifugation, serum was stored at −70°C, pending analysis.

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TABLE 1. Subjects studied and culture findings

Subject	Predisposing factor(s)	Location of abscess	Previous antibiotic treatment (antibiotic/duration)	Bacteria isolated from abscess	MIC (mg/liter) for isolated bacteria		No. of cefotaxime doses before surgery
					ctx[a]	desctx[a]	
1	Eisenmenger syndrome, sinusitis	Temporal lobe	Cefuroxime/7 days	*Streptococcus faecium*, group B streptococci, peptostreptococci	0.25 ND[b] 0.125	1.0 ND 1.0	1
2	Sinusitis	Parietotemporal lobe	None	Unspecified microaerophilic streptococci	0.125	0.5	3
3	Meningioma operation	Temporal lobe	None	No growth			6
4	Sinusitis	Frontal lobe	Chloramphenicol/1 day	*Streptococcus pneumoniae*	0.007	0.06	2
5	Intracerebral hematoma operation	Occipitoparietal lobe	Cefuroxime/3 days	*Staphylococcus epidermidis*	0.5	2.0	1
6	Tooth infection, maxillary osteitis	Parietooccipital lobe	Chloramphenicol/1 day	*Streptococcus milleri*	0.5	2.0	2
7	None found	Parietotemporal lobe	None	No growth			7
8	None found	Frontal lobe	Cefuroxime/7 days + chloramphenicol/1 day	*Streptococcus intermedius*	0.02	0.06	3

[a] ctx, cefotaxime; desctx, desacetylcefotaxime.
[b] ND, not determined.

Excision of the abscess was performed in all patients. Samples from the abscess contents were obtained by needle aspiration before the excision and after careful hemostasis. Part of the aspirate was sent for culture. The remainder was stored at −70°C until analyses of cefotaxime and desacetylcefotaxime concentrations were performed.

Aerobic and anaerobic bacteriological cultures were grown according to routine laboratory methods. Specimens were delivered to the laboratory within an hour of sampling, and all cultures were incubated on the same day as the operation.

Analytical methods. Antibiotic concentrations in plasma and samples from abscess fluid were determined by a newly developed microbiological agar diffusion assay which permits separate determination of cefotaxime and desacetylcefotaxime (23a). All assays were performed in triplicate by using plates prepared in 16-cm petri dishes with DST agar (Oxoid) as medium. For assay of cefotaxime, a strain of *Proteus morganii* which is resistant to desacetylcefotaxime was chosen (27). However, no bacterial strain has been described that is susceptible to the metabolite but resistant to the parent compound. The principal method ideas were therefore (i) to determine the sum of the cefotaxime and desacetylcefotaxime concentrations, using a test strain yielding the same inhibition zones for both substances, and (ii) to subtract the separately measured cefotaxime concentration from the value obtained. A locally isolated *Providencia rettgeri* strain (PRU 1) was found to give almost identical inhibition zone diameters for both cefotaxime and desacetylcefotaxime.

Concentrations in plasma were analyzed together with standards prepared in pooled human serum. Since it was not possible to obtain brain abscess fluid for preparation of standards, the antibiotic concentrations in abscess fluid were determined with a standard prepared in phosphate-buffered saline.

The samples were analyzed after completion of the study. The storage time was less than 18 months. Seven samples of cefotaxime dissolved in phosphate-buffered saline with concentrations ranging from 0.5 to 50 mg/liter were analyzed before and after storage at −70°C for 18 months. There was a reduction in the concentration of 2.1% ± 1.1% (± standard error). If no measurable cefotaxime concentration was obtained, the limit of detection, 0.5 mg/liter, was subtracted from the sum of the concentrations.

The method error of the desacetylcefotaxime-cefotaxime determination, expressed as the mean coefficient of variation of spiked samples with a concentration interval 1.0 of 10.0 mg/liter, was 6.7%, while that of cefotaxime was 5.4%. For the calculated desacetylcefotaxime value, the corresponding error was 7.6%.

Since chloramphenicol and cefuroxime were given to some patients before entry in the study, the influence on the test strains of different concentrations of these antibiotics from 2 mg/liter with twofold increases to 64 mg/liter was investigated. A zone inhibition diameter greater than that obtained by the lowest detectable concentration for the *Providencia rettgeri* strain was obtained with a cefuroxime concentration of 32 mg/liter and a chloramphenicol concentration of >64 mg/liter. Corresponding concentrations for the *Proteus morganii* strain were >64 and 64 mg/liter, respectively. The MICs of cefotaxime and desacetylcefotaxime for the bacteria isolated from the patients were determined by using twofold serial dilutions of the antibiotics in Mueller-Hinton broth with a bacterial inoculum of 10^5 CFU/ml.

Statistical methods. Regression analysis was used to test the relationship between time since the last dose and the abscess:plasma concentration ratios. Student's *t* test (two-tailed) was used to test the significance of the slope of the regression line. Values are given as mean ± standard deviation unless otherwise indicated.

RESULTS

Culture findings, MICs for isolated bacteria, and the number of cefotaxime doses before surgery are shown in Table 1. In six abscesses at least one microorganism was cultured.

The abscess fluid samples were obtained 6.0 ± 1.8 h after the dose preceding surgery. A measurable concentration of cefotaxime was found in all abscesses but one. In the seven patients whose abscesses contained cefotaxime, the cefotaxime concentration was 2.1 ± 1.6 mg/liter. A measurable desacetylcefotaxime concentration, 4.0 ± 2.2 mg/liter, was found in samples from all patients. The concentrations of

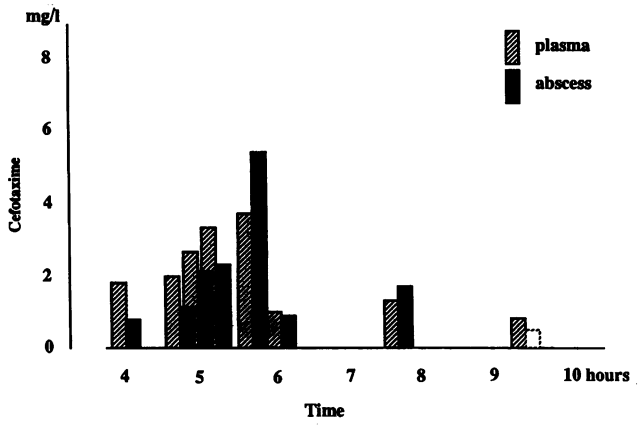

FIG. 1. Relationship between the concentration of cefotaxime in the abscess fluid and in plasma at various times following dosing in the eight patients. Unfilled bar represents concentration below the detection limit, 0.5 mg/liter.

cefotaxime and desacetylcefotaxime in plasma at the time of sampling were 2.0 ± 1.0 and 3.9 ± 1.8, respectively. Individual data on the concentrations of cefotaxime and desacetylcefotaxime in abscess fluid and plasma and the time interval following cefotaxime dosing are shown in Fig. 1 and 2. As shown in Fig. 3, there was a statistically significant increase in the abscess:plasma desacetylcefotaxime concentration ratios with time ($r = 0.74$; $P < 0.05$). The abscess:plasma cefotaxime concentration ratios showed a similar tendency ($r = 0.78$), if the patient in whom no measurable cefotaxime was found was excluded from the calculations. Results for patients given only one dose of cefotaxime are located below the regression line, while results for the two patients given six and seven doses, respectively, are located well above.

DISCUSSION

As shown in Fig. 4, the microbiological assay gave similar concentration profiles in plasma for cefotaxime and desacetylcefotaxime, as has previously been reported by using high-pressure liquid chromatography (15). The precision and accuracy are within the range reported for microbiological

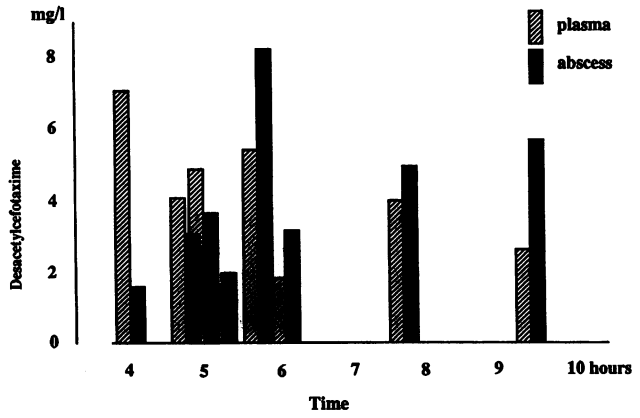

FIG. 2. Relationship between the concentration of desacetylcefotaxime in the abscess fluid and in plasma at the various times following dosing in the eight patients.

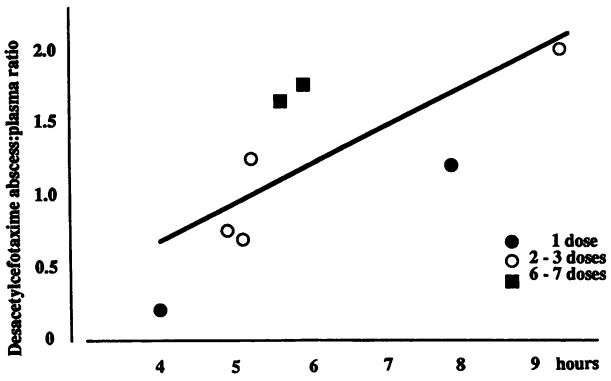

FIG. 3. Relationship between the desacetylcefotaxime abscess:plasma concentration ratio and the time interval between abscess fluid sampling and cefotaxime dosing in the eight patients. The calculated regression line, the equation of which is $y = 0.26x - 0.35$, and the number of cefotaxime doses administered before surgery are given.

assays, and it is very unlikely that antibiotics given prior to cefotaxime therapy would have reached the concentrations required to interact with the test strains. Since the abscess fluid samples were analyzed against a protein-free standard, concentrations obtained might be considered minimum levels.

Blood contamination of the abscess fluid is a potentially serious source of error for two reasons. First, concentrations in blood are often different from those measured in the abscess fluid, and second, it has been shown that cefotaxime is metabolized to desacetylcefotaxime in the presence of hemolyzed blood (26). However, since these abscess fluid samples were obtained after careful hemostasis by needle aspiration under visual control and the volume obtained

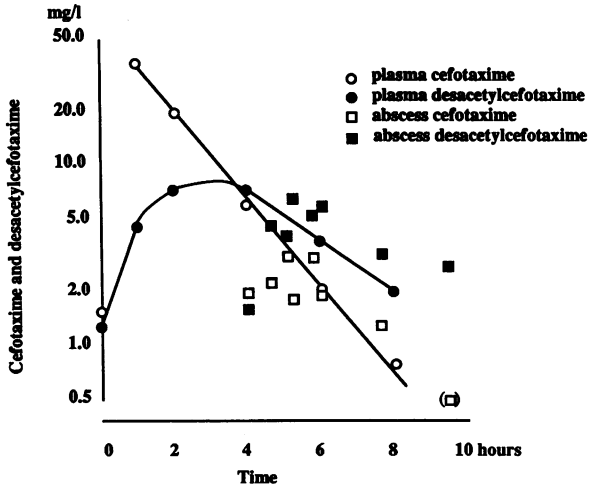

FIG. 4. Calculated abscess concentration time curves of cefotaxime and desacetylcefotaxime. All patients have been normalized to the mean plasma concentration time curve in order to reduce the influence of the high interindividual variation in plasma. The individual abscess:plasma ratios obtained from Fig. 1 and 2 have been applied to the mean concentration profiles in plasma.

ranged from 5 to 10 ml, no significant blood contamination might be expected.

There were measurable amounts of desacetylcefotaxime in the abscess fluid in all the patients and of cefotaxime in all but one. Previously the abscess:plasma antibiotic concentration ratio has been used as an index for the ability to penetrate into a brain abscess (20, 21). However, our data, with a significant rise in this ratio occurring with increasing time following dosing and possibly also with the number of doses, invalidate such an index. To allow interpretation of antibiotic abscess penetration data, information should be given about the time interval since the preceding dose, the number of doses, and the possibility of blood contamination of the samples.

Because it is impossible to take repeated samples from a human brain abscess, pharmacokinetic data for antibiotics in single individuals cannot easily be obtained. From our measured data (Fig. 1 and 2) it is difficult to determine the pharmacokinetic profile of cefotaxime and desacetylcefotaxime in the abscesses. This is probably mainly due to interindividual variation in the concentrations of the two substances in plasma caused by variation in body size, renal function, and hepatic cefotaxime metabolism. However, the influence of the interindividual variation in the concentrations in plasma on the concentration in the abscess may be reduced by multiplying the mean concentration in plasma at the time of sampling by the individual abscess:plasma concentration ratio, as shown in Fig. 4. In this way, concentrations in the brain abscess at various times following dosing are normalized for differences in the plasma pharmacokinetics. The resulting concentrations in abscesses exhibited a concentration-time profile with a peak concentration appearing 5 to 6 h after dosage. This time lag was expected because an abscess is a site with a low surface-area-to-volume ratio (3). The higher concentration of desacetylcefotaxime was also expected, since this compound is less hydrophilic than cefotaxime.

The standard empiric therapy for brain abscess is usually penicillin G in combination with chloramphenicol or metronidazole. The penetration of penicillin G into brain abscesses has in most cases been shown to be acceptable if high doses are given (5, 9). However, in some cases measurable penicillin concentrations are not achieved, despite very high doses (2, 9). Chloramphenicol has been considered an antibiotic with good pharmacokinetic properties (11, 29) for brain abscess treatment. This decision was based on early studies of antibiotic penetration into uninfected brain tissue, where it was found that chloramphenicol was concentrated in the brain tissue of 10 patients (19). However, data on penetration into brain abscess fluid are fewer and show much lower values and in some instances no measurable concentration at all (2, 9). This discrepancy may be explained by the fact that chloramphenicol, like other lipophilic drugs, may accumulate within cells, while the interstitial fluid concentrations are much lower (3, 4). It has also been shown that bacteria sensitive to penicillin and chloramphenicol may be cultured for prolonged periods during therapy (1, 2, 5). The reasons for this persistence are not known, but subtherapeutic concentrations, as discussed above, inactivation by bacterial or leukocytic enzymes (10, 17), and/or antagonism between penicillin and chloramphenicol have been proposed as explanations (5, 24, 25). Since achievable concentrations of penicillin and choramphenicol often seem to be close to the MICs for infecting bacteria, an antagonism between these antibiotics, well documented in vitro (16), may be of clinical significance. Penetration data for metronidazole into brain abscesses, obtained from four patients, are very favorable with high concentration values in all patients (12, 14).

The older cephalosporins have not been found to penetrate into brain abscesses (9), but there are previous reports on the penetration of expanded- and broad-spectrum cephalosporins. Brückner et al. have found cefotaxime concentrations of >2.2 mg/liter in three out of four patients, and similar cefoxitin concentrations in two patients following single-dose administration of 2 g of cefotaxime and cefoxitin, respectively (2a). Chun et al. (5) found 6.3 mg/liter in one patient who had received 2 g every 6 h. However, no information on whether a selectively cefotaxime-sensitive test strain was employed in the assay was given by these authors. Recently, penetration of ceftazidime into intracranial abscesses has been demonstrated (13).

As can be seen from Fig. 1 and 2, all patients had detectable levels of at least one of the antibiotics in the abscess fluid, in spite of the simultaneous corticosteroid treatment, which has been shown to reduce the penetration of lipid-insoluble antibiotics (18). The concentrations obtained exceeded the MIC for 90% of strains tested of most causative agents, with the exceptions of *Staphylococcus epidermidis* and *Bacteroides fragilis* (23).

In comparison with data on penicillin and chloramphenicol penetration, our data indicate that the combination 0.5 g of metronidazole–3 g of cefotaxime intravenously gives a reliable therapeutic antibiotic activity in brain abscesses. Furthermore, synergistic or at least additive effects between cefotaxime and its metabolite may be expected rather than the possible antagonism between chloramphenicol and penicillin previously discussed (5, 23–25). However, the possibility that inhibitory levels will not be achieved for some strains of *S. epidermidis*, which are sometimes encountered in postoperative and posttraumatic abscesses, must be further discussed. The MICs for 90% of the strains tested of cefotaxime and desacetylcefotaxime for strains of *S. epidermidis* have been determined as 8 and 32 mg/liter, respectively (23), and are higher than concentrations in abscesses obtained in the present study, but it must be considered that in our study, with the standards used in the assay, minimum concentrations in abscesses have been determined and that these concentrations will most probably continue to increase over the following days when more doses of cefotaxime have been given, as indicated in Fig. 3. If strains of *S. epidermidis* with a high MIC of cefotaxime or with methicillin resistance are found in the culture from a brain abscess, various other antibiotics, e.g., fusidic acid, rifampin, vancomycin, or clindamycin, may be alternatives, but underlying data are scarce and further investigations of concentrations of these antibiotics in brain abscesses are necessary.

It is concluded, in the lack of clinical trials, that the combination of cefotaxime and metronidazole may be used as an alternative in the treatment of brain abscesses, since both cefotaxime and metronidazole penetrate well into the brain abscess, reaching concentrations above the MIC for most common causative bacteria. Furthermore, desacetylcefotaxime concentrations in brain abscesses exceed those of cefotaxime, and for most bacteria causing brain abscesses, synergy or at least additive effects between cefotaxime and its metabolite may be expected.

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