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An evaluation of the penetration of cefuroxime axetil into human paranasal sinus tissue

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SUMMARY

Nineteen patients presentingfor sinus surge,y were studied to evaluate the percentage penetrationfrom serum to paranasal sinus tissue ofa single orally administered dose of cefuroxime axetiI The methods and results are presented. Cefuroxime penetrates well into human sinus mucosafollowing oral administration and the concentrations obtained exceed minimum inhibit0ty concentrations of cefuroxime for the most common pathogens in sinusitis.

INTRODUCTION

Sinusitis is a common disease needing antimicrobial therapy when relief of acute symptoms is required, for prevention of serious intracranial and orbital complications and to avoid recurrent or chronic infection. Whilst *Streptococcus pneumoniae* and *Haemophilus influenzae* are still the most frequently isolated pathogens (Sydnor et al., 1988, 1989) a wide range of other organisms are commonly found including *Staphylococcus aureus, Moraxella catarrhalis, Streptococcus pyogenes* and various anaerobes (Gwaltney and Haydn, 1982; Sydnor et al., 1988). The emergence of ,8-lactamase-producing strains of ***H*** *injluenzae* and ***M*** *catarrhalis* will influence the choice of antimicrobial agent (Shurin et al., 1983, Roge et al., 1989).

Cefuroxime axetil is the 1-acetoxyethyl ester of cefuroxime and is a pro-drug of that compound. Following oral administration the ester linkage is hydrolysed in the intestinal mucosa resulting in therapeutic concentrations of cefuroxime in serum.

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Clinical studies have shown cefuroxime axetil to be an effective treatment in acute sinusitis (Griffiths et al., 1987; Hebblethwaite et al., 1987; Mackay and Lund, 1988; Brodie et al., 1989). The therapeutic efficacy of an antibiotic may be assessed by its ability to achieve a concentration at the focus of infection greater than the minimum inhibitory concentration of the bacteria causing the infection (Sunberg et al., 1983). Serum levels do not necessarily give an accurate indication of the drug concentration in the target compartment and therefore, tissue penetration studies are necessary. The pharmacokinetic profile of cefuroxime axetil in serum is well characterized (Sommers et al., 1984; Williams and Harding, 1984; Wise et al., 1984; Adams et al., 1985; Ginsberg et al., 1985), but data are lacking concerning penetration of the drug into paranasal sinus tissue. The aims of this study were to evaluate the penetration of orally administered cefuroxime axetil into paranasal sinus tissue and to compare the concentrations achieved in sinus tissue with its in vitro antibacterial activity.

MATERIAL AND METHODS

Nineteen patients were entered into this prospective dual centre, non-comparative study. There were nine men and ten women, their ages ranged from 22 to 76 years (mean 47 years) (Table 1). All patients were admitted for evaluation and surgical treatment of chronic sinusitis either by sinoscopy or functional endoscopic sinus surgery. A sinus mucosal biopsy was obtained during these procedures from either the maxillary or ethmoid sinuses. The surgery was performed under general anaesthesia using a premedication of an opiate analgesic (papaveretum or pethidine) and an anticholinergic agent (hyosine or atropine). Induction of anaesthesia involved sodium thiopentone and suxamethonium and was maintained by spontaneous respiration with oxygen, nitrous oxide and either isoflurane or halothane.

Those patients known to be allergic to penicillins or cephalosporins, with renal or hepatic insufficiency, with cystic fibrosis, who received antibiotic therapy in the previous three days or were receiving any decongestants and pregnant or lactating women were excluded.

After overnight fasting a single oral dose of 500 mg cefuroxime axetil was administered. Blood samples (5 ml) were taken just before given the cefuroxime

Table 1. Distribution of patients by age and sex.

	male	female	total
number of patients	9	10	19
age in years:			
mean	47.6	46.4	46.9
range	22-76	25-76	22-76

and then at half-hourly intervals up to and simultaneously with the sinus mucosal biopsy. After collection the blood samples were centrifuged and the serum collected. Mucosal specimens were placed in preweighed plastic cupules, sealed to prevent weight loss by dessication and then reweighed. Both were stored at -20 °C prior to assay. Cefuroxime levels in the serum and tissue samples were assayed by high performance liquid chromatography.

RESULTS

The serum and tissue concentrations of cefuroxime are shown in Table 2. In two patients no cefuroxime was detected in either the serum or the tissue sample and in four other patients no tissue level could be detected. In all six cases the time between dosing and sampling was short and maximum serum levels low. All had received their premedication within a short time of taking cefuroxime axetil. It seems likely that absorption had been delayed as a result of the premedication and the fasting state. In the analysis the worst scenario was assumed and undetectable values were presumed to be zero.

The median sinus mucosal cefuroxime concentration in all patients was 1.2 mg/kg sufficient to be therapeutically active against *Streptococcus pneumoniae* and *Haemophilus influenzae* the most commonly isolated pathogens in sinusitis. The in vitro activity of cefuroxime (MIC90 mg/1) for *S. pneumoniae is* 0.06, for *H.*

Table 2. Tissue obtained from maxillary of ethmoid sinus.

time from dosing to sampling	serum level *(μglml)*	tissue level *(μgig)*	tissue weight (mg)	% penetration
0.50	0.9	**ND**	60	0
1.00	0.8	1.2	80	150
1.36	0.3	**ND**	160	0
2.05	**ND**	**ND**	24	0
2.15	1.2	ND	30	0
2.30	ND	**ND**	265	0
2.30	0.2	**ND**	74	0
2.30	2.9	1.2	70	40
2.40	1.6	1.1	80	69
3.25	0.7	0.5	120	71
3.26	3.2	2.4	100	75
3.30	0.8	2.2	42	275
3.30	1.2	2.1	50	175
3.35	1.7	1.8	250	106
3.40	2.1	1.7	150	81
4.05	0.4	0.2	140	50
4,30	1.5	1.3	111	87
4.30	4.2	4.4	41	105
4.48	3.9	2.8	190	72
median value		1.2		71

injluenzae 1.O and for *B. catarrhalis* 2.0. The percentage penetration of cefuroxime from serum into sinus mucosa at the time of biopsy varied between 0-275% with a median value of 71% for all patients. Serum concentrations of cefuroxime were from 0-11.2 mg/1 (median 1.6 mg/1) with a median value at the time of biopsy of 1.2 mg/1 which also exceeds the MIC90.

DISCUSSION

In the literature the reported range of antibiotic penetration of tissue is often wide and cases where expected levels of medication were not achieved are frequently encountered (Jeppesen et al., 1973; Bergholm, 1983). Previous respiratory tract tissue penetration studies of cefuroxime have shown variable results. In a study by Winter and Dhillon (1989) on bronchial mucosa, comparatively higher mucosa! and serum concentrations were measured with a mean percentage penetration of 52%.

However, a similar study by Wise et al. (1989) demonstrated a much higher percentage penetration, ranging from 44-900%. It is noteworthy that in both studies cefuroxime was not detected in a third of patients examined.

Measurements of cefuroxime levels in the sinus mucosa! tissue was dependent on first achieving good absorption from the gastro-intestinal tract. In this respect the patients chosen were not ideal as surgery was performed under general anaesthesia and this necessitated overnight fasting and premedication including narcotic analgesics. Firstly, the bioavailability of cefuroxime axetil when taken after food is 50-60%, but is reduced to 30-40% when taking fasten (Williams and Harding, 1984). Secondly, narcotic analgesics are known to delay gastric emptying and absorption oforally administered drugs (Nimmo et al., 1975; Todd and Nimmo, 1983).

In tissue, total antibiotic concentration represents the mean ofboth extracellular and intracellular compartments (Schentag, 1989). For those agents which remain predominantly extracellular, such as the (]-lactams, tissue levels will be low in relation to blood levels. However, this does not correlate with a low clinical cure rate as the bacteria are also primarily extracellular. Under these circumstances the serum concentration may better predict antibacterial activity.

Furthermore, the infectious process itself can affect antibiotic blood flow and the volume of extracellular fluid. Whilst it has been suggested that such changes are insufficient in acute infections to substantially alter tissue pharmacokinetics, the same may not be true of chronically inflamed mucosa accompanied by fibrosis and significant alterations in vascularity (Paavolainen et al., 1977).

It would seem that cefuroxime axetil should enable effective treatment of acute bacterial sinusitis as the median sinus mucosa! level was above the MIC.

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