

## Cefuroxime axetil versus clarithromycin in the treatment of acute maxillary sinusitis\*

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### SUMMARY

*Acute maxillary sinusitis is a common condition requiring broad-spectrum therapy to prevent development of chronic disease. A randomised, double-blind, multicentre study was performed to compare the efficacy and safety of cefuroxime axetil 250 mg twice daily (n=185) and clarithromycin 250 mg twice daily (n=185), both administered for 10 days, in the treatment of patients with acute sinusitis. Efficacy was determined by assessment of clinical response at post-treatment and follow-up, and by radiological assessment at pre-treatment and follow-up. Assessment of days absent from work due to illness was also made. In the cefuroxime axetil group, 169/185 (91%) patients were cured/improved at post-treatment, as were 172/185 (93%) patients receiving clarithromycin and, of these, 137/169 (81%) and 143/172 (83%) maintained their response at follow-up. Follow-up radiography showed a reduction in incidence of air fluid level and/or opacification from 96% to 15% (cefuroxime axetil) and from 96% to 11% (clarithromycin), and a decrease in frequency of mucosal thickening from 58% to 28% (cefuroxime axetil) and from 56% to 29% (clarithromycin). Only 10% of patients in either group experienced adverse events and days absent from work were comparable. This study demonstrated clinical equivalence between twice-daily cefuroxime axetil and clarithromycin, both treatments being effective and well tolerated.*

*Key words: Acute maxillary sinusitis, cefuroxime axetil, clarithromycin.*

### INTRODUCTION

Sinusitis is a common medical problem in children and adults, affecting approximately one in three individuals. The symptoms of acute sinusitis – fever, nasal congestion and discharge, headache and facial pain – are indistinguishable from other upper respiratory disorders (Herr, 1991; Williams et al., 1995) and the gold standard for diagnosis is culture of sinus aspirate obtained by direct puncture. Since this procedure is rarely performed in general practice, primary care physicians may rely on radiographic evidence and prescribe empirical oral treatment with a broad-spectrum antibiotic.

Early treatment of sinusitis is considered necessary to prevent the progression of mucosal damage which can lead to development of chronic sinusitis, intracranial complications or other chronic sequelae such as frontal osteomyelitis (Farr and Gwaltney, 1988). Such treatment should provide coverage against the pathogens most commonly implicated in acute sinusitis, namely *Streptococcus pneumoniae* and *Haemophilus influenzae* (Gwaltney et al., 1992).

Among patients with acute sinusitis, approximately 40% recover spontaneously, and cost and safety of empirical therapy are paramount (Low et al., 1997). Amoxicillin has long been the first-line agent of choice, with trimethoprim/sulphamethoxazole as an alternative in patients with penicillin allergy. The efficacy of amoxicillin in comparison with other agents has been demonstrated repeatedly (Mattucci et al., 1986; Casiano, 1991; Karma et al., 1991) but there are concerns that its effectiveness may be compromised by the increasing prevalence of beta-lactamase-producing isolates, particularly of *H. influenzae* (Rolinson, 1994). Rising antimicrobial resistance rates in community and clinical practice have driven the search for alternative therapies.

Cefuroxime axetil is the orally-administered ester of the "second generation" cephalosporin cefuroxime. Cefuroxime axetil is well-tolerated and effective in the treatment of a variety of infections at doses ranging from 125 to 500 mg twice-daily (Perry, 1996). The macrolide antibiotic clarithromycin is a semi-synthetic derivative of erythromycin with a methoxy substituent.

tion in the C-6 position, which improves bioavailability and tissue distribution. Clarithromycin has a longer half-life and a lower incidence of adverse effects compared with erythromycin (Langtry and Brogden, 1996; Piscitelli et al., 1992).

Cefuroxime axetil and clarithromycin have activity against a broad spectrum of aerobic and anaerobic Gram-positive and Gram-negative organisms, and are therefore particularly suitable for the treatment of respiratory tract infections (Perry and Brogden, 1996; Langtry and Brogden, 1997; Marx and Fant, 1988; Hardy, 1993). Both agents have proven effective in the treatment of sinusitis when tested with comparators such as amoxicillin, with or without clavulanate, and cefaclor (Karma et al., 1991; Dubois et al., 1993; Camacho et al., 1992; Sydnor et al., 1989). The rationale for the present phase IV study was to compare directly the efficacy and safety of cefuroxime axetil and clarithromycin administered twice-daily in the treatment of acute sinusitis. Efficacy was measured by subjective assessment of the clinical signs and symptoms associated with sinusitis, and safety was assessed by monitoring the adverse events reported during the trial. A secondary aim of the study was to assess the cumulative days missed from work (due to sinusitis) by the employed study population for each treatment regimen.

## MATERIALS AND METHODS

### *Patient population and study design*

This was a randomised, double-blind, parallel-group, multicentre study conducted at 22 centres in eight countries (Czech Republic, Finland, Iceland, Israel, Jordan, Poland, South Africa and Sweden). Regulatory approval was obtained where appropriate and the study was approved by local ethics committees. All patients gave their written informed consent to participate in the study. Male or female patients aged 18 years and older, presenting with a clinical diagnosis of sinusitis with the initial onset of symptoms within 30 days of study entry, were recruited. Radiographic evidence of opacification and/or air fluid level in the maxillary sinus (Water's view) was required. In addition, patients had at least two of the following essential symptoms indicating moderate or severe sinusitis – rhinorrhoea, nasal congestion, facial pain.

Patients were excluded if they had: received any systemic antibacterial drug within the previous seven days; a diagnosis of chronic sinusitis (>30 days' duration) or received antibiotic treatment for recurrent sinusitis during the previous 30 days; received nasal steroid preparations or nasal washout; undergone or required sinus surgery; known hypersensitivity to cephalosporins or macrolides; reduced renal function or marked hepatic impairment; immune deficiency; or participated in a clinical trial within one month prior to enrolment.

Patients were randomised to receive oral treatment with either cefuroxime axetil 250 mg bd for 10 days or clarithromycin 250 mg bd for 10 days. In addition to their active treatment, patients received twice-daily placebo and all doses were taken after meals. Concurrent treatment with other systemic antibiotics or steroid-containing nasal preparations was not permitted. Patients requiring additional antibacterial therapy were withdrawn from the trial.

### *Assessments*

Assessments were performed at pre-treatment, after 5–7 days of treatment, 1–3 days after completion of treatment (post-treatment) and at 28–35 days post-treatment (follow-up). Pre-treatment assessments included physical examination and sinus X-ray. At each visit, 15 clinical symptoms (rhinorrhoea, nasal congestion, facial pain, fever, cough, post-nasal drip, headache, sore throat, malodorous breath, tooth pain, ear pain, malaise, hyposmia, speech indicating sinus fullness and cervical lymphadenopathy) were assessed by the investigator. Each symptom was recorded as absent, mild, moderate or severe; although this assessment of symptom severity was subjective, patients within each participating centre were reviewed by the same investigator throughout the study. Sinus X-rays were repeated at follow-up to provide radiographic evidence of response to treatment. In addition, patients in employment were asked how many cumulative days they were absent from work during the treatment and the follow-up periods. Patients withdrawing from the study due to treatment failure or relapse (i.e. persistence of at least one of the essential symptoms with severe or moderate severity, or of all three symptoms with mild severity) continued to be monitored for pharmaco-economic evaluation. This included, for employed patients, the number of cumulative days missed from work during their illness, assessment of their clinical signs and symptoms 1–3 days after alternative treatment completion and then 28–35 days after the completion of the alternative treatment.

The clinical response to treatment was classified as cure (clinical signs and symptoms improved or resolved at post-treatment and absent at follow-up, confirmed by radiographic evidence), improvement (improvement but incomplete resolution of clinical signs and symptoms, confirmed by radiographic evidence at follow-up), failure (no improvement in clinical signs and symptoms at post-treatment, or discontinuation due to drug-related adverse event), relapse (resolution or improvement of clinical signs and symptoms at post-treatment with recurrence of clinical symptoms including radiographic evidence at follow-up) or unevaluable.

Safety was assessed by the collection of all adverse events reported during the study, and these were classified according to severity and possible relationship to the study drug. A pharmaco-economic evaluation was made at each visit by recording the number of days absent from work for patients in employment.

### *Statistical analysis*

The sample size was based on an anticipated cure or improvement rate of 90% with a treatment difference of  $\leq 15\%$  being considered clinically insignificant. At least 149 evaluable patients were required in each group to demonstrate equivalence at post-treatment, with a one-sided test of significance at the 5% level, with 90% power (Makuch and Simon, 1978). No formal statistical testing was performed on the demographic and baseline characteristics. The balance between treatment groups with respect to withdrawals was examined using Fisher's exact test to detect potential bias in the efficacy analysis. The efficacy data were analysed on the intent-to-treat (ITT) population, with re-

analysis after exclusion of protocol violators (clinically-evaluable population). The primary measure of efficacy was the clinical response at post-treatment, and was summarised as the proportion of patients either cured or showing improvement in signs and symptoms. The treatments were deemed to be equivalent if the lower limit of the 90% confidence interval for the difference in treatment response rates lay within  $\pm 15\%$  using the normal approximation to the binomial distribution. The treatment groups were compared for incidence of adverse events using Fisher's exact test, with the occurrence of at least one drug-related adverse event being analysed using the Chi-square test. The number of days absent from work by each treatment group were compared using the Mantel-Haenszel method.

RESULTS

Patient demographics and disposition

Three-hundred-and-seventy patients were recruited into the study (the ITT population) of whom 185 were randomised to each treatment group. Demographic characteristics and the distribution of pre-treatment conditions were similar in each group (Table 1). X-ray examination showed that 357/370 (96%) patients had pre-treatment evidence of air fluid level and/or opacification. The three key symptoms of acute maxillary sinusitis – rhinorrhoea, nasal congestion and facial pain – were experienced with moderate to severe intensity in 318/370 (86%), 346/370 (94%) and 304/370 (82%) patients, respectively. Thirty-nine patients (11%) were discontinued from the study (22 from the cefuroxime axetil 17 from the clarithromycin groups). The principal reasons were failure to return (11 cefuroxime axetil, 8 clarithromycin), lack of efficacy (seven in each group) and adverse events (two clarithromycin). The overall withdrawal rate was slightly greater in the cefuroxime axetil group ( $p=0.416$ ). Twenty-four (6%) patients were excluded from the clinically-evaluable population as a result of protocol violations.

Table 1. Demographic characteristics of the intent-to-treat population.

Characteristic	Cefuroxime axetil n (%)	Clarithromycin n (%)	Total n (%)
Number of patients	185	185	370
Sex (male/female)	85/100	72/113	157/213
Age (years $\pm$ SD)	36.5 $\pm$ 13.4	37.2 $\pm$ 12.8	36.8 $\pm$ 13.0
Ethnic origin			
Caucasian/white	170 (92)	171 (92)	341 (92)
Black	1 (<1)	1 (<1)	2 (<1)
Oriental	9 (5)	7 (4)	16 (4)
Asian	2 (1)	1 (<1)	3 (<1)
Air fluid level and/or opacification present	179 (96)	178 (96)	357 (96)
Mucosal thickening present	107 (58)	104 (56)	211 (57)
Rhinorrhoea*	160 (86)	158 (85)	318 (86)
Nasal congestion*	171 (92)	175 (94)	346 (94)
Facial pain*	153 (82)	151 (82)	304 (82)

\* moderate to severe

Post-treatment clinical response

Among 185 patients in the ITT population receiving cefuroxime axetil, 169 (91%) were cured or improved, as were 172/185 (93%) clarithromycin-treated patients (Table 2). The overall difference of 2% (95% confidence interval: -8%, 4%) therefore indicated clinical equivalence. The unevaluable patients had mainly violated the entry criteria, taken prohibited concurrent medication or had no available assessment. There was no difference noted between regions (countries) for clinical response ( $p=0.694$ ). The percentage of patients in each treatment group with moderate-to-severe rhinorrhoea, nasal congestion and facial pain at the post-treatment assessment was reduced to  $\leq 5\%$  from  $\geq 80\%$  (Figure 1). The distribution of symptoms reported was similar in each treatment group, and there was no evidence that clinical response to treatment was influenced by pre-treatment symptom severity.

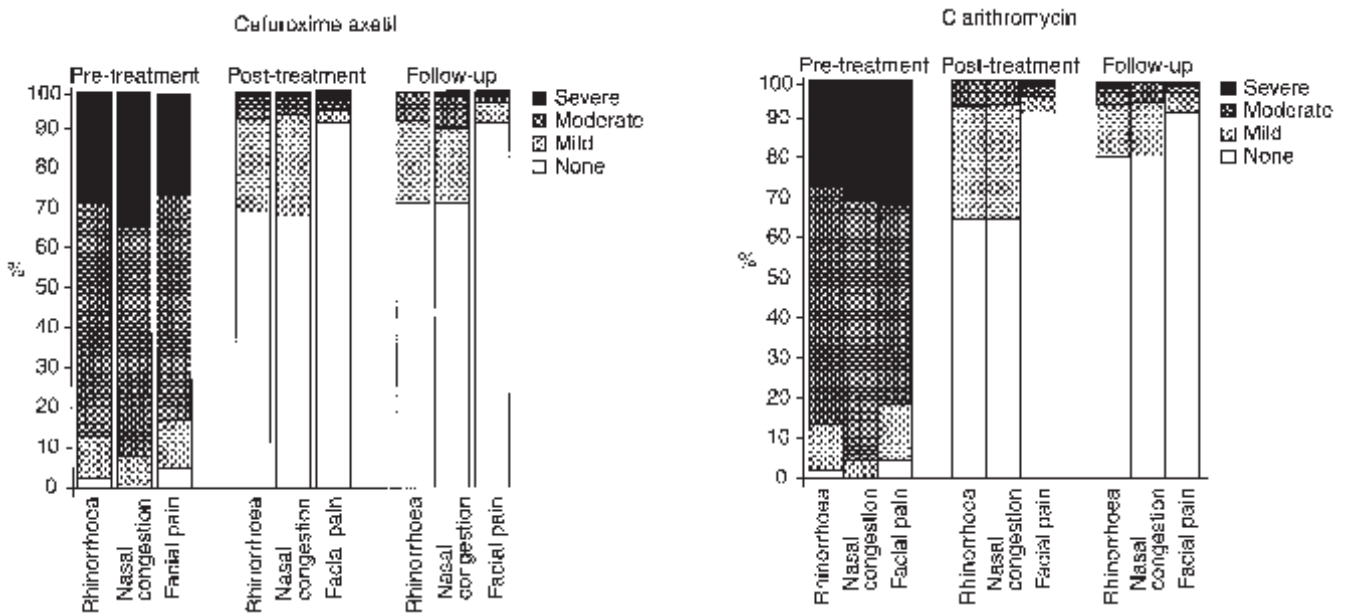


Figure 1. Incidence of essential clinical symptoms at pre-treatment, post-treatment and follow-up in patients with acute maxillary sinusitis receiving cefuroxime axetil 250 mg bd or clarithromycin 250 mg bd.

Table 2. Clinical response rates at post-treatment and follow-up in patients receiving either cefuroxime axetil 250 mg bd or clarithromycin 250 mg bd (ITT population).

	Cefuroxime axetil n (%)	Clarithromycin n (%)
<i>Post-treatment</i>		
Cured/improved	169 (91)	172 (93)
Failure	6 ( 3)	7 ( 4)
Unevaluable	10 ( 5)	6 ( 3)
<i>Follow-up</i>		
Cured/improved	137 (74)	143 (77)
Relapse	11 ( 6)	6 ( 3)
Failure	6 ( 3)	7 ( 4)
Unevaluable	31 (17)	29 (16)
% patients maintaining cure/improvement at follow-up*	81%	83%

\* cured/improved at post-treatment

Results obtained from analysis of the clinically-evaluable population (n=346; n=171 cefuroxime axetil, n=175 clarithromycin) were similar to those from the ITT population.

*Follow-up*

At follow-up, the distribution of patients cured/improved, relapsed, failed and unevaluable was 137 (74%), 11 (6%), 6 (3%) and 31 (17%), respectively, for cefuroxime axetil and 143 (77%), 6 (3%), 7 (4%) and 29 (16%), respectively, for clarithromycin (Table 2). Among patients who were cured/improved at post-treatment, the percentage maintaining cure/improvement was 81% for cefuroxime axetil and 83% for clarithromycin.

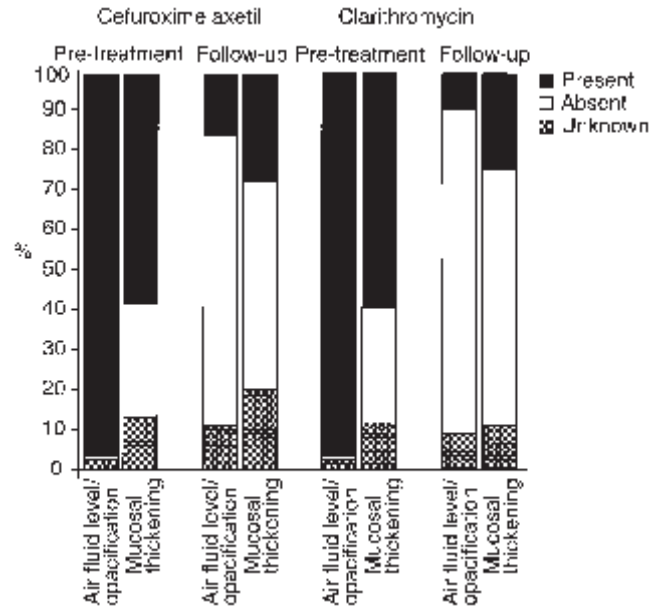


Figure 2. Comparison of the radiological responses at pre-treatment and follow-up in patients with acute maxillary sinusitis receiving cefuroxime axetil 250 mg bd or clarithromycin 250 mg bd.

Clinical equivalence between the two treatments was also established at follow-up, in both the ITT and clinically-evaluable populations.

On radiographic examination, 96% of patients in each group had pre-treatment air fluid level and/or opacification, and just over half the patients had mucosal thickening. At follow-up, the incidence of air fluid level and/or opacification in patients was re-

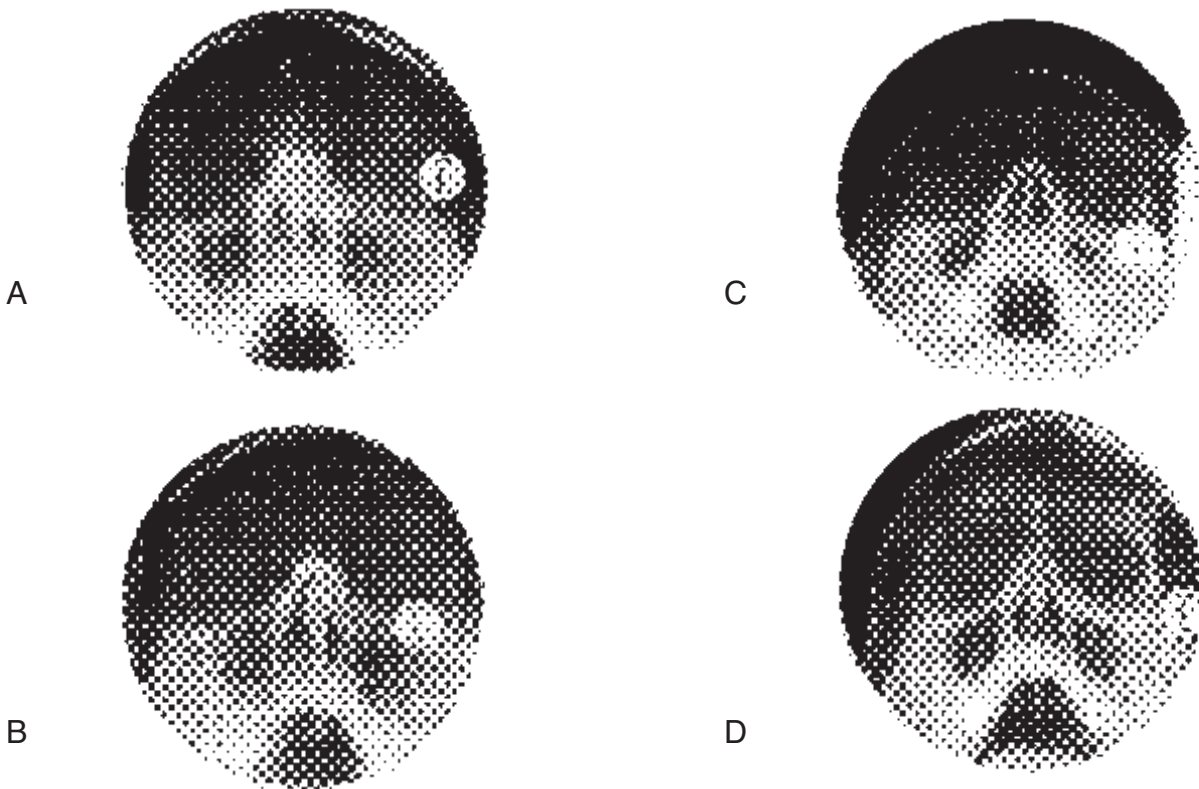


Figure 3. Sinus radiographs demonstrating changes in response to treatment with cefuroxime axetil 250 mg bd. Pre-treatment, the frontal sinuses show an unclear muco-periosteal line (B, C), and there is evidence of mucosal thickening and opacification, particularly in (B). After treatment (A, D) the mucoperiosteal lines and mucosal thickening are clearer, and there is no opacification.



duced to 15% (n=26) in patients receiving cefuroxime axetil and to 11% (n=20) in patients receiving clarithromycin (Figure 2). Radiographic examples of improvement from pre- to post-treatment are demonstrated in Figure 3. A reduction in the proportion of patients with mucosal thickening was also seen.

#### Correlation between radiological and clinical response

Patients with presence of air fluid level and/or opacification or mucosal thickening were evaluated for absence (a positive radiological response) or presence (negative response) at follow-up. There was a positive correlation between radiological response and follow-up clinical response (Table 3). Among 267 patients satisfying the criteria for air fluid level and/or opacification and who had a positive radiological response, 245 (85%) were cured/improved. Likewise, 116 patients fulfilled the criteria for mucosal thickening and had a positive radiological response, and 104 of these (62%) were cured/improved.

Table 3. Correlation between radiological and clinical responses in the ITT population.

Clinical response	Patients with pre-treatment air fluid level and/or opacification (n = 313)		Patients with pre-treatment mucosal thickening (n = 188)	
	Radiological response		Radiological response	
	Positive (n = 267)	Negative (n = 46)	Positive (n = 116)	Negative (n = 72)
Cured/improved	245	31	104	57
Relapse	1	13	1	6
Unevaluable	21	2	11	9

#### Pharmacoeconomic assessment of cumulative days missed from work

The number of patients who were in employment during the study was 277/370 (75%) (Table 4). They were assessed for the number of days missed from work through the study period. During the initial treatment period, 94/140 (67%) and 95/137 (69%) patients in the cefuroxime axetil and clarithromycin groups, respectively, had missed no days from work.

Table 4. Number of days missing from work by patients with acute maxillary sinusitis treated with cefuroxime axetil 250 mg bd or clarithromycin 250 mg bd.

	Cefuroxime axetil n (%)	Clarithromycin n (%)	Total n (%)
No. of patients	185	185	370
No. of employed patients	140(76)	137(74)	277(75)
No. of days of work missed during treatment	0 94(67) 0.5-2 15(11) 2.5-5 18(13) >5 12(9)	95(69) 13(9) 17(12) 10(7)	189(68) 28(10) 35(13) 22(8)
Unknown	1(>1)	2(1)	3(1)
All days missed, i.e. >0.5	45(33)	40(28)	85(31)
No. of days of work missed at follow-up	0 90(64) 0.5-2 14(10) 2.5-5 17(12) >5 19(14)	94(69) 12(9) 15(11) 16(12)	184(66) 26(9) 32(12) 35(13)
All days missed, i.e. >0.5	50 (36)	43 (32)	93 (34)

A further 18/140 (13%) and 17/137 (12%) patients in the respective groups had missed 2.5-5 days from work, and 12/140 (9%) and 10/147 (7%) had missed more than five days from work (Table 4). Over the treatment period, 84/277 (31%) of patients in employment had missed more than half a day due to their sinusitis. At the follow-up visit, 90/140 (64%) and 94/137 (69%) patients in the cefuroxime axetil and clarithromycin groups, respectively, had missed no days from work since the post-treatment visit. A further 50/140 (36%) and 43/137 (32%) patients in the respective groups (a total of 93/377 (34%) study patients) missed more than half a day from work.

#### Safety

Both study medications were well-tolerated. During treatment, 17/185 (9%) cefuroxime axetil and 18/185 (10%) clarithromycin patients reported a drug-related adverse event. These were mainly gastrointestinal in nature (13 cefuroxime axetil, 8 clarithromycin). Three clarithromycin-treated patients had infection or inflammation of the reproductive tract. Serious adverse events were recorded in three clarithromycin-treated patients: maxillary antral abscess, convulsions and collapse during local anaesthesia.

#### DISCUSSION

The principal causes of acute sinusitis are obstruction of sinus drainage and retention of mucous secretions. Factors contributing to sinus obstruction include mucosal hyperplasia and loss of normal cilia function (Kern, 1984). Preceding viral infection or epithelial damage compromises mucosal defences and promotes entry of bacteria into the sinus cavity (Evans et al., 1975). Diagnosis of acute bacterial sinusitis is often complicated by the non-specificity of symptoms. Sinus puncture, followed by aspiration and culture of sinus secretions, remains the gold standard for diagnosis (Low et al., 1997), but is impractical in general practice. Diagnosis is often reliant on clinical signs and symptoms such as rhinorrhoea, nasal congestion, facial pain, headache and cough, though radiographic examination can improve the diagnostic accuracy in acute sinusitis (Evans et al., 1975; Williams et al., 1992). On the basis of this diagnostic approach, the benefits of empirical antibacterial therapy for acute sinusitis are widely recognised.

The results of this multicentre study showed that treatment with cefuroxime axetil or clarithromycin was effective and well-tolerated in patients with acute maxillary sinusitis. A 10-day course of cefuroxime axetil 250 mg twice daily was clinically-equivalent to a 10-day course of clarithromycin 250 mg twice daily, in terms of alleviation of the clinical signs and symptoms of acute sinusitis. Reduction in the incidence of symptoms was reflected in the radiological response to treatment, which showed marked changes in air fluid level and opacification and, to a lesser extent, mucosal thickening, from pre-treatment to follow-up assessments. A significant proportion of patients cured or improved at the post-treatment assessment maintained their response at follow-up.

The results suggested a positive relationship between the radiological response and the follow-up clinical response. Bacteriological assessment was not carried out in this study because of the non-routine nature of sinus puncture and aspira-

tion in general practice and primary healthcare units. Culture of anterior nasal swabs is generally an unsatisfactory alternative and correlates poorly with direct aspirate cultures (Evans et al., 1975). Maxillary sinus X-ray is commonly used to confirm the diagnosis of acute sinusitis and there is a strong positive relationship between maxillary antral opacity and abnormal aspirates containing leukocyte counts of greater than 1000 per mm<sup>3</sup> and bacterial titres in excess of 10<sup>5</sup> per ml. The presence of mucosal thickening also correlates well with the presence of abnormal aspirates (Evans et al., 1975).

The results of the present study were in agreement with those obtained in studies where sinus puncture was performed for bacteriological evaluation. A review of studies over a 15-year period showed that a 10-day course of cefuroxime axetil 250 mg twice daily produced bacteriological cure in over 90% of patients with acute sinusitis (Gwaltney et al., 1992). Similarly, in a trial with clarithromycin 250mg twice daily in acute sinusitis, a clinical cure rate of 94% was achieved together with bacteriological cure in 93% of patients (Langtry and Brogden, 1997).

Comparison of the ITT and clinically-evaluable populations showed equivalence in clinical response at both post-treatment and follow-up assessments, major protocol violations were few and did not affect the outcome of the study. Compliance with the study medication was high in both treatment groups.

The number of days missed from work by the employed study patients in each treatment group were comparable at each assessment point in the study and the majority of the patients in the study did not miss days from work. It is notable that both at the post-treatment assessment and at the follow-up assessment approximately a third of the study patients had missed a minimum of half a day from work and, for a proportion of those patients, the time missed from work had been more than five days.

#### CONCLUSION

In conclusion, this study demonstrated that cefuroxime axetil and clarithromycin were clinically equivalent when given for 10 days in the treatment of acute maxillary sinusitis. Twice-daily administration of either treatment resulted in significant clinical and radiological changes, achieved with minimal side effects, and the results would therefore support the use of these agents in the empirical therapy of acute bacterial sinusitis.

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