16 Torabinejad M, Cymerman JJ, Frankson M, Lemon RR, Maggio JD, Schilder H. Effectiveness of various medications on postoperative pain following complete instrumentation. *Journal of Endodontics* 1994;**20**:345-54.
17 Bentley KC, Head TW. The additive analgesic efficacy of acetaminophen 1000 mg and codeine 60 mg in dental pain. *Clin Pharmacol Ther* 1987;**42**:634-40.
18 Kjaersgaard-Andersen P, Nafei A, Skov O, Madsen F, Andersen HM, Kroner K, *et al.* Codeine plus paracetamol versus paracetamol in longer-term treatment of chronic pain due to osteoarthritis of the hip. A randomised, double blind, multi-centre study. *Pain* 1990;**43**:309-18.
19 Gertzbein SD, Tile M, McMurty RY, Kellman JF, Hunter GA, Keith RG, *et al.* Analysis of the analgesic efficacy of acetaminophen 1000 mg, codeine phosphate 60 mg, and the combination of acetaminophen 1000 mg and codeine phosphate 60 mg in the relief of postoperative pain. *Pharmacotherapy* 1986;**6**:104-7.
20 Forbes JA, Kolodny AL, Beaver WT, Shackleford RW, Scarlett VR. A 12-hour evaluation of the analgesic efficacy of diflunisal, acetaminophen, an acetaminophen-codeine combination, and placebo in postoperative pain. *Pharmacotherapy* 1983;**3**(suppl 1):47-54S.
21 Honig S, Murray KA. An appraisal of codeine as an analgesic: single-dose analysis. *J Clin Pharmacol* 1984;**24**:96-102.
22 Sunshine A, Marrero I, Olson N, McCormick N, Laska EM. Comparative study of flurbiprofen, zomepirac sodium, acetaminophen plus codeine, and acetaminophen for the relief of postsurgical dental pain. *Am J Med* 1986;**80**(suppl 3A):50-4.
23 Cooper SA, Firestein A, Cohn P. Double-blind comparison of meclofenamate sodium with acetaminophen, acetaminophen with codeine and placebo for relief of postsurgical dental pain. *Journal of Clinical Dentistry* 1988;**1**:31-4.
24 Dionne RA, Snyder J, Hargreaves KM. Analgesic efficacy of flurbiprofen in comparison with acetaminophen, acetaminophen plus codeine, and placebo after impacted third molar removal. *J Oral Maxillofac Surg* 1994;**52**:919-24.
25 Forbes JA, Beaver WT, White EH, White RW, Neilson GB, Shackleford RW. Diflunisal. A new oral analgesic with an unusually long duration of action. *JAMA* 1982;**248**:2139-42.
26 Forbes JA, Butterworth GA, Burchfield WH, Yorio CC, Selinger LR, Rosenmertz SK, *et al.* Evaluation of flurbiprofen, acetaminophen, an acetaminophen-codeine combination, and placebo in postoperative oral surgery pain. *Pharmacotherapy* 1989;**9**:322-30.
27 Forbes JA, Kehm CJ, Grodin CD, Beaver WT. Evaluation of ketorolac, ibuprofen, acetaminophen, and an acetaminophen-codeine combination in postoperative oral surgery pain. *Pharmacotherapy* 1990;**10**:94-105S.
28 Skoglund LA, Skjelbred P, Fyllingen G. Analgesic efficacy of acetaminophen 1000 mg, acetaminophen 2000 mg, and the combination of acetaminophen 1000 mg and codeine phosphate 60 mg versus placebo in acute postoperative pain. *Pharmacotherapy* 1991;**11**:364-9.
29 Cooper SA, Beaver WT. A model to evaluate mild analgesics in oral surgery outpatients. *Clin Pharmacol Ther* 1976;**20**:241-50.
30 Cooper SA, Kupperman A. The analgesic efficacy of flurbiprofen compared with acetaminophen with codeine. *Journal of Clinical Dentistry* 1991;**2**:70-4.
31 Levin HM, Bare WW, Berry FN, Miller JM. Acetaminophen with codeine for the relief of severe pain in postpartum patients. *Current Therapeutic Research, Clinical and Experimental* 1974;**16**:921-7.
32 Skjelbred P, Lokken P. Codeine added to paracetamol induced adverse effects but did not increase analgesia. *Br J Clin Pharmacol* 1982;**14**:539-43.
33 Arendt-Nielsen L, Nielsen JC, Bjerring P. Double-blind, placebo controlled comparison of paracetamol and paracetamol plus codeine—a quantitative evaluation by laser induced pain. *Eur J Clin Pharmacol* 1991;**40**:241-7.
34 Cooper SA, Breen JF, Giuliani RL. The relative efficacy of indoprofen compared with opioid-analgesic combinations. *J Oral Surg* 1981;**39**:21-5.
35 Quiding H, Persson G, Ahlström U, Bangens S, Hellem S, Johansson G, *et al.* Paracetamol plus supplementary doses of codeine. An analgesic study of repeated doses. *Eur J Clin Pharmacol* 1982;**23**:315-9.
36 Quiding H, Häggquist SO. Visual analogue scale and the analysis of analgesic action. *Eur J Clin Pharmacol* 1983;**24**:475-8.
37 Becker J, Beckmann J, Bertelt C, Gundert-Remy U, Röhmel J, Ohlendorf D. Doppelblindstudie über postoperative Analgetikawirkungen. *Deutsche Zahnärtzliche Zeitschrift* 1990;**45**:36-8.
38 Cooper SA. Five studies on ibuprofen for postsurgical dental pain. *Am J Med* 1984;**9**:70-7.
39 Boelen-van der Loo WJC, Driessen FGWHM. Pijnpreventie en pijnbestrijding bij (adeno)tonsillectomie. *Ned Tijdschr Geneeskd* 1992;**136**:1409-13.
40 Beaver WT, Feise G. Comparison of the analgesic effect of acetaminophen and codeine and their combination in patients with postoperative pain. *Clin Pharmacol Ther* 1978;**23**:108.
41 Somogyi A, Bochner F, Chen ZR. Lack of effect of paracetamol on the pharmacokinetics and metabolism of codeine in man. *Eur J Clin Pharmacol* 1991;**41**:379-82.
42 Sonne J, Enghusen Poulsen H, Loft S, Dossing M, Vollmer-Larsen A, Simonson K, *et al.* Therapeutic doses of codeine have no effect on acetaminophen clearance or metabolism. *Eur J Clin Pharmacol* 1988;**35**:109-11.
43 Sindrup SH, Brosen K, Bjerring P, Arendt-Nielsen L, Larsen U, Angelo HR, *et al.* Codeine increases pain thresholds to copper vapor laser stimuli in extensive but not poor metabolizers of sparteine. *Clin Pharmacol Ther* 1990;**48**:686-93.
44 Sackett DL, Hayes RB, Guyatt GH, Tugwell P. *Clinical epidemiology.* 2nd ed. Boston: Little, Brown and Co, 1991.
45 Stewart PK. Multidose short-term analgesic studies. In: Max MB, Portenoy RK, Laska EM, eds. *The design of analgesic clinical trials.* New York: Raven Press, 1991:137-49.

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Randomised, double blind, placebo controlled trial of penicillin V and amoxycillin in treatment of acute sinus infections in adults

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Abstract

***Objective*—To compare the effectiveness of penicillin V and amoxycillin with placebo in treatment of adult patients with acute sinusitis.**

***Design*—Randomised, double blind, placebo controlled trial.**

***Setting*—Norwegian general practice.**

***Subjects*—130 adult patients with a clinical diagnosis of acute sinusitis confirmed by computed tomography.**

***Main outcome measures*—Subjective status after three and 10 days of treatment, difference in clinical severity score between day 0 and day 10 as evaluated by the general practitioner, difference in score from computed tomography on day 0 and day 10, and duration of sinusitis.**

***Results*—Amoxycillin and penicillin V led to significantly faster and better recovery than placebo. By day 10, 71 patients receiving antibiotic treatment (86%) considered themselves to be recovered or much better compared with 25 (57%) receiving placebo. The mean (95% confidence interval) reductions in clinical severity scores by day 10 were 5.4 (5.0 to 5.8) for penicillin V, 5.5 (4.9 to 6.0) for amoxycillin, and 3.4 (2.8 to 4.0) for placebo. For the antibiotic groups combined the number of patients with the greatest degree of improvement on computed tomography (scale 0-16)—that is, score 5-16 on day 10—was 31/83 (37%) compared with 10/44 (23%) receiving placebo. The median duration of the sinusitis was nine days in the amoxycillin group, 11 days in the penicillin V group, and 17 days in the placebo group.**

***Conclusion*—Penicillin V and amoxycillin are significantly more effective than placebo in the treatment of acute sinusitis.**

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Introduction

Acute sinusitis, an inflammation in the paranasal sinuses lasting no longer than one month, is a common clinical problem in general practice.[1-3] Acute sinusitis is a common reason for the prescription of antibiotics in adult patients.[4]

The effectiveness of antibiotic treatment, however, has been poorly documented. Only two placebo controlled, randomised studies with clinical findings and objective visualisation as inclusion criteria have been found in the literature, one in children[5] and one in adults.[6] The last study has met with criticism.[7]

Antibiotic treatment of acute sinusitis varies between countries.[8-10] In Scandinavia penicillin V is the drug of choice.[8] The most common bacteria in acute sinusitis are *Streptococcus pneumoniae* and *Haemophilus influenzae*, and the reason for using broad spectrum antibiotics is mainly the prevalence of *H influenzae*, which may have a low sensitivity to penicillin V.[11 12]

Computed tomography of the paranasal sinuses has mainly been used in evaluating patients in need of nasal or sinus procedures and in staging patients with chronic sinusitis.[13 14] Lately it has also been used in the diagnostic process of acute sinusitis,[15 16] documenting involvement of several sinuses, mainly the maxillary and

ethmoid sinuses.[17 18] Computed tomography was used as a reference standard in the present study.

We compared the effectiveness of penicillin V, amoxycillin, and placebo given to patients with acute sinusitis. The comparisons included subjective status after three and 10 days of treatment, as evaluated by the patient; difference in clinical score between day 0 and day 10, as evaluated by the general practitioner; difference in results of computed tomography from day 0 and day 10, as evaluated by the radiologist; and duration of sinusitis, as evaluated by the patient.

Patients and methods

We included in the study patients from general practice in the Tønsberg region in southern Norway. The patients were suspected of having acute sinusitis, which was confirmed by a computed tomography. Exclusion criteria were age 15 or under, pregnancy, ongoing antibiotic treatment, immunosuppressive treatment, previous operations in the nose or sinus region, misuse of alcohol or narcotics, rheumatic disease, and allergy to penicillin. If the symptoms had persisted for more than 30 days the patient was excluded because of possible chronic sinusitis. Patients with high fever and strong pain were not included because of ethical considerations.

CLINICAL EVALUATION

All patients were examined by one experienced general practitioner according to a standardised clinical procedure on the same day as the computed tomography was performed. The clinical signs and symptoms evaluated were scored according to being present or not or to severity. The symptoms and signs registered are all common in acute sinusitis.[3 16 19 20] The presence of either hyposmia or anosmia, symptoms lasting longer than seven days before the first visit, unilateral facial pain, pain in upper teeth, pain worsening on bending forward, or two phases in the disease history each scored one point. Nasal obstruction, rhinorrhoea, sinus pain, and malaise estimated by the patient gave a maximum of one point each. Rectal temperature between 37.6 and 38.0°C scored 0.5 and above 38.0 °C one point. Purulent secretion in the nasal floor, which is a fairly consistent sign of purulent sinusitis,[1 16] was given two points. The points were summated for each patient, resulting in a "clinical severity score" of a maximum of 13 points. A bacteriological sample from the nasopharynx was taken at the time of the clinical examination.

COMPUTED TOMOGRAPHY

Computed tomography was performed with contiguous 5 mm thick coronal slices through the sinus complex including all the paranasal sinuses (window width 1500 HU, level 100-400 HU). The scans were evaluated independently by two experienced radiologists. If they disagreed in interpretation, they reassessed jointly and reached a consensus. The patients were grouped according to the results into three groups: normal; mucosal thickening without fluid level or total opacification; and acute sinusitis. The criteria for confirming the diagnosis of acute sinusitis were presence of fluid level or total opacification in any sinus.[21-23]

The patients with sinusitis underwent further computed tomography at the return visit after 10 days. Both scans were evaluated at day 0 and day 10 with the same scoring system, and the difference in scoring between these two days was calculated. This system was a modified version of that introduced by Lund and Mackay for staging chronic rhinosinusitis.[14] The four sinus regions were assessed bilaterally, in total eight regions. A score was estimated for each sinus region according to the following criteria: 0—negative sinus or mucosal thickening <5 mm; 1—mucosal thickening ≥5 mm; 2—total opacification or fluid level.

In the ethmoid cells the limit of 5 mm was difficult to use because of their small size; thus the distinction between no opacification and partial or total opacification was used. The maximum score for each patient was 16 points.

STUDY GROUP

From January to May 1994 and November 1994 to May 1995 we recruited 244 patients to the study. Forty four had negative results on computed tomography, 70 had mucosal thickening, and 130 had sinusitis. Of the 130, 85 were women. The mean age was 38.6 (range 16-74) years.

The size of the present study was determined by a power calculation ($\alpha = 0.05$, $\beta = 0.10$) based on duration of illness, which suggested a sample size of 60 patients in each treatment group. For practical reasons we stopped the trial when 130 patients with sinusitis had been included, mainly because of problems with recruiting more patients within a reasonable period. The randomisation code was broken and the data analysed after the decision to stop recruitment was made.

RANDOMISATION AND TREATMENT

The trial was double blind; neither the patients, the general practitioner, nor the radiologists were aware of the allocation of treatment. Patients with sinusitis were stratified according to clinical severity score <9.0 or ≥9.0 and localisation of the sinusitis—unilateral maxillary sinusitis, bilateral maxillary sinusitis, or sinusitis in at least one of the remaining sinus regions. If the patient had maxillary sinusitis in combination with sinusitis in one of the other sinus regions, she or he was stratified to one of the maxillary sinusitis groups. The randomisation was performed in blocks of three within each of these six subgroups by using a dice to generate the random allocations. The patients were randomised into one of three treatment alternatives—penicillin V 1320 mg × 3 for 10 days; amoxycillin 500 mg × 3 for 10 days; or placebo × 3 for 10 days—each given as two similar appearing tablets three times a day. In addition the patients were allowed nasal decongestants and mild analgesics (paracetamol).

FOLLOW UP

After inclusion, stratification, and randomisation the patients were instructed to keep a diary in which each morning they marked on four visual analogue scales the degree of nasal obstruction, rhinorrhoea, sinus related pain, and malaise. Lastly, they were to answer the question "Do you think you still have sinusitis today?" with yes, uncertain, or no.

EVALUATION OF OUTCOME

On day 3 and day 10 the patients assessed their own clinical condition as restored, much better, somewhat better, unimproved, or worse. On day 10 all patients came to a follow up visit, and a new clinical severity status was estimated by the same general practitioner according to the same scoring scheme as on day 0. The difference in clinical severity between day 0 and day 10 was calculated.

Patients who answered "No" to the question of still having sinusitis stopped their diary on day 10. The others continued their registration until they answered "No" to this question; this day was registered as the day of cure. Maximum time limit of registration on the visual analogue scale was set to 20 days, but patients with episodes lasting more than 20 days recorded the total number of days until recovery, the maximum

Table 1—*Patients' evaluation of clinical course during treatment, evaluated after three and 10 days. Figures are numbers (percentages) of patients*

Treatment group	Restored	Much better	Somewhat better	Unimproved	Worse	Total
Penicillin V:						
Day 3	0	8 (21)	24 (62)	6 (15)	1 (3)	39 (100)
Day 10	12 (31)	20 (51)	6 (15)	1 (3)	0	39 (100)
Amoxycillin:						
Day 3	0	9 (20)	26 (59)	9 (20)	0	44 (100)
Day 10	20 (45)	19 (44)	4 (9)	1 (2)	0	44 (100)
Placebo:						
Day 3	0	1 (2)	16 (36)	19 (44)	8 (18)	44 (100)
Day 10	5 (11)	20 (45)	14 (32)	4 (9)	1 (2)	44 (100)

χ^2 Test for trend: day 3—amoxycillin *v* placebo P<0.001, penicillin *v* placebo P<0.001, amoxycillin *v* penicillin P = 1.00; day 10—amoxycillin *v* placebo P<0.001, penicillin *v* placebo P = 0.004, amoxycillin *v* penicillin P = 0.19.

Table 2—*Clinical severity score measured on scale from 0-13. Reduction between day 0 and day 10 for each treatment group and difference in reduction between antibiotic groups and placebo group. Figures are mean severity scores (95% confidence intervals)*

Treatment group	Day 0	Day 10	Reduction	Difference in reduction (antibiotics - placebo)
Penicillin V	8.3 (7.9 to 8.8)	2.9 (2.4 to 3.3)	5.4 (5.0 to 5.8)	2.0 (1.3 to 2.7)
Amoxycillin	8.4 (7.9 to 8.8)	2.9 (2.4 to 3.3)	5.5 (4.9 to 6.0)	2.1 (1.3 to 2.9)
Placebo	8.3 (7.8 to 8.7)	4.8 (4.2 to 5.4)	3.4 (2.8 to 4.0)	—

Student's *t* test: penicillin V *v* placebo P<0.0001, amoxycillin *v* placebo P<0.0001, penicillin V *v* amoxycillin P = 0.58.

Table 3—*Difference in score on computed tomography measured on scale from 0-16 between day 0 and day 10 for each treatment group. Figures are numbers (percentages) of patients*

Treatment group	Worsened < 0	Unchanged 0	Degree of improvement 1-2	3-4	5-16	Total
Penicillin V	3 (8)	3 (8)	7 (18)	12 (31)	14 (36)	39 (100)
Amoxycillin	1 (2)	5 (11)	5 (11)	16 (36)	17 (39)	44 (100)
Placebo	7 (16)	8 (18)	13 (30)	6 (14)	10 (23)	44 (100)

χ^2 Test for trend: penicillin V *v* placebo P = 0.02, amoxycillin *v* placebo P = 0.002, penicillin V *v* amoxycillin P = 0.66.

observation time being 30 days. In estimating the length of the sinusitis episode, a Kaplan-Meier plot was used.

If the patient asked for another antibiotic because she or he felt unchanged or just slightly better after 10 days, the patient was given amoxycillin 500 mg × 3 for another 10 days. In these cases the code of the original treatment was not broken.

Possible side effects of the medication were registered by each patient in two different ways. One was a registration of what, if any, side effects had been experienced, the other a subjective evaluation of the severity of side effects experienced indicated on a visual analogue scale.

An intention to treat analysis was performed. We used χ^2 test, χ^2 test for trend, Student's *t* test, Fisher's exact test, and the two sided log rank test for statistical analysis with a significance of 5% in all tests.

Results

The three treatment groups were similar in terms of sex, mean age, mean clinical severity score, and mean score on computed tomography at day 0 and of the proportion of patients with unilateral and bilateral maxillary sinusitis and with sinusitis in other sinus regions. Ninety three out of 130 patients had maxillary sinusitis.

Drop outs—Twelve out of 130 patients stopped the treatment before 10 days, and the code was broken. Three patients, two receiving penicillin V and one receiving amoxycillin, stopped the initial treatment after a few days because of severe gastrointestinal side effects and did not get any further treatment. They were included in the table of side effects but were not included in the other analyses because of lack of registration of data after they dropped out of the study. Seven patients in the placebo group and two patients in the amoxycillin group stopped the treatment before 10 days. Six of the patients receiving placebo were given amoxycillin. The seventh patient was given penicillin V, referred to an otorhinolaryngologist, and had her maxillary sinuses punctured. One of the two patients receiving amoxycillin had her maxillary sinuses punctured and was given doxycycline. The other patient received doxycycline from day 5. According to the principle of intention to treat they were included in the analyses in the groups to which they were originally randomised.

Subjective status—Table 1 gives the patients' evaluations of the clinical course after three and 10 days. After three days and 10 days there were significantly more patients who felt better in the two antibiotic groups than in the placebo group. There was no significant difference between the antibiotic groups. After 10 days 86% (71) of the patients in the two antibiotic groups felt restored or much better compared with 57% (25) of the patients in the placebo group.

Clinical severity score—Table 2 gives the clinical severity score on day 0 and day 10. The two antibiotic groups improved significantly more than the placebo group (P<0.0001), and the reduction in severity score was 60% larger in the antibiotic groups than in the placebo group.

Differences in computed tomography—Table 3 shows the differences in evaluation by computed tomography between day 0 and day 10. The two antibiotic groups had a significantly higher degree of improvement than the placebo group. The amoxycillin group had a higher degree of improvement than the penicillin V group, although the difference was not significant (P = 0.66).

Duration of episode of illness—Figure 1 illustrates the length of the sinusitis episode for each treatment group. The Kaplan-Meier plot shows the share of patients still feeling ill at any one day. The amoxycillin group (P<0.001) and the penicillin V group (P = 0.008) had a significantly greater share of patients restored than the placebo group. The length of the sinusitis episode was estimated from the median value in each patient group. The median was nine days in the amoxycillin group, 11 days in the penicillin V group, and 17 days in the placebo group. In addition to the nine patients who stopped the original treatment, four patients in the amoxycillin group, eight in the penicillin V group, and 13 in the placebo group were given extended treatment as they did not feel measurably better at day 10.

Bacteriology—Bacteriological specimens were obtained from the nasopharynx of 125 patients. Thirty

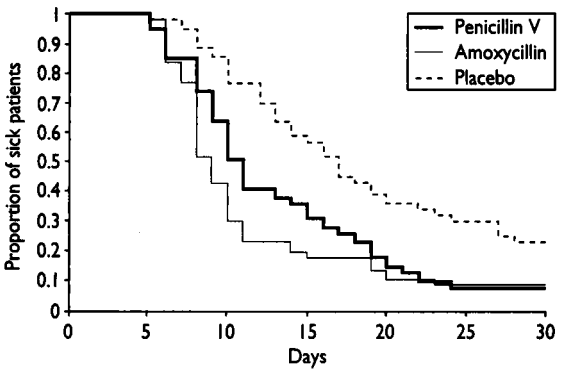

Fig 1—*Proportion of 127 patients in three treatment groups by days from start of treatment*

Table 4—*Specified side effects in 130* patients in three treatment groups and severity of side effects evaluated by patients on visual analogue scale running from 0-100 mm. Figures are numbers (percentages) of patients*

Treatment group	Penicillin V (n = 41)	Amoxycillin (n = 45)	Placebo (n = 44)	Mean (range) scale score	P value
Diarrhoea	15 (37)	21 (47)	5 (11)	33 (2-93)	0.001†
Nausea/vomiting	10 (24)	14 (31)	5 (11)	43 (10-90)	0.07†
Rash	0 (0)	5 (11)	2 (5)	42 (20-85)	0.07‡
Vaginal discharge	0 (0)	5 (11)	1 (2)	13 (7-20)	0.05‡
Other (headache, asthenia)	4 (10)	5 (11)	6 (14)	24 (2-96)	0.9‡
None	17 (41)	20 (44)	28 (64)	—	0.08†

*Two patients receiving penicillin V and one patient receiving amoxycillin who dropped out of study because of gastrointestinal side effects are included. Patients could state more than one side effect.
†χ^2 Test, df = 2.
‡Fisher's exact test.

one (25%) had *Streptococcus pneumoniae*, all sensitive to the two antibiotics; 16 (13%) had *Haemophilus influenzae*, one producing penicillinase and the rest sensitive to both antibiotics; 14 (11%) had *Staphylococcus aureus*, seven resistant to penicillin V, the rest sensitive to both antibiotics; five (4%) had haemolytic streptococci group A, all sensitive to both antibiotics; five (4%) had *Moraxella catarrhalis*, three resistant to both antibiotics; and one (1%) had *Escherichia coli* sensitive to amoxycillin. Fifty three (42%) patients had "normal nasal flora" comprising mainly *Staphylococcus epidermidis, Streptococcus viridans*, and diphtheroid. There were no significant differences between the three treatment groups as to the incidence of haemophilus and pneumococci.

Side effects—Table 4 shows the number and extent of side effects experienced by the patients in the different treatment groups. More than half of the patients in the antibiotic groups experienced some degree of side effects. Diarrhoea was most commonly reported, the difference between the antibiotic groups and the placebo group being significant. The experienced severity of the side effects is stated on the visual analogue scale.

Discussion

Previous studies of antibiotic treatment of acute sinusitis[5 6] have met criticism.[7] To meet this criticism the present study was randomised, double blind, and placebo controlled, with matched treatment groups of patients seen in general practice.

The use of computed tomography to determine fluid level or total opacification as inclusion criteria is well established.[21-23] Questions have been raised concerning the rate of false positive results in computed tomography of the sinus.[24] Incidental findings of total opacification or fluid level in asymptomatic patients, however, have been found only rarely.[24 25] Even though we used computed tomography as a reference standard in this study, this does not imply that we recommend it as a routine examination in general practice for patients with suspected acute sinusitis.

The difference we found between treatment with placebo and antibiotic is in our opinion considerable and clinically relevant. The difference in clinical severity score between day 0 and day 10 was 60% greater in the two antibiotic groups than in the placebo group. A difference of seven days' illness duration with and without antibiotic treatment was also significant. This is in line with the considerations of Sackett *et al*, who state that differences in relative risk of 50% almost always are clinically significant.[26] The difference in illness duration has not been reported before. Our study confirms that acute sinusitis in some cases is a self limiting disease, as over half of the patients in the placebo group felt restored or much better after 10 days.

Key messages

- Penicillin V and amoxycillin are significantly more effective than placebo in treating acute sinusitis
- The median duration of sinusitis with different treatment was nine days for amoxycillin, 11 days for penicillin V, and 17 days for placebo
- More than half of the patients receiving antibiotic treatment reported side effects but few gave severe discomfort
- Half of the patients receiving placebo tablets felt restored or much better after 10 days

An intention to treat principle was followed when we analysed our results, and we found significant differences in all four outcome measures. Almost half of the placebo group was given antibiotics after the initial treatment period. When the patients were analysed by the treatment they actually received in the whole study period, the differences were even higher for all outcome measures.

Penicillin V and amoxycillin were both effective in the treatment of acute sinusitis, and the side effects were similar in the two antibiotic treatment groups. The side effects registered correspond with previous findings.[27 28] There was, however, a trend in the outcome measures for amoxycillin being somewhat more effective than penicillin V, none of the differences being significant.

In this study high dosages of antibiotics were used, which was necessary to ensure effect against *H influenzae* and because the absorption of penicillin V is variable.[8] When we evaluated outcomes and side effects together, our results indicated that the Scandinavian tradition of treating acute sinusitis with penicillin V in high doses is reasonable.

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1 Hovelius B, Widäng K. Forkylning eller bihåleinflammasjon? (Common cold or sinusitis?) In: Mårdh Per-Anders, ed. *Infektioner I primärvård*. Stockholm: Almquist and Wiksell, 1986:75-9.
2 Royal College of General Practitioners, Office of Population Censuses, Department of Health and Social Security. *Morbidity statistics from general practice 1981-82*. London: HMSO, 1986.
3 Van Duijn NP, Brouwer HJ, Lamberts H. Use of symptoms and signs to diagnose maxillary sinusitis in general practice: comparison with ultrasonography. *BMJ* 1992;**305**:684-7.
4 Moss AJ, Parson VL. *Current estimates from the national health interview survey, United States 1985*. Hyattsville, Maryland: National Center for Health Statistics, 1986:667.
5 Wald ER, Chiponis D, Ledesma-Medina J. Comparative effectiveness of amoxycillin and amoxycillin-clavulanate potassium in acute paranasal sinus infections in children: a double-blind placebo-controlled trial. *Pediatrics* 1986;77:795-800.
6 Axelsson A, Chidekel N, Grebelius N, Jensen C. Treatment of acute maxillary sinusitis. A comparison of four different methods. *Acta Otolaryngol (Stockh)* 1970;70:71-6.
7 Brett AS. Does this patient have sinusitis?. *JAMA* 1994;271:502.
8 Lindbæk M. Acute infections in nose and paranasal sinuses—diagnosis and treatment. In: Madsen S, Wærsted A, Westbye O, Beermann B, Strandberg K, eds. *Treatment of acute infections of the respiratory tract in primary health service*. Oslo: Statens Legemiddelkontroll, Läkemedelsverket, 1995:125-36.
9 Melker RA de, Kuyvenhoven MM. Management of upper respiratory tract infection in Dutch general practice. *Br J Gen Pract* 1991;41:504-7.
10 Winther B, Gwaltney JM. Therapeutic approach to sinusitis: anti-infectious therapy as the baseline of management. *Otolaryngol Head Neck Surg* 1990;103:876-9.
11 Ylikoski J, Savolainen S, Jousimies-Somer H. The bacteriology of acute maxillary sinusitis. *ORL J Otorhinolarngol Relat Spec* 1989;5:175-81.

12 Kallings LO. Bacteriological aspects of infections of the upper respiratory tract. *Scand J Infect Dis* 1983;**39**(supp)l:9-13.
13 Stammberger H. Endoscopic endonasal surgery. Concepts in treatment of recurring rhinosinusitis. I. Anatomic and pathophysiologic considerations. *Otolaryngol Head Neck Surg* 1986;**94**:143-56.
14 Lund VJ, Mackay IA. Staging in rhinosinusitis. *Rhinology* 1993;**31**:183-4.
15 Hansen JG, Schmidt H, Rosborg J, Lund E. Predicting acute maxillary sinusitis in a general practice population. *BMJ* 1995;**311**:233-6.
16 Lindbæk M, Hjortdahl P, Johnsen U. Use of symptoms, signs, and blood tests to diagnose acute sinus infections in primary care: comparison with computed tomography. *Fam Med* 1996;**28**:181-6.
17 Facer GW, Kern EB. Sinusitis: Current concepts and management. In: BJ Bailey, ed. *Head and neck surgery otolaryngology*. Philadelphia: Lippincott, 1993:366-76.
18 Lindbæk M, Johnsen U, Kaastad E, Dølvik S, Møll P, Lærum E, *et al.* CT-findings in general practice patients with suspected acute sinusitis. *Acta Radiologica* 1996 (in press).
19 Berg O, Carenfeldt C. Analysis of symptoms and clinical signs in the maxillary sinus empyema. *Acta Otolaryngol* 1988;**105**:343-9.
20 Williams JW, Simel DL. Does this patient have sinusitis? Diagnosing acute sinusitis by history and physical examination. *JAMA* 1993;**270**:1242-6.
21 Zeifer BA. Sinus imaging. In: BJ Bailey, ed. *Head and neck surgery otolaryngology*. Philadelphia: Lippincott, 1993:350-65.
22 Laine FJ, Smoker WRK. The osteomeatal unit and endoscopic surgery: anatomy, variations, and imaging findings in inflammatory diseases. *AJR Am J Roentgenol* 1992;**159**:849-57.
23 Pollei S, Harnsberger HR. The radiologic evaluation of the sinonasal region. *Postgraduate Radiology* 1989;**9**:242-66.
24 Havas TE, Motbey JA, Gullane PJ. Prevalence of incidental abnormalities on computed tomographic scans of the paranasal sinuses. *Arch Otolaryngol Head Neck Surg* 1988;**114**: 856-9.
25 Cooke LD, Hadley DM. MRI on the paranasal sinuses: incidental abnormalities and their relationship to symptoms. *J Laryngol Otol* 1991;**105**:278-81.
26 Sackett DL, Haynes RB, Guyatt GH, Tugwell P. *Clinical epidemiology—a basic science for clinical medicine*. Boston: Little, Brown, 1991:187-248.
27 Søderstrøm M, Blomberg J, Christensen P, Hovelius B. Erythromycin and phenoxy-metylpenicillin (penicillin V) in the treatment of respiratory tract infections as related to microbiological findings and serum C-reactive protein. *Scand J Infect Dis* 1991;**23**:347-54.
28 Goodman A, Gilman A, Rall TW, Nies AS, Taylor P, eds. *Goodman and Gilman's pharmacological basis of therapeutics*. 8th ed. New York: McGraw Hill, 1990.

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Opening Pandora's box: the unpredictability of reassurance by a normal test result

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Abstract

***Objectives*—To determine the rate of failure of patient reassurance after a normal test result and study the determinants of failure.**

***Design*—Replicated single case study with qualitative and quantitative data analysis.**

***Setting*—University teaching hospital.**

***Subjects*—40 consecutive patients referred for echocardiography either because of symptoms (10 patients) or because of a heart murmur (30). 39 were shown to have a normal heart.**

***Interventions*—Medical consultations and semistructured patient interviews were tape recorded. Structured interviews with consultant cardiologists were recorded in survey form.**

***Main outcome measures*—Patient recall of the explanation and residual understanding, doubt, and anxiety about the heart after the test and post-test consultation.**

***Results*—All 10 patients presenting with symptoms were left with anxiety about the heart despite a normal test result and reassurance by the consultant. Of 28 patients referred because of a murmur but shown to have no heart abnormality, 20 became anxious after detection of the murmur; 11 had residual anxiety despite the normal test result.**

***Conclusions*—Reassurance of the "worried well"—anxious patients with symptoms or patients concerned by a health query resulting from a routine medical examination or from screening—constitutes a large part of medical practice. It seems to be widely assumed that explaining that tests have shown no abnormality is enough to reassure. The results of this study refute this and emphasise the importance of personal and social factors as obstacles to reassurance.**

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Introduction

Reassurance of patients concerned about a possible health problem is perhaps the commonest clinical transaction of all. Clinicians and textbooks generally assume that reassurance must logically follow a clear and confident statement that no disease has been found. Failure of reassurance may then be ascribed to neurosis or labelled as abnormal illness behaviour.[1] The anxiety which remains can seriously impair quality of life and result in unnecessary reinvestigations, which are a burden on both the patient and the healthcare system. Despite the manifest importance of patient reassurance there has been remarkably little empirical study. We investigated this issue on the assumption that "The scientific resolution of most problems in clinical medical management will come from analyses of events and observations that occur in non-experimental circumstances during the interaction of nature, people, technological artefacts and clinical practitioners."[2]

Study population and methods

Six cardiologists in private practice and with university affiliation were each asked to recruit 10 consecutive patients who were referred to one of three laboratories (one public, two private) for the exclusion of heart disease. No cardiologist refused. Three recruited patients as requested and the remainder provided 10 patients between them. The sample of 40 patients recruited was sufficient to allow analysis in each major data category according to the principle of theoretical sampling.[3] Twenty five patients were female and 15 male, and their average age was 32 years (range 3-74).

The symptomatic group (10 patients) presented because they were worried by symptoms, usually palpitations or chest pain or both. In the incidental group (30 patients) referral was for assessment of a systolic murmur detected during a routine examination in primary care (21 patients) or in the course of a pre-employment or insurance check (nine patients). A systolic murmur had been heard in 36 patients. Doubt had previously been raised about the heart in 13 patients—in one no fewer than four times—and echocardiography had been performed previously in six. Three patients had previously taken medication for the heart.

DATA ACQUISITION AND ANALYSIS

Data analysed consisted of medical records, transcripts of tape recordings of the medical consultation in which the cardiologist had explained the test result, structured interviews with the cardiologists, and semistructured patient interviews.

The *cardiologist interview*, conducted by a consultant cardiologist, utilised a questionnaire developed for a previous study.[4] Data recorded included the reason for ordering the test, plans for patient management, and gradings of perceived patient anxiety before and after the test. The pretest likelihood of cardiac normality was