Rhinology, 36, 7–11, 1998

Antibiotic treatment of patients with mucosal thickening in the paranasal sinuses, and validation of cut-off points in sinus CT*

Morten Lindbæk[1], Esben Kaastad[2], Sverre Dølvik[2], Ulf Johnsen[3], Even Lærum[1], Per Hjortdahl[1]

[1] Department of General Practice, University of Oslo, Norway
[2] Department of Otorhinolaryngology, Ullevål Hospital, University of Oslo, Norway
[3] Department of Neuroradiology, Ullevål Hospital, University of Oslo, Norway

SUMMARY

We compared the efficacy of penicillin V and amoxycillin treatment with placebo in 70 adult patients from Norwegian family practice with a clinical diagnosis of acute sinusitis and mucosal thickening on CT, but without fluid level or total opacification. The study was randomized and double-blind. Three different outcomes were evaluated; subjective status after 10 days of treatment, difference in clinical score between day 0 and day 10, and duration of the illness episode. Amoxycillin and penicillin V gave no better response to treatment than placebo, evaluated by all three outcome measures. The median duration of the sinusitis episode was 10 days in the amoxycillin- and placebo groups and 13 days in the penicillin-V group. In patients with a clinical diagnosis of acute sinusitis, fluid level and total opacification on CT are good criteria to differentiate between groups of patients that need or do not need antibiotic treatment.

Key words: acute sinusitis, computed tomography, family practice, mucosal thickening

INTRODUCTION

In family practice, acute sinusitis is often regarded as a clinical entity which should be treated with antibiotics. However, clinical experience demonstrates that some patients respond well to antibiotic treatment, while others do not. One method to divide these patients is to use computed tomography (CT), dividing the patients in three groups: (1) normal CT; (2) mucosal thickening without fluid level or total opacification; and (3) acute sinusitis. Accepted CT-criteria for confirming the diagnosis of acute sinusitis are presence of fluid level or total opacification in any sinus (Pollei and Harnsberger 1989; Laine and Smoker, 1992; Zeifer 1993).

In a previous publication we have demonstrated that antibiotic treatment is better than placebo in patients with acute sinusitis confirmed by CT (Lindbæk et al., 1996a). In this part of the study, we wanted to compare the efficacy of penicillin V, amoxycillin and placebo given to patients with mucosal thickening on CT without fluid level or total opacification. The comparisons included: (1) subjective status after 10 days of treatment, as evaluated by the patient; (2) clinical score from visual analogue scales; and (3) duration of the sinusitis episode, as evaluated by the patient. Furthermore, we wanted to carry out a validation of the cut-off points used in these clinical studies to separate the patients who can profit from antibiotic treatment.

MATERIAL AND METHODS

Included in the study were family practice patients from the Tønsberg region in southern Norway, who were clinically diagnosed as having acute sinusitis, and had mucosal thickening without fluid levels or total opacification upon CT examination. Exclusion criteria were an age of 15 years or younger, pregnancy, ongoing antibiotic treatment, immuno-suppressive treatment, previous operations in the nose/sinus region, abuse of alcohol or narcotics, rheumatic disease, and penicillin allergy. If the symptoms had persisted more than 30 days, the patient was excluded due to a possible chronic sinusitis. Patients with high fever and considerable pain were not included due to ethical considerations.

Clinical evaluation

All patients were examined by an experienced family physician according to a standardized clinical procedure, the same day as the CT was performed. The clinical signs and symptoms evaluated were scored according to being present or not, or to sever-

* Received for publication May 6, 1997; accepted October 27, 1997

ity. The symptoms and signs registered are all common in acute sinusitis (Berg and Carenfeldt, 1988; Van Duijn et al., 1992; Williams and Simel, 1993; Lindbæk et al., 1996b). The presence of either hyposmia or anosmia, duration of symptoms more than seven days prior to first visit, unilateral facial pain, pain in upper teeth, pain worsening at bending forward, and double sickening (two phases in the same illness period) prior to first visit, each scored one point. Nasal obstruction, rhinorrhoea, sinus pain, and malaise as estimated by the patient, gave a maximum of one point each. Rectal temperature between 37.6°C and 38.0°C scored 0.5 points and above 38.0°C 1 point. Purulent secretion in the nasal floor, which is a fairly consistent sign of purulent sinusitis (Williams and Simel, 1993; Lindbæk et al., 1996b), was given 2 points. The points were summated for each patient, resulting in a "clinical severity score" of maximum 13 points.

CT-evaluation

The CT examinations were performed with contiguous 5 mm-thick coronal slices through the sinus complex including all the paranasal sinuses (W: 1500 HU; L: 100-400 HU). The CT examinations were evaluated independently by two experienced radiologists. If disagreeing in interpretation, they reassessed jointly and reached a consensus. The patients were grouped according to the CT results into three groups: (1) normal CT; (2) mucosal thickening of 5 mm or more in any sinus, without fluid or total opacification; and (3) presence of fluid level or total opacification in any sinus, which are the CT-criteria of acute sinusitis (Pollei and Harnsberger 1989; Laine and Smoker, 1992; Zeifer 1993).

The sinus systems evaluated were the frontal, ethmoid, maxillary and sphenoid sinuses, divided into a left- and right-sided group. CT was defined as negative with mucosal thickening less than 5 mm (Rak et al., 1991; Gwaltney et al., 1994). In the ethmoid cells this limit was difficult to use due to the small size of the ethmoid cells. Thus, the distinction between no, partial or total opacification was used in this sinus region.

Study group

During the periods January to May 1994 and November 1994 to May 1995, 244 patients were recruited to the study. 44 patients had negative CT, 130 patients had fluid level or total opacification, and 70 patients had mucosal thickening as evaluated by CT. The latter constituted the study group, and of these 43 patients were women (61%) and 27 were men (39%), and the mean age was 39.7 years (range: 16-83 years).

Randomisation and treatment

The trial was double-blind: Neither the patients, the general practitioner nor the radiologists were aware of the treatment allocation. The patients were randomized into one of three treatment alternatives: (1) penicillin V (1,320 mg thrice daily for 10 days); (2) amoxycillin (500 mg thrice daily for 10 days); and (3) placebo (thrice daily for 10 days). Each were 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 and randomization the patients were instructed to keep a diary, in which each morning they marked on four visual analogue scales (VAS scales) the degree of nasal obstruction, rhinorrhoea, sinus-related pain, and malaise. Finally, they were to answer the question: "Do you think you still have sinusitis today?" and given three possibilities: "yes", "uncertain" and "no".

Outcome evaluation

The four VAS scales were summated on day 0 and day 10, and a difference was estimated for each patient. On day 10 the patients assessed their own clinical condition, having the following options: "restored", "much better", "somewhat better", "unimproved" and "worse".

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, the maximal 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 cure because she or he felt unchanged or just slightly better after 10 days, the patient was given 500 mg amoxycillin thrice daily for another 10 days. In these cases the code of the original treatment was not broken. An intention-to-treat analysis was performed. In the statistical analysis Chi-square test, the Mann-Whitney U test, and the two-sided log-rank test were used. A significance level of 5% was used in all tests.

Table 1. Characteristics of study population.

	treatment groups		
	penicillin V	amoxycillin	placebo
number of patients	20	22	21
sex: men/women	8/12	11/11	6/15
mean age (SD)	41.2 (13)	37.1 (13)	42.5 (20)
mean clinical severity score day 0 (95%CI)	5.3 (4.3, 6.3)	5.8 (4.9, 6.7)	5.8 (4.9, 6.7)
bilateral maxillary affection	1	4	3
unilateral maxillary affection	11	9	10
ethmoid, sphenoid or frontal affection	8	9	8

* patients with maxillary affection in combination with affection of one of the other sinus regions, were grouped in one of the two maxillary affection groups.

RESULTS

Table 1 shows that the three treatment groups were similar as to gender, mean age, mean clinical severity score on day 0, proportion of patients with unilateral and bilateral maxillary affection, and with sinus affection in other sinus regions. Two out of 70 patients were taken out of the study because of bad quality of the CT-scans and were not included in the further evaluations.

Drop-outs

Five patients did not return their diary and no further data were registered, thus leaving 63 patients in the study. Three other patients, one receiving penicillin V and two receiving amoxycillin, stopped the initial treatment after a few days due to marked gastro-intestinal side effects. Furthermore, one patient in the placebo group and one patient in the amoxycillin group stopped the treatment within 10 days. Their treatment codes were not broken, and they recovered without further treatment. One patient in the placebo group and one patient in the amoxycillin group did not feel well on day 11 and received extended treatment with amoxycillin. Six patients, two in each treatment group, did not recover during the registration period and they were assigned 30 days as their illness duration. According to the principle of intention-to-treat, all these patients were included in the analyses by the groups they were originally randomised.

Subjective status

The patients' own evaluation of the clinical course after 10 days is given in Table 2. There were no significant differences between the three groups. After 10 days, 75% of the patients in the antibiotic groups felt restored or much better, as compared to 67% of the patients in the placebo group (p=0.99).

Clinical score

Table 3 shows the sum of the four VAS-scales on day 0 and day 10, and the difference between the two days. The clinical scores on day 0 and the differences between day 0 and day 10 were similar for all groups and showed no significant differences (p-values: 0.62-0.89).

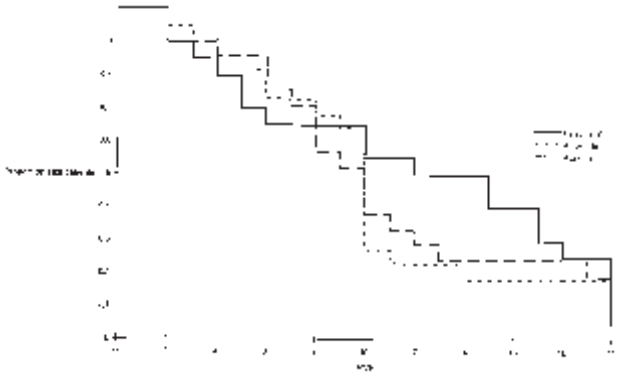

Figure 1. Proportion of 63 patients in the three groups by days from start of treatment.

Duration of the illness episode

The length of the sinusitis episode for each treatment group is given in Figure 1. The Kaplan-Meier plot shows the proportion of patients still feeling ill at any one day. There was no significant difference between the three groups (p=0.89, 0.99 and 0.76). The length of the sinusitis episodes were estimated from the median value in each patient group. The median was 10 days in the placebo and the amoxycillin groups, and 13.5 days in the penicillin-V group.

In order to estimate the number of patients needed to show significant clinical differences, we performed a power analysis based on the number of patients who felt better (85% in all three groups) or unimproved, and the reduction in clinical score (60-65%) (Sackett et al., 1991). This indicated that we needed at least 20 patients in each group in order to detect a risk reduction of at least 25%.

Table 2. The patients' evaluation of the clinical course after 10 days treatment.

	restored n (%)	much better n (%)	somewhat better n (%)	unimproved n (%)	worse n (%)	total n (%)
penicillin V	6 (30)	9 (45)	3 (15)	2 (10)	0 (0)	20 (100)
amoxycillin	9 (41)	8 (36)	2 (9)	2 (9)	1 (5)	22 (100)
placebo	9 (43)	5 (24)	4 (19)	3 (14)	0 (0)	21 (100)

Mann Whitney U-test corrected for ties: amoxycillin vs. placebo: p = 0.87; penicillin vs. placebo: p = 0.85; amoxycillin vs. penicillin: p = 0.66; antibiotics vs placebo: p = 0.99.

Table 3. Clinical score summated from four VAS-scales with a maximum of 4.0 points.

	mean clinical score		
	day 0 score (95% CI)	day 10 score (95% CI)	reduction score (95% CI)
penicillin V	1.8 (1.5, 2.2)	0.7 (0.4, 1.0)	1.1 (0.8, 1.5)
amoxycillin	1.6 (1.2, 2.0)	0.5 (0.2, 0.9)	1.1 (0.6, 1.6)
placebo	1.6 (1.3, 1.9)	0.6 (0.3, 0.9)	1.0 (0.7, 1.3)

students t-test: penicillin V vs. placebo: p = 0.62; amoxycillin vs. placebo: p = 0.89; penicillin V vs amoxycillin: p = 0.80; antibiotics vs. placebo: p = 0.75

DISCUSSION

The present study has been randomized, double-blind and placebo-controlled, with matched treatment groups of patients seen in family practice. We have studied those patients who had mucosal thickening in any sinus, but without fluid level or total opacifications. We have demonstrated that there were no significant differences between the three groups, neither in the subjective status after 10 days and the difference in clinical score, nor the duration of illness. These findings are in contrast to our previous study of patients with fluid level or total opacification on CT, where significant differences between similar treatment groups, using the same outcome measures, were found (Lindbæk et al., 1996a).

According to our power analysis we had sufficient patients to detect a risk reduction of 25% or more. This is the basis of our conclusion that there are no significant differences between the three groups and that antibiotics are no more effective than placebo in the treatment of patients with mucosal thickening but without signs of fluid in CT.

Cut-off points used on CT-scans

Sinus CT has rarely been used as reference standard in the study of acute sinusitis. In our project we have chosen to divide the patients in three groups: (1) fluid level and/or total opacification; (2) mucosal thickening without fluid level or total opacification; and (3) normal CT. We have validated whether these cut-off points were useful in the evaluation of clinical findings and response to antibiotic treatment.

1. Acute sinusitis

In patients with suspected acute sinusitis the main issue is to demonstrate fluid in the sinus regions. The CT-radiological hallmarks of acute sinusitis are: (1) fluid level in one or more sinuses; and/or (2) total opacification in one or more sinuses. These findings are interpreted as fluid in the sinuses in this study, in accordance with previous studies (Pollei and Harnsberger 1989; Laine and Smoker, 1992; Zeifer, 1993). Hansen et al. (1995) have demonstrated in a subgroup of their study that pus or mucopus is found by sinus puncture in 90% of patients with a fluid level in the maxillary sinus on CT images.

In some studies questions have been raised concerning the rate of false-positive results in sinus CT. Great differences in the incidental findings of mucosal affection in asymptomatic subjects have been reported, ranging from 7% (Iemma et al., 1992) to 42% (Havas et al., 1988). Cysts, mucoceles and polyps may rarely give total opacification on CT scans. However, incidental findings of total opacification or fluid level in asymptomatic patients have been found only rarely (Havas et al., 1988; Rak et al., 1991; Cooke and Hadley, 1991). The interpretation of fluid levels may be difficult on CT images and a "tilting test", such as used in ordinary X-ray, is difficult to perform. However, our interobserver study shows substantial agreement in the interpretation of fluid level on coronal CT scans (Lindbæk et al., 1996c).

On CT scans of patients with acute sinusitis bubbling and standing in a fluid-filled sinus cavity may be seen (Zeifer, 1993).

CT provides a good opportunity to evaluate the involvement of the acute disease in all sinuses. This gives good objective information in addition to other clinical information. A score system introduced by Lund and Mackay (1993) developed for staging of rhinosinusitis may be used. As this system is mainly intended for patients with chronic sinusitis, the system has been modified on some points. We assess four sinus regions on both sides, in total eight regions, the anterior and posterior ethmoid cells being assessed together. The score is estimated for each sinus region: 0 points: negative sinus or mucosal thickening (<5 mm); 1 point: partial opacification (>5 mm); and 2 points: total opacification or fluid level. The ostiomeatal complex is also assessed, but does not contribute to the score. The maximum score for each patient is 16 points. In our study of antibiotic treatment of patients with CT-confirmed acute sinusitis, this score system shows differences between the groups that corresponded well with other clinical outcome measures (Lindbæk et al., 1996a; Willett, 1997) .

2. Mucosal thickening

The clinical significance of mucosal thickening is debated. Gwaltney et al. (1994) have shown that the sinus mucosa is involved with slight thickening in the common cold. However, only a few of their patients have had mucosal thickening of 5 mm or more, and only one patient of 31 had a fluid level. Rak et al. (1991) have concluded, using MRI as reference standard, that mucosal thickening under 4 mm lacks clinical significance in asymptomatic patients. Thus, it appears that a 5-mm mucosal thickening may be a reasonable cut-off point. A mucosal thickening over this size may represent an intermediate stage between the common cold and acute sinusitis. Polypoid formations are commonly seen. The criteria for this are the appearance and the lack of full opacification.

In our previous clinical study we assessed the clinical findings in patients with signs of fluid in any sinus, mucosal thickening and negative CT (Lindbæk et al., 1996b). When the symptoms and signs of patients with significant mucosal thickening were compared with those of the other groups, they were generally more similar to patients with negative CT scans than those with sinusitis.

3. Negative CT

In both our studies, a significant number of patients with a clinical diagnosis of acute sinusitis actually had negative CT: 24% in one study (Lindbæk et al., 1996c) and 18% in the other (Lindbæk et al., 1996a). These patients may have had pain conditions, such as tension headache, mandibular joint dysfunction, atypical migraine and trigeminus neuralgia, which are the most common differential diagnosis of acute sinusitis (Lindbæk, 1995); in some cases in combination with a common cold.

The choice of CT as a method for research

Stammberger (1986) states in his study that the ethmoid cells and the infundibulum area play an important role in the pathogenesis of sinusitis, being a potential primary locus of the

infection, also for maxillary sinusitis. The 64 out of 84 patients with fluid level or total opacification of the maxillary sinus, also had opacification of the ethmoid sinuses (Lindbæk et al., 1996c). Furthermore, a majority of patients with opacified ethmoid cells had significant mucosal thickening of the maxillary sinus, indicating a possible connection between maxillary and ethmoid sinus infections.

The advantage of CT as a method for research is its ability to visualize all parts of the sinus systems. It is a great advantage to be able to visualize the small sinuses which otherwise are difficult to evaluate on plain X-rays or with ultrasonography. False-positive investigations have been raised as a problem with CT of the sinuses (Havas et al., 1988; Hansen et al., 1995). However, the findings represent mainly small mucosal thickening. Total opacification or fluid levels were almost never described in these studies. When using the latter as radiological hallmarks of sinusitis, the risk of false-positive investigations appears to be negligible.

The accessibility of CT has been a problem so far. However, it is becoming more common in many countries to have CT equipment at the local hospitals, and this provides for increased use also in primary care. We, however, still do not recommend to use CT as a routine examination in primary care patients with sinusitis. Radiation has been used as an argument against the use of CT (Howe, 1993). In our computation, sinus CT gives a moderate radiation, somewhat larger than ordinary sinus X-rays (Hansen et al., 1995). The radiation dose is dependent on the thickness of the slices used and the kind of programme employed.

CONCLUSIONS

Antibiotics are no more effective than placebo in the treatment of patients with mucosal thickening but without signs of fluid in CT. The cut-off points with total opacification and fluid level versus mucosal thickening that were used in our studies are useful in differentiating patients with a clinical diagnosis of acute sinusitis into clinically relevant groups. These groups are different both in the clinical findings and in response to antibiotic treatment.

ACKNOWLEDGEMENTS

We thank Professor Iain Mair (ENT Department, Ullevål Hospital) and L. Sandvik for valuable comments, and Dr. Falkenberg (Tønsberg Røntgeninstitutt) for making and assessing the CT scans. We also thank the 29 primary care physicians in Tønsberg and its vicinity, who recruited patients to the study. The study was approved by the National Ethical Committee, and was supported by the Norwegian Research Council.

REFERENCES

1. Berg O, Carenfeldt C (1988) Analysis of symptoms and clinical signs in the maxillary sinus empyema. Acta Otolaryngol (Stockh) 105: 343-349.
2. Cooke LD, Hadley DM (1991) MRI on the paranasal sinuses: Incidental abnormalities and their relationship to symptoms. J Laryngol Otol 105: 278-281.
3. Gwaltney JM, Phillips CD, Miller RD, Riker DK (1994) Computed tomography of the common cold. N Engl J Med 330: 25-29.
4. Hansen JG, Schmidt H, Rosborg J, Lund E (1995) Predicting acute maxillary sinusitis in a family practice population. BMJ 311: 233-236.
5. Havas TE, Motbey JA, Gullane PJ (1988) Prevalence of incidental abnormalities on computed tomographic scans of the paranasal sinuses. Arch Otolaryngol Head Neck Surg 114: 856-859.
6. Howe DB (1993) Imaging for sinusitis. JAMA 270: 2686-2687.
7. Iemma M, Maurer J, Mann W (1992) The incidence and location of inflammatory paranasal sinus lesions in CT. Acta Otorinolaring Ital 12: 135-142.
8. Laine FJ, Smoker WRK (1992) The ostiomeatal unit and endoscopic surgery: Anatomy, variations, and imaging findings in inflammatory diseases. AJR 159: 849-857.
9. Lindbæk M (1995) Acute infections in nose and paranasal sinuses. Diagnosis and treatment. In: S Madsen, A Wærsted, O Westbye, B Beermann, K Strandberg (Eds.) Treatment of Acute Infections of the Respiratory Tract in Primary Health Service. Statens Legemiddelkontroll Läkemedelsverket, Oslo, pp. 125-136.
10. Lindbæk M, Hjortdahl P, Johnsen UL-H (1996a) Randomised, double-blind, placebo-controlled trial of penicillin V and amoxycillin in treatment of acute sinus infections in adults. BMJ 313: 325-329.
11. Lindbæk M, Hjortdahl P, Johnsen UL-H (1996b) Use of symptoms, signs, and blood tests to diagnose acute sinus infections in primary care: Comparison with computed tomography. Fam Med 28: 181-186.
12. Lindbæk M, Johnsen UL-H, Kaastad E, Dølvik S, Møll P, Lærum E, Hjortdahl P (1996c) CT-findings in family practice patients with suspected acute sinusitis. Acta Radiol 28: 183-188.
13. Lund VJ, Mackay IA (1993) Staging in rhinosinusitis. Rhinology 31: 183- 184.
14. Pollei S, Harnsberger HR (1989) The radiologic evaluation of the sinonasal region. Postgrad Radiol 9: 242-266.
15. Rak KM, Newell JD, Yakes WF, Damiano MA, Luethke JM (1991) Paranasal sinuses on MR images: Significance of mucosal thickening. AJR 156: 381-384.
16. Sackett DL, Haynes RB, Guyatt GH, Tugwell P (1991) Clinical Epidemiology. A Basic Science for Clinical Medicine. Little, Brown and Company, Boston, pp. 187-248.
17. Stammberger H (1986) Endoscopic endonasal surgery. Concepts in treatment of recurring rhinosinusitis. Part I. Anatomic and pathophysiologic considerations. Otolaryngol Head Neck Surg 94: 143-156.
18. Van Duijn NP, Brouwer HJ, Lamberts H (1992) Use of symptoms and signs to diagnose maxillary sinusitis in family practice: Comparison with ultrasonography. BMJ 305: 684-768.
19. Willett LR (1997) Commentary on "Penicillin V and amoxycillin improved health status in sinusitis." ACP J Club 126: 10.
20. Williams JW, Simel DL (1993) Does this patient have sinusitis? Diagnosing acute sinusitis by history and physical examination. JAMA 270: 1242-1246.
21. Zeifer BA (1993) Sinus imaging. In: BJ Bailey (Ed.) Head and Neck Surgery/Otolaryngology. Lippincott, Philadelphia, pp. 350-365.

Dr. Morten Lindbæk
Department of General Practice
University of Oslo
Box 1130
Blindern
N-0317 Oslo
Norway