Chloramphenicol eye drops in the treatment of conditions indicative of maxillary sinusitis

BACKGROUND Our own clinical experience of general practice over the last 15 years has indicated that chloramphenicol eye drops may have a favourable effect on many patients troubled by symptoms indicative of acute maxillary sinusitis. We wanted to conduct a pilot study to test whether this observation could be verified.

MATERIAL and METHOD Treatment with chloramphenicol eye drops or systemic peroral antibiotics was tested on patients with symptoms indicative of acute maxillary sinusitis. The patients were randomised to two groups, one of which received systemic peroral antibiotics, the other received chloramphenicol eye drops.

RESULTS A total of 33 patients were included in the trial – 27 women and six men –15 of whom were randomised to the tablet group and 18 of whom were randomised to the chloramphenicol group. The patients who were treated with tablets experienced clear improvement after an average of 5.0 days, while patients who were treated with chloramphenicol eye drops, experienced improvement after 3.7 days (p = 0.047). Of the patients in the chloramphenicol group, 14 described improvement within three days, while this applied to only five patients in the tablet group.

INTERPRETATION Treatment with chloramphenicol eye drops appears to represent a treatment option for some patients with symptoms indicative of acute maxillary sinusitis. In the pilot study, the period of treatment before symptoms improved was shorter in patients who were given eye drops than in patients who were given systemic peroral antibiotics. These promising results give grounds to undertake studies on a larger scale.

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MAIN MESSAGE

It appears that certain patients with symptoms indicative of acute maxillary sinusitis may be effectively treated with chloramphenicol eye drops.

The pilot study has demonstrated few side effects from the use of chloramphenicol eye drops, high patient satisfaction and a shorter treatment period than for peroral antibiotics.

The results give cause to conduct studies on a larger scale.

Sinusitis is a problem commonly encountered in general practice. Every year, 1–5 % of the adult population in Europe catches sinusitis, and 0.5–2 % of all patients with cold symptoms develop symptoms of acute bacterial sinusitis (1, 2). The infection may be localised in the frontal, ethmoidal and maxillary sinuses. Sinusitis imaging is achieved with CT or ultrasound examination (3, 4). It is not normal for imaging diagnostics to be used in general practice before treatment commences, as the diagnosis is clinical. The bacterial flora present in maxillary sinusitis in Norway are primarily *Streptococcus pneumoniae* and *Haemophilus influenzae* (5). The standard Norwegian peroral antibiotics treatment for acute sinusitis has until now been phenoxymethylpenicillin 0.66–1.3 g × 3–4 for 7–10 days (6).

Increasing resistance in *S. pneumoniae* to phenoxymethylpenicillin and macrolides has given rise to increased use of new and broader-spectrum antibiotics. A number of studies undertaken in recent years provide no certainty that peroral antibiotics are particularly beneficial in the treatment of acute sinusitis, as most patients recover even without such treatment (7–9). Trials with reference standards (e.g. CT examination of the sinuses) have established differences between the effectiveness of treatment with antibiotics and placebo. This has not been found in studies with purely clinical endpoints (8).

In a double-blind, randomised, placebo-controlled trial, the effect of treatment with peroral amoxicillin was compared to the effect of treatment with budesonide nasal spray (10). The conclusion was that neither antibiotics nor budesonide, alone or in combination, provide an effective treatment for acute maxillary sinusitis. Consensus has not been reached over the interpretation of these results (11), and peroral antibiotics treatment of acute sinusitis in general practice has been criticised as over-treatment (12).

Our own clinical experience of patients (IRN) in general practice over the last 15 years has indicated that chloramphenicol eye drops may have a favourable effect on patients with symptoms indicative of acute maxillary sinusitis. We wanted to conduct a pilot study to test whether this observation was verifiable. The objective was to compare the period of treatment before patients experienced improvement, the rate of patient satisfaction, and the side effects of using chloramphenicol eye drops applied in conjunctiva and treatment with peroral antibiotics in patients with symptoms indicative of acute maxillary sinusitis.

Material and method

In the autumn of 2008 all general practitioners (GPs) in the county of Møre og Romsdal (a total of approx. 220 doctors) were contacted by post and invited to take part in the

project. In order to eliminate the pollen season, the period chosen was November/December. The GPs were asked to use an audit form (13) to record all patients diagnosed with sinusitis in the chosen period, including those who did not meet the inclusion criteria. Patients would have to meet at least two of the following inclusion criteria (14):

- Purulent discharge from nose/rear of throat
- Tenderness/throbbing pain above the maxillary sinus
- Pain in the upper jaw when bending forwards
- Toothache when walking or chewing
- Two-phased clinical course

The exclusion criteria were chronic sinusitis, allergy to chloramphenicol, age below 18 years, and patients for whom poor compliance might be expected, with no further specification given.

The GPs were asked to diagnose patients with maxillary sinusitis clinically, without employing any supplementary diagnostic methods such as CT or ultrasound examination. This was to ensure that the diagnostic procedure would be as similar as possible to that encountered in normal clinical general practice.

For each patient included in the pilot study, their GP would have to contact the researcher (IRN) by telephone for patients to be instantly randomised to the tablet group or the chloramphenicol group. Patients who were randomised to the chloramphenicol group were given prescriptions for chloramphenicol eye drops to be applied to both eyes 8–10 times a day for a period of 2–4 days or until their symptoms disappeared. Patients who were randomised to the tablet group were given a course of antibiotics chosen by the GP.

All included patients were given a questionnaire and asked to complete it once their treatment had come to an end and then return it to their GP. The form asked them to specify how many days passed before they noticed a clear improvement (main outcome). If the patient experienced no improvement, this was recorded as ten days before improvement occurred, since this is normally the upper limit for the length of a course of systemic antibiotics. Patients were also asked about any side effects of the treatment. The patients in the chloramphenicol group were also asked whether they had applied the drops as prescribed and what treatment they would prefer were they to experience symptoms indicative of maxillary sinusitis again. The GPs returned all submitted patient questionnaires to the researcher (IRN) with their completed audit forms.

The number of days before the patient noticed improvement was considered to be the main outcome. For the purpose of calculating the strength of the results, the measure for a clinically significant difference between traditional treatment (antibiotics) and trial treatment (chloramphenicol eye drops) was set to a 20 % reduction in the number of days before improvement was noticed. This roughly corresponds to one treatment day. We used a standard deviation (SD) of two days and a significance level of 5 % ($p = 0.05$) for both treatment groups. In a two-sided trial, this produces a strength of 80 % with 60 patients in each group. The strength of the trial is close to 90 % with 80 patients in each group. These calculations are based on an expected average of five days before clear improvement in the tablet group and four days in the chloramphenicol group. If there was less spread in the groups (lower standard deviation), fewer patients in each of the groups would have sufficed.

All statistics were calculated using the SPSS statistics software. To compare the average number of days before patients in the two groups reported improvement, a Mann-Whitney U test was performed.

The pilot study has been approved by the Regional Committee for Medical and Health Research Ethics (Central Norway), Norwegian Social Science Data Services (NSD) and the Norwegian Medicines Agency, and it was registered in EudraCT (European Clinical Trial Database) in 2008.

Results

A total of 22 GPs responded to our letter. A total of 38 patients were randomised for the pilot study. Three of the patients in the tablet group withdrew from the trial with no further grounds given. One of the patients in the chloramphenicol group had to discontinue due to allergic reactions, and one patient failed to complete the form due to language problems. The pilot study included 33 patients: 27 women and six men. Of these, 18 were randomised to the chloramphenicol group, 15 to the tablet group. The age distribution of the two groups was virtually identical: 22–61 years in the chloramphenicol group and 27–67 years in the antibiotics group.

Only three of the 33 patients included met all five inclusion criteria: purulent discharge from nose /rear of throat, tenderness/throbbing pain above the maxillary sinus, pain in the upper jaw when bending forwards, toothache when walking or chewing, and a two-phased clinical course. Eight patients met two criteria, ten patients met three and 12 patients met four. In each of the groups a total of three patients received additional treatment in the form of nasal spray or saline rinse.

Table 1 Number of patients reporting clear improvement, distributed between treatment groups and days from treatment start

Days from treatment start	Chloramphenicol group, number of patients reporting improvement	Tablet group, number of patients reporting improvement
1	3	1
2	9	2
3	2	2
4	0	4
5	0	1
6	0	1
7	0	1
10 or no improvement	4	3
Total	**18**	**15**

Effect

The average number of days before clear improvement was reported was 5.0 for patients treated with antibiotics, while patients treated with chloramphenicol reported clear improvement after 3.7 days ($p = 0.047$). This means that on average, patients in the chloramphenicol group experienced improvement 1.3 days sooner than patients in the tablet group. Table 1 shows how the number of days before clear improvement are distributed between the two patient groups.

Patient satisfaction

Patients in the chloramphenicol group were asked which treatment they would prefer should they ever experience similar symptoms again. 12 of them would prefer the same treatment, while six would prefer peroral antibiotics or some other treatment. The patients also responded to whether they had followed the advice of applying the drops 8–10 times a day. Only one patient indicated a less frequent administration regime than that prescribed.

Side effects

One patient in the chloramphenicol group had to discontinue the treatment due to allergic reactions in the form of headache, nausea and cold flashes. This patient is not included in the analysis of the results. Two other patients experienced irritation in the form of dry eyes, but these did not discontinue their treatment. In the tablet group, six

patients (43 %) reported adverse effects in the form of stomach pain (diarrhoea, obstipation, nausea and anal itch). None of these withdrew from the trial.

Discussion

As far as we know, the treatment of conditions indicative of maxillary sinusitis with chloramphenicol eye drops has not previously been described. In this pilot study, in which peroral antibiotics were compared to chloramphenicol eye drops, 14 of 18 patients in the chloramphenicol group (78 %) answered that they noticed clear improvement after three days of treatment, while the corresponding number in the group treated with peroral antibiotics was five of 15 (33 %). On average, patients in the chloramphenicol group reported improvement 1.3 days sooner than patients in the tablet group.

Ideally, this study should have compared treatment with chloramphenicol eye drops to placebo. However, patients who see their GP because they suffer from symptoms indicative of sinusitis expect to receive «effective» treatment that works fast. Consequently, no placebo group was formed, nor a group for no treatment.

Our study did not collect information about which types of peroral antibiotics the GPs chose to prescribe. It is a matter for discussion whether a standardised choice of antibiotics might have contributed to a more homogenous basis for comparison between the two groups. On the other hand, our design ensured that the treatment was as similar as possible to the treatment the GPs would have chosen in normal practice.

The trial's total follow-up period was ten days from commencement of treatment. This was primarily a pilot study looking at effectiveness, side effect frequency and patient satisfaction, and was thus not specifically designed to look into the presence of residual symptoms after treatment had been completed. Later trials should include this matter as part of their remit.

A more recent literature review concludes that antibiotics have limited effect and that their use should be limited in the treatment of clinically diagnosed acute sinusitis (15). For this reason, it may now be better to compare treatment with chloramphenicol eye drops to saline drops applied in the conjunctiva or no medicinal treatment. However, studies suggest that saline nasal spray scores no better than placebo in the treatment of conditions indicative of acute sinusitis (16).

If our results can be confirmed by studies conducted on a larger scale, treatment with chloramphenicol eye drops may become an option in cases of acute maxillary sinusitis. The benefits may be a shorter treatment period and fewer side effects. Nevertheless, this treatment will never represent an option for everyone suffering from this type of condition. For many, a saline rinse or no treatment will still be a possibility, while treatment with systemic antibiotics should be reserved for febrile patients whose general state of health has been reduced by sinusitis, and for patients who are allergic to chloramphenicol.

Our study recorded fewer side effects in the chloramphenicol group than in the antibiotic tablet group, which is an important benefit. It is a general objective in general practice to minimise the use of systemic antibiotics, as this may reduce the development of resistance to antibiotics and cause fewer side effects in patients (17, 18).

Potential explanations as to why chloramphenicol eye drops are effective against conditions indicative of acute maxillary sinusitis, may be that they inhibit the growth of bacteria in the nasal cavity or that they dissolve a potential blockage that obstructs the sinus drainage tract. Normalisation of the sinus drain may be the immediate cause of rapid recovery, but it may also be that the local effect on the nasal mucous membrane is decisive. If this is the case, a chloramphenicol nasal spray may prove to be just as efficacious.

This pilot study had few participants, which makes the statistical calculations uncertain. It will also be difficult to achieve statistically significant differences between the groups being compared. Our results nevertheless show significantly faster recovery times for treatment with chloramphenicol eye drops compared to systemic antibiotics. However, the restricted scope of the study suggests that the outcomes should be interpreted with caution, and that the results should be tested in a larger randomised study. Because the treatment of sinusitis with chloramphenicol eye drops involves an entirely new principle, further trials should be of great interest. If the results of our pilot study can be confirmed, we will have an efficacious and inexpensive treatment option involving few side effects for patients with symptoms indicative of acute maxillary sinusitis.

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