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Placebo-controlled, randomized double-blind clinical trial with Sinupret® sugar coated tablets on the basis of a therapy with antibiotics and decongestant nasal drops in acute sinusitis

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Summary

On the basis of therapy with antibiotics and nasal decongestants the efficacy of an additional treatment with the herbal combination Sinupret containing gentian root, cowslip flowers, sour dock herbs, elder flowers and shop vervain wort herbs was assessed in a randomized, placebo-controlled double-blind clinical trial involving 160 patients with acute bacterial sinusitis. Primary outcome criteria were radiographic findings and patient assessment. Secondary variables were several clinical symptoms of sinusitis which served as indicators of the pharmacological profile. The results showed that, according to the radiographic findings and the patient assessments, therapy with antibiotic and decongestants achieved a significant improvement in the treatment group; changes in clinical signs showed good correlation with the radiographic findings and the patient assessments. Conventional therapy for acute bacterial sinusitis can be improved markedly by including Sinupret in the therapeutic regimen.

Key words: Sinusitis, herbal combination, *Gentiana lutea* (gentian), *Primula veris* (cowslip), *Rumex acetosa* (sour dock), *Sambucus nigra* (elder), *Verbena officinalis* (shop vervain wort), controlled clinical trial.

Introduction

Sinusitis occurs with various degrees of severity, each requiring a different therapy. In cases of acute bacterial sinusitis, antimicrobial therapy is regarded as the most important medication, usually in combination with local decongestant to treat the obstruction of the paranasal ostia and the intranasal cavity. Current recommendations include additional mucoactive therapy with mucolytic or secretolytic substances (King and Mabry, 1993; Plinkert, 1993). The aim of this study was to investigate whether the results of therapy with antimicrobial substances and local decongestants could be improved by an additional therapy with a herbal combination having secretolytic (Chibanguza et al., 1984) and immunomodulating properties (Ottendorfer, 1991; Schmolz, 1992). In addition to empirical evidence to justify such a therapeutic regimen (Zimmer, 1985; Plinkert, 1993) there are also theoretical reasons which are discussed.

In acute bacterial sinusitis *Staphylococcus aureus* and *Hemophilus influenzae* are reported as the most common pathogens present (Mann and Pelz, 1979; Meyers, 1984; Albegger, 1992). Purulent discharge (identified by anterior or posterior rhinoscopy), overall clinical impression and case histories are sufficient reasons for antimicrobial therapy. According to the spectrum of pathogens, doxycycline was routinely used as the antibiotic when the study was planned and conducted (1985–1987). Today, recommendations have changed to account for the development of

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antibiotic resistance (Adam et al., 1993); xylometazoline was used as the decongestant; both preparations are usually prescribed in the Ear, Nose and Throat-Department of an army hospital, where the study was conducted; the introduction of the herbal combination was, in fact, the only unusual component in the therapeutic regimen.

The herbal combination Sinupret is a preparation which has been used for the treatment of sinusitis since 1934 (in liquid form) and since 1968 as sugar coated tablets. The composition of both formulations is similar; in this study sugar-coated tablets were used. 1 sugar-coated tablet contains the following drugs, pulverized at low temperature: 6 mg Radix Gentianae luteae (gentian root), 18 mg Flos Primulae veris cum calycibus (cowslip flowers with calyx), 18 mg Herba Rumicis acetosae (sour dock herbs), 18 mg Flos Sambuci nigri (elder flowers) and 18 mg Herba Verbenae off. (shop vervain wort herbs). As a commercial preparation, the product is subject to stringent quality control concerning ingredients and manufacturing procedures in order to guarantee reproducible quality. The standards for phytochemical quality are higher than defined in the monographs of the German phamacopoia DAB 10 and the DAC 1986 (Deutscher Arzneimittel Kodex) and were developed by the company according to the standard of the Arzneimittelprüfrichtlinien rsp. guideline 75/318/EWG. Pharmacological investigations have revealed secretolytic (Chibanguza et al., 1984) and immunomodulatory/antiinflammatory properties for certain components and the combination (Schmolz, 1992; Ottendorfer, 1992). As demonstrated in a double-blind, placebo-controlled clinical trial, the combination has already been found to have significant therapeutic effects in chronic sinusitis (Richstein and Mann, 1980). Several open studies have described the therapeutic value and safety of the preparation (Folberth, 1975; Folle, 1984; Goroll and Stehle, 1982; Khan, 1982; Löw, 1975; Menger, 1975; Schmidt, 1975; Wilde, 1972). In this study a dose of 3 x 2 sugar coated tablets/day was used.

Methods

Study design and treatments: The study reported here was conducted as a placebo-controlled randomized double-blind trial in patients with acute bacterial sinusitis who received antimicrobial and decongestant therapy as the usual treatment for this disease (Hamory et al., 1979; Hildmann, 1991; Meyers, 1984; Perkins and Morris, 1993); the aim was to test whether the response rates could be improved by adding the herbal combination to this regimen. Vibramycin® (doxycycline) was employed as the antibiotic and Otriven® (xylometalzoline) as the decongestant substance. Sinupret sugar-coated tablets, absolutely identical placebos, the randomization list and case report forms were supplied by the sponsor as well as a sealed emergency code.

Patients, outcome criteria: The inclusion criterion was the clinical diagnosis of an acute sinusitis in connection with an opacification of the plain sinus radiogram. Clinical diagnosis was carried out by anterior and posterior inspection of the nose assessing mucosal inflammation (swelling and increased blood circulation), obstruction of the paranasal sinuses and patency of the nose, purulence of discharge and postnasal drip strictly as pathologic/nonpathologic; as a typical complaint in acute sinusitis the presence of headache was recorded. Patients with extreme anatomical deviations of the nasal septum were excluded as well as patients with known intolerance for doxycycline. A randomization list was generated with a computer programme. According to this list the patients were assigned to receive additional therapy with Sinupret and placebo (2 sugar-coated tablets t.i.d.) respectively over two weeks. The primary outcome criteria were the radiographic finding (completely opaque/shadowed/nothing abnormal) and the patient assessment of the therapy (three categories: asymptomatic/good effect/no effect) recorded at the follow-up visit; secondary variables were clinical findings (mucosa findings, secretions, patency of the nose, headache). The study was designed to assess the improvement of an effective treatment; therefore the case number was increased compared with simple efficacy studies and had to be roughly estimated since no prior results were available. The original number of patients included in the study was 177, but in 17 (7/10) patients only some of the clinical symptoms were present; in combination with a less marked opacification of the radiogram and a case history of prior infections of the nose they were categorized as having chronic sinusitis. Their data were analysed separately on a descriptive basis. One follow-up visit took place after two weeks of therapy.

Data analysis: An SPSS database was created with the SPSS Data Entry programme; further statistical analysis of the data was carried out with the SPSS/PC+/V2.0 statistical package; confidence intervals were calculated and plotted with the SYSTAT/SYGRAPH software. Primary criteria (roentgenographic findings, patient assessment) and secondary criteria (mucosal swelling, obstruction of drainage, headache, discharge, patency of the nose) were clinically assessed as trichotomous and dichotomous variables respectively and evaluated by contingency tables (first visit x follow-up-visit); from those tables the proportion of patients with improvements, i.e. the response rates, in each group were read; around the difference of these response rates the 95% confidence intervals were calculated (Kramer, 1988), a technique that obtains the amount of a difference together with its significance. The evaluations of the secondary criteria were performed by the same method on an exploratory level to assess the pharmacological profile of activity of the preparation. No corrections for repeated testing were made.

Results

All 160 patients in the acute bacterial sinusitis group had a complete or partially opacified roentgenogram (inclusion criterion). Eighty-one patients were treated with drug, 79 with placebo.

Data in Tables 1 and 2 demonstrate successful randomization with good comparability (demographic homogeneity and proportion of clinical findings) of the groups at the beginning of therapy. In none of the clinical findings did initial incidences differ by more than 7%. Compliance could only be checked by inquiry. Of the patients, 10% received oily nose drops or inhalations with camomile in addition to the basic medication (protocol violation); such cases were equally distributed among the treatment groups.

Therapeutic effects based on the primary variable "radiographic findings" are presented in Table 3. Contingency table analysis of these data gives a χ^2-value of 15.5049 with 5 degrees of freedom (df); p = 0.0084; concentrating on effect vs. no effect in a 2 x 2 table χ^2 = 5.1152; the corresponding p = 0.02372; df = 1). Thus, the results in favour of the test-group regarding radiographic findings are highly significant.

Analysis of the patient assessments recorded at the end of the therapy again showed significant results in favour of the Sinupret group (Table 4).

Analysis of the clinical variables – which are not independent of the radiographic findings and were, therefore, subject to exploratory analysis – resulted in significant differences showing superiority of the Sinupret group for the variables mucosal swelling, nasal obstruction, headache and positive trends for nasal patency. No difference regarding secretion was found.

The results for all variables are presented in Fig. 1, showing the difference of the response rates and the 95-% confidence intervals around these differences:

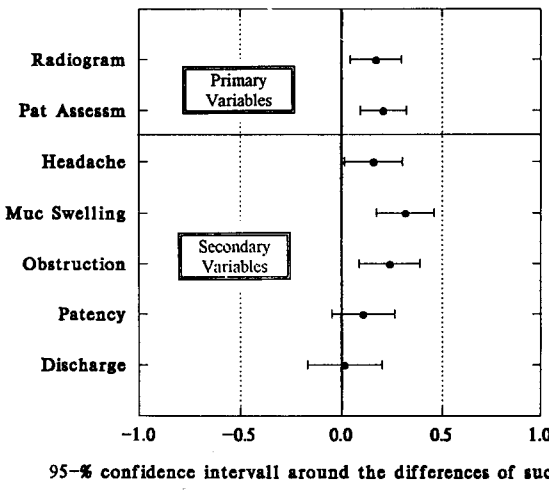

Fig. 1. Differences in response rates with 95-% confidence intervals for primary variables (radiographic findings and patient assessment) and secondary variables (headache, mucosal swelling, obstruction of drainage, patency of the nose and discharge). Groups differ significantly when the 0-boarder is not covered by the confidence interval.

Table 1. Patient characteristics (mean and standard deviation): age, weight, all patients were male.

Patient characteristics		
	Sinupret	Placebo
age: mean	24.1	24.9
std deviation	8.0	7.3
weight: mean	73.8	72.7
std deviation	5.8	5.9

Table 2. Comparability of treatment groups regarding radiographic and clinical findings at the beginning of the treatment; patients classified as chronic sinusitis (not shown) had a similar comparability with a lower degree of severity.

Acute sinusitis Characteristics of treatment groups: Pretherapy comparability		
	Sinupret	Placebo
Roentgenogram		
completely opaque	73.4%	67.1%
shaded	24.7%	32.9%
mucosal swelling	98.8%	98.7%
purulent discharge	61.7%	59.0%
obstruction	90.1%	82.3%
local inflammation	98.8%	94.9%
patency	84.0%	92.4%

Table 3. Changes in radiographic findings during therapy (acute sinusitis) in %. χ^2 = 15.5049; p = 0.0084 with 5 degrees of freedom; "n.a.d.": nothing abnormal detected; N_{Si} rsp. N_{pl}: case numbers in treatment groups.

Observed Change	Sinupret %	placebo %	N_{Si}/N_{pl}
opaque ⇒ n.a.d.	42.3	18.2	33/14
shadowed ⇒ n.a.d.	21.8	18.2	17/14
opaque ⇒ shadowed	23.1	33.8	18/26
shadowed ⇒ shadowed	3.8	13.0	3/10
opaque ⇒ opaque	9.0	15.6	7/12
shadowed ⇒ opaque	0.0	1.3	0/1

Table 4. Patient assessment (acute sinusitis) after two weeks of therapy. Twenty-four observations are missing; these are equally distributed among both groups (13/11). χ^2 = 21.45517 with 2 degrees of freedom; p = 0.000.

Patient assessment	Sinupret %	Placebo %	N_{Si}/N_{pl}
asymptomatic	60.3	25.0	41/17
good effect	35.5	50.0	24/34
no effect	4.2	25.0	3/17

Overall tolerability of the therapy was good. Drop-outs were not recorded, but isolated data were missing in both groups for reasons not due to the medication. This is unusual in such a relatively large study, but it is probably due to the fact that patients were members of the army and, therefore, probably more "disciplined" than the average patient.

Discussion

The basic therapy applied in our study is the most usual for the treatment of acute bacterial sinusitis. The results from this and other studies show that overall efficacy of a single therapy with doxycycline may be unsatisfactory regarding the response rate and the time required for a successful treatment (Rantanen, 1973; Zimmer, 1985). Our results show that the overall response rate and the quality of the response was improved by the additional treatment with the herbal combination in a statistically significant and clinically relevant way. More than 50 out of 78 patients were radiologically diagnosed as "n.a.d." in the drug group compared with 28 out of 77 in the placebo group. In a similar study, Zimmer found even more pronounced improvements in a study without placebo control (Zimmer, 1985). The time period was not covered by the study design; thus, discussing the increased response rates under the aspect of shortening of the course of the disease would be speculative. The first study that addressed this topic in detail was published in 1994 (Leopold et al., 1994), but it was not reported if other than antimicrobial medications – which were not allowed – were taken. The medication scheme of our study is rather complicated from the patients' point of view and bears a potential for bias through individual variations of compliance; on the basis of a relatively large number of patients, such disturbing effects can considered to be equally distributed among the groups.

From our data, it is not possible to clarify the underlying mechanisms of the improvements. The following hypotheses are possible:

a) the secretolytic action of Sinupret (Chibanguza et al., 1984) may have compensated a mucospissic action of the basic therapy; antibiotics and decongestants are known to have this effect (Braga, 1988); b) compensation of immunotoxic effects of doxycycline (Descotes, 1988), that were shown *in vitro* in different assays with human cells and even in humans (Belsheim, 1979 a,b): Humoral immunity, cellular immunity and non-specific host defences were found to be decreased by doxycycline, effects which must be tolerated with respect to risk-benefit considerations. The herbal combination was shown to have immunomodulatory effects *in vitro* and *in vivo* (Schmolz, 1992; Ottendorfer, 1992); c) secretolytic agents may stimulate secretion of the antimicrobial substance into respiratory secretions and thereby increase the concentration of the antibiotic (Offenmeier and Miller-Brandt, 1972). The same mechanism is used as a bioassay to screen secretolytic activities of drugs (Engler and Szelenyi, 1984; Curle, 1992). Further studies designed to investigate these hypotheses are necessary.

Results for the secondary outcome variables, i. e. the clinical findings such as mucosal swelling, obstruction of sinus drainage and headache, showed the Sinupret group to be superior with two exceptions: patency of the nasal cavity and discharge. Due to the design of the study, local decongestants were used by all patients; patency of the nose is to a great extent influenced by decongestants; on the other hand mucosal swelling was found to be significantly reduced in the drug group; this inconsistency cannot be resolved by our data. Purulent discharge was influenced in both groups to the same extent, precisely reflecting the effects of the antimicrobial therapy: In the placebo group, discharge in 33 out of 35 cases changed from purulent to nonpurulent secretion compared to 28 out of 31 cases in the drug group; in this group, one case of purulent secretion developed. In summary the enhancement of the basic therapy by the herbal combination has been clearly demonstrated. Furthermore, it can be deduced from our results that any negative interaction between the herbal preparation and the basic therapy was not observed; such interaction is known for the mucolytic substance acetylcysteine with penicillins, amphotericin, erythromycin and some tetracyclines (Bethge, 1990).

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