

# EFFICACY OF A COMPLEX HOMEOPATHIC MEDICATION (SINFRONTAL) IN PATIENTS WITH ACUTE MAXILLARY SINUSITIS: A PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER CLINICAL TRIAL

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**Background:** There is a demand for clinical trials that demonstrate homeopathic medications to be effective and safe in the treatment of acute maxillary sinusitis (AMS).

**Objective:** The objective of this clinical trial was to demonstrate the efficacy of a complex homeopathic medication (Sinfrontal) compared with placebo in patients with AMS confirmed by sinus radiography.

**Design:** A prospective, randomized, double-blind, placebo-controlled, phase III clinical trial was conducted for a treatment period of 22 days, followed by an eight-week posttreatment observational phase.

**Setting:** The clinical trial was conducted at six trial sites in the Ukraine.

**Participants:** One hundred thirteen patients with radiography-confirmed AMS participated in the trial.

**Interventions:** Fifty-seven patients received Sinfrontal and 56 patients received placebo. Additionally, patients were allowed saline inhalations, paracetamol, and over-the-counter medications, but treatment with antibiotics or other treatment for sinusitis was not permitted.

**Main Outcome Measures:** Primary outcome criterion was change of the sinusitis severity score (SSS) from day zero to day seven. Other efficacy assessments included radiographic and clinical cure, improvement in health state, ability to work or to follow usual activities, and treatment outcome.

**Results:** From day zero to day seven, Sinfrontal caused a significant reduction in the SSS total score compared with placebo ( $5.8 \pm 2.3$  [6.0] points vs  $2.3 \pm 1.8$  [2.0] points;  $P < .0001$ ). On day 21, 39 (68.4%) patients on active medication had a complete remission of AMS symptoms compared with five (8.9%) placebo patients. All secondary outcome criteria displayed similar trends. Eight adverse events were reported that were assessed as being mild or moderate in intensity. No recurrence of AMS symptoms occurred by the end of the eight-week posttreatment observational phase.

**Conclusion:** This complex homeopathic medication is safe and appears to be an effective treatment for acute maxillary sinusitis.

**Key words:** Complementary medicine, homeopathy, clinical trial, radiography, sinusitis severity score, sinusitis integrative medicine outcomes scale, general well-being, EQ-VAS, EQ-5D (*Explore* 2007; 3:98-109. © Elsevier Inc. 2007)

## INTRODUCTION

Acute sinusitis is one of the most common healthcare conditions in the United States, with up to one billion cases reported annually.<sup>1</sup> Americans spend \$2.2 billion per year on over-the-

counter and prescription medications to treat sinusitis.<sup>2</sup> Acute sinusitis is the fifth most common primary care condition where antibiotics are prescribed,<sup>3</sup> and results from the National Ambulatory Medical Care Survey conducted in the United States demonstrated that diagnosis rates and antibiotic prescriptions for acute sinusitis are increasing.<sup>4</sup> In 1996, antibiotic prescriptions for respiratory tract infections generated healthcare expenditures of \$3.39 billion in the United States. Moreover, sinusitis also involves productivity losses on the part of the employers in particular and the national economy in general.<sup>5</sup> Although not exactly known, these indirect costs must be considerable.

Acute maxillary sinusitis (AMS) is a community-acquired infection occurring during the evolution of a common cold—a viral rhinosinusitis.<sup>6</sup> The percentage of sinus infections during common cold episodes varies between 0.5% and 5% depending on immune status, age, hygiene conditions, and underlying pathologies of the patients (eg, smoking, allergies, or polyposis).<sup>7</sup> The bacterial colonization of the sinus mucosa occurs after the onset of the viral infection, usually by exogenous organisms (mainly *Streptococcus pneumoniae* and *Haemophilus influenzae*) but

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†Marianne Heger passed away on August 24, 2005 before the results of her medical and scientific contributions to this paper could be realized. Her fellow authors pay tribute to the leadership, guidance, and enthusiasm she contributed that was critical to the successful completion of these studies.

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sometimes by potentially pathogenic organisms of asymptomatic nasal carriage.<sup>6</sup> The resulting inflammatory edema of the sinus mucosa results in obstruction of the sinus ostia, alterations in oxygenation, and epithelial damage—all factors that then conspire to favor the rapid multiplication of the bacteria and increases in anaerobic flora.

A major problem in the management of acute sinusitis is the difficulty in establishing an accurate diagnosis, and clear guidelines for the diagnosis and treatment of acute sinusitis are lacking. This is partly because many symptoms of acute sinusitis are nonspecific and are difficult to differentiate from those associated with upper respiratory tract infections.<sup>8</sup> Little and coworkers<sup>9</sup> state that physicians put the most emphasis on purulent nasal discharge and sinus tenderness in establishing a diagnosis of acute sinusitis.

These clinical criteria are not sufficient for a reliable diagnosis of acute sinusitis according to Lindbaek and Hjortdahl,<sup>10</sup> who suggest the use of diagnostic tests to increase the probability of correctly diagnosing acute sinusitis. Sinus puncture is considered to be the gold standard, with purulent secretions on aspiration providing the direct evidence for the condition.<sup>9</sup> However, sinus puncture can only be rarely clinically justified, given its invasive nature, inconvenience, and discomfort for the patient.<sup>11</sup> Sinus radiography offers a pragmatic alternative, and a meta-analysis of clinical trials, including the diagnosis of acute sinusitis,<sup>12</sup> showed that sinus radiography is the most common and most accurate acceptable method for AMS diagnosis. Thus, sinus radiography is recommended as the best diagnostic test to confirm clinical findings.

Antibiotic treatment for acute sinusitis is directed at reducing the severity and duration of symptoms and lowering the risk of locoregional extension.<sup>6</sup> In a series of clinical trials studying the efficacy of antibiotic treatment for acute sinusitis, only a few displayed a clear benefit.<sup>6</sup> For example, van Buchem and coworkers<sup>13</sup> could not demonstrate any significant benefit with amoxicillin after two weeks of treatment; the symptoms had disappeared or improved in 83% of patients with amoxicillin and in 77% of patients with placebo. Chow<sup>8</sup> suggests that watchful waiting before prescribing antibiotics is reasonable, and a more recent review of the use of antibiotics for upper respiratory tract infections recommends that clinicians weigh the moderate benefits of antibiotic treatment against the potential for adverse events.<sup>14</sup> Moreover, the widespread prescription of antibiotics over the past two decades has led to the development of antibiotic resistance by many bacterial respiratory tract pathogens,<sup>15-17</sup> which makes bacterial conditions increasingly difficult to treat.<sup>6</sup> In particular, the emergence of multi-drug-resistant pathogens is a major concern to public health.<sup>15</sup> For all these reasons, there is a need for medications—effective in these conditions—that alleviate the symptoms without the problems of side effects or bacterial resistance associated with antibiotics.

The medication used in this clinical trial is a homeopathic medicinal product (Sinfrontal) that is used for the treatment of acute and chronic ear, nose, throat (ENT), and respiratory tract infections in children and adults. In Germany, it has been on the market since 1952, and its efficacy has been investigated in two prospective, randomized or quasi-randomized, placebo-controlled clinical trials<sup>18,19</sup> and two open observational stud-

ies,<sup>20,21</sup> which included a total of 2,642 patients with diagnoses of acute and chronic sinusitis.

In two placebo-controlled clinical trials with patients with acute and chronic sinusitis,<sup>18,19</sup> the efficacy of Sinfrontal was found to be statistically superior to placebo after two ( $P = .001$ )<sup>18</sup> and four weeks ( $P = .01$ )<sup>19</sup> of treatment. In two prospective, open observational studies,<sup>20,21</sup> this medication was found to be safe, effective, and well tolerated in acute sinusitis patients investigated in everyday practice. Moderate improvements in sinusitis-specific symptoms occurred within three days (35.6%-38.3% of patients), and by seven days after treatment with this medication, 70.7% to 82.9% of patients had noticed improvements of their symptoms. These studies, however, did not confirm the diagnosis of AMS by using radiography.

Sinfrontal appears to demonstrate many of the characteristics desired in an effective medication to treat the symptoms of AMS. It has been accepted as a homeopathic product but will require more safety and efficacy studies<sup>22,23</sup> before it can be accepted fully as primary therapy for AMS.

The present trial was designed to demonstrate the efficacy and safety of Sinfrontal compared with placebo in patients with AMS confirmed by sinus radiography. As well as measuring the clinical efficacy of this homeopathic medication, the study also investigated the ability of subjects to work and/or to follow their usual activities of daily living—both during and following treatment with active medication compared with placebo—to assess the treatment success of this homeopathic medication as an integrated symptomatic therapy for AMS.

## METHODS

### Trial Design

This was a multicenter, prospective, randomized, double-blind, parallel-group, placebo-controlled, phase III clinical trial using a multistage adaptive-sequential design. The double-blind phase of this trial consisted of a 22-day treatment period, with the baseline on day zero and three follow-up contacts on days seven, 14, and 21, with the last contact including a final assessment. The double-blind trial was followed by an eight-week postobservational phase in which the patients no longer took the study medication.

The trial was conducted at six ENT clinics and outpatient departments in Kiev, Ukraine from February 6, 2004 to May 20, 2005. It was conducted in accordance with the Declaration of Helsinki (Edinburgh, October 7, 2000), the recommendations of the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95, 1997), and the legal regulations of the Ukraine.

### Patients

After approval by the Authorities and the Ethics Committee (Institutional Review Board) in Kiev, Ukraine, in December 2003, the screening of patients at the investigational sites began in February 2004. The data for all screened patients were recorded in electronic case report forms. During the recruitment period, the investigators registered all screened and suitable patients with symptoms of AMS in the electronic case report forms, including all relevant medical history and assessment of the sinusitis severity score (SSS).

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