สารศิริราช
SIRIRAJ HOSPITAL GAZETTE

จัดพิมพ์โดยอนุมัติคณะกรรมการคณะแพทยศาสตร์ศิริราชพยาบาล
Published Under the Auspices of the Faculty of Medicine, Siriraj Hospital

ปีที่ 54, ฉบับที่ 7, กรกฎาคม 2545	Volume 54, Number 7, July 2002

An Open-Label Study of the Efficacy and Safety of a Herbal Secretolytic Preparation as a Sole Therapy in Patients with Sinusitis

Perapun Jareoncharsri, M.D.*
Chaweewan Bunnag, M.D.*
Prayuth Tunsuriyawong, M.D.*
Mongkon Atipas, M.D.*
Siriporn Voraprayoon, B.Ed.*

Abstract : **This is an open-label, non-comparative controlled study of the efficacy and safety of a herbal secretolytic preparation (Sinupret®) as a single therapy in patients with sinusitis. The study was conducted at the Department of Otolaryngology, Siriraj Hospital, Bangkok, during the period January - December 2000. Thirty-nine patients with symptoms and signs of sinusitis, which were confirmed by abnormal endoscopic findings and abnormal radiological findings, were included. All patients received Sinupret®, two sugar-coated tablets orally three times a day for 21 days. Symptoms and signs were evaluated on three occasions; the first (day 0, V1) before the treatment started, the second (V2) on day 14, and the third (V3) on day 21. There were no other additional adjunctive treatments. Primary outcome measures were the change in the percentage of patients who had three main symptoms (i.e. nasal obstruction, nasal discharge and sinus headache), abnormal endoscopic findings (i.e. mucosal swelling and nasal secretion), and abnormal radiological findings (i.e. air-fluid level, opacification, and mucoperiosteal thickening). Global assessment was rated by the patients using a visual analogue scale (VAS). The clinical response was classified as cure, improvement, failure, and relapse. Treatment success was defined as cure or improvement. Adverse events were also recorded.**

There were 14 males and 25 females, with a mean age of 39.7 ± 14.1 years (16-75). Twenty three patients had chronic sinusitis (CS) and 16 patients had acute sinusitis (AS). The duration of symptoms in the CS group was 16.4 ± 25.6 months (1-96), and in the AS group was 21.3 ± 9.4 days (7-30). At V1, 34 patients (87.2%) had nasal discharge, 26 patients (66.7%) had obstruction, and 25 patients (64.1%) had sinus headache. At V3, the percentages of patients who had symptoms decreased significantly to

Rhinology Division, Department of Otolaryngology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

64.1%, 41.0% and 38.5% for these three symptoms respectively. The same was true for the percentage of patients who had abnormal endoscopic findings. The percentage of patients showing radiological evidence of improvement was 61.5% (33.3% normal, 28.2% improvement), with no change in 38.5% of patients. Treatment success was recorded in 31 out of 39 patients (79.4% : cure 23.0%, improvement 56.4%). In four patients (10.3%) treatment failed and in four other patients (10.3%) there was a relapse in symptoms and signs. Adverse events were reported in 4 patients (10.3%), which were mild and resolved spontaneously.

This study showed the efficacy and safety of a 3-week course of a herbal secretolytic preparation (Sinupret®) in the treatment of sinusitis, either acute or chronic. The incidence of adverse events was low and they were tolerated by the patients. The use of this herbal secretolytic preparation as a sole treatment is effective in most cases of uncomplicated sinusitis. This can decrease the risk of adverse drug reactions from antibiotic therapy and is a cheaper treatment.

Key words : herbal secretolytic preparation, acute sinusitis, chronic sinusitis

เรื่องย่อ : **การศึกษาประสิทธิภาพและความปลอดภัยของการใช้สมุนไพรสกัดที่มีคุณสมบัติละลายเสมหะ (ไซนูเพรท®) ในการรักษาผู้ป่วยโรคไซนัสอักเสบ**

พีรพันธ์ เจริญชาศรี พ.บ.*, ฉวีวรรณ บุนนาค พ.บ.*, ประยุทธ ตันสุริยวงษ์ พ.บ.*, มงคล อธิภาส พ.บ.*, ศิริพร วรประยูร ค.บ.*

**สาขานาสิกวิทยา, ภาควิชาโสต นาสิก ลาริงซ์วิทยา, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กรุงเทพมหานคร 10700.*

สารศิริราช 2545; 54: 379-386.

ได้ทำการศึกษาประสิทธิภาพและความปลอดภัยของสมุนไพรสกัดที่มีคุณสมบัติละลายเสมหะ (Sinupret®) ในการรักษาผู้ป่วยโรคไซนัสอักเสบที่ภาควิชา โสต นาสิก ลาริงซ์วิทยา โรงพยาบาลศิริราช ระหว่างเดือนมกราคม - ธันวาคม 2543 การศึกษาครั้งนี้เป็นการศึกษาแบบเปิด ผู้ป่วยที่ได้รับการคัดเลือกเข้าศึกษา จะได้รับ Sinupret® ในรูปเม็ดเคลือบน้ำตาล ครั้งละ 2 เม็ด วันละ 3 ครั้ง เป็นเวลา 3 สัปดาห์ โดยไม่ได้รับยาอื่นเสริม ผู้ป่วยทั้งสิ้นจำนวน 39 ราย เป็นชาย 14 ราย หญิง 25 ราย อายุเฉลี่ย 39.7 ± 14.1 ปี (16-75 ปี) เป็นไซนัสอักเสบชนิดเฉียบพลัน 16 ราย และชนิดเรื้อรัง 23 ราย ระยะเวลาที่เป็นโรคเฉลี่ย 21.3 ± 9.4 (7-30) วัน และ 16.4 ± 25.6 (1-96) เดือน ในผู้ป่วยที่เป็นชนิดเฉียบพลันและเรื้อรัง ตามลำดับ

ผลการศึกษาพบว่าหลังจากสิ้นสุดการรักษาผู้ป่วยมีอาการลดลงอย่างมีนัยสำคัญ และผลการตรวจโพรงจมูกด้วยกล้องเทเลเอนโดสโคปพบว่าเยื่อบุจมูกยุบบวมลง และน้ำมูกลดลงอย่างมีนัยสำคัญ ภาพถ่ายรังสีเป็นปกติ ร้อยละ 33.3 และดีขึ้น ร้อยละ 28.2 ของผู้ป่วยทั้งหมด การประเมินผลการรักษาพบว่าได้ผลดี ร้อยละ 79.4 (หาย ร้อยละ 23.0, ดีขึ้น ร้อยละ 56.4) ไม่ได้ผล ร้อยละ 10.3 และกลับเป็นใหม่ ร้อยละ 10.3 ผู้ป่วยที่เป็นไซนัสอักเสบเฉียบพลันจะได้ผลดี ร้อยละ 87.5 (หาย ร้อยละ 37.5, ดีขึ้น ร้อยละ 50) ส่วนผู้ป่วยที่เป็นไซนัสอักเสบเรื้อรังจะได้ผลดี ร้อยละ 74.0 (หาย ร้อยละ 13, ดีขึ้น ร้อยละ 61) ผลข้างเคียงที่เกิดขึ้นระหว่างการรักษา พบร้อยละ 10.3 ซึ่งไม่รุนแรงและหายไปได้เอง ผลการศึกษาครั้งนี้แสดงว่าสมุนไพรสกัดที่มีคุณสมบัติละลายเสมหะนี้มีประสิทธิภาพและปลอดภัย

ในการใช้รักษาผู้ป่วยโรคไซนัสอักเสบทั้งชนิดเฉียบพลันและชนิดเรื้อรัง การใช้สมุนไพรสกัดชนิดนี้มีประโยชน์ในการรักษาผู้ป่วยไซนัสอักเสบที่ไม่มีภาวะแทรกซ้อน ซึ่งจะช่วยลดโอกาสเกิดผลข้างเคียงที่อาจเกิดจากการใช้ยาด้านจุลชีพ และช่วยประหยัดค่าใช้จ่ายในการรักษาโรคไซนัสอักเสบ

INTRODUCTION

The medical management of sinusitis consists of treatment of infections, medication to improve ostial patency and thus promote ventilation and drainage of the sinuses, promotion of mucociliary function and to reduce inflammation of the sinonasal mucosa. According to various guidelines for the treatment of sinusitis, antibiotics are the first line of therapy.[1-5] Amoxycillin, co-trimoxazole and erythromycin used empirically are the drugs of choice, because of the difficulty in obtaining sinus specimens for culture and sensitivity. Even if the specimens can be obtained, a few days delay are needed before the results of the culture are reported. For acute sinusitis, the recommended duration of antibiotic therapy is 14 days, and in patients with chronic sinusitis, this usually requires 3 to 6 weeks of therapy.

However, recent studies have questioned the value of antibiotics in treating acute sinusitis.[6] In well-controlled studies of antral aspiration culture in patients with acute maxillary sinusitis, bacteria were found in only 60 to 80% of the patients.[7-12] From this we can assume that the remaining 20 to 40% of acute maxillary sinusitis cases are not bacterial in origin, so administration of antibiotics in these cases may be unnecessary and a waste of money. Furthermore, the increased incidence of drug resistant organisms and adverse drug reactions with antibiotic therapy have detrimental effects,[13] which favours the idea of non-antibiotic therapy for acute, uncomplicated sinusitis. Some studies have even predicted that this is the end of antibiotic treatment in adults with acute sinusitis-like complaints.[14]

The adjunctive non-pharmacologic treatments that provide additional symptomatic benefits are steam inhalation (with eucalyptus, tea tree, or lavender oil), astringents, spicy foods, saline irrigation and herbal remedies.[15]

A plant-based secretolytic compound (Sinupret®) consisting of gentian root, vervain leaves, elder flowers, sorrel leaves, and primrose flowers and calyces, has been used in the treatment of acute and chronic inflammation of the sinuses and respiratory tract.[16-21] The activity profile of this herbal secretolytic agent is characterized by marked secretolysis and anti inflammatory activity.[17-19]

The objective of this study is to demonstrate the clinical efficacy and safety of the herbal secretolytic agent (Sinupret®) in the treatment of Thai patients with sinusitis.

MATERIALS AND METHODS

This was an open-label, non-comparative controlled study, conducted at the Department of Otolaryngology, Siriraj Hospital, Bangkok, Thailand, during the period January-December 2000. The study was approved by the Ethical Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Siriraj Hospital, Mahidol University.

Out-patient adult males and females aged 16 years or older with either acute, chronic or an acute exacerbation on chronic sinusitis, were included. Diagnosis was established on the basis of clinical symptoms (i.e. nasal discharge, nasal obstruction and sinus headache), and the presence of discharge in the nasal cavity or in the middle meatus or from the sinus ostia on endoscopic examination. The diagnosis was confirmed by abnormal radiological findings in one or more of the paranasal sinuses (i.e. air fluid level, opacification, and mucoperiosteal thickening). Written informed consent was obtained from all patients.

Patients were excluded from the study if they had a severely deviated nasal septum or nasal polyps that obstructed the osteomeatal complex. Odontogenic maxillary sinusitis was also excluded. Patients with respiratory diseases that required drug therapy (i.e. asthma, chronic bronchitis and COPD), chronic liver disease, renal failure and other systemic diseases

were all additional criteria for exclusion. Pregnant or lactating women were also excluded from the study.

Patients who fulfilled the inclusion criteria, received the herbal combination preparation (Sinupret®, Bionorica, Germany), given as a sugar-coated tablet, two tablets, three times a day for 21 days. There were no additional medicines given for the treatment of sinusitis. Patient compliance was measured by counting the remaining tablets at the follow up visits.

Symptoms and signs were evaluated on three occasions, i.e., the first (day 0, V1) before treatment started, the second (V2) on day 14, and the third (V3) on day 21. The presence of three main symptoms (nasal discharge, nasal obstruction, and sinus headache) was recorded by physicians. Nasal endoscopic examination to detect mucosal swelling and secretions in the nasal cavity or in the middle meatus was also performed. A plain x-ray of the sinus (Caldwell and Waters' views) was done at V1 and again at the end of treatment (V3) to observe any changes in the radiological findings. The clinical response was classified as cure, improvement, failure or relapse at day 14 and day 21 of treatment. Cure was defined as complete resolution of symptoms and signs and/or no radiological evidence of disease; improvement if there was incomplete resolution of symptoms and signs and/or radiological improvement; and failure if there was no change in the symptoms and signs or radiological findings; and relapse if an initial improvement or cure was followed by a worsening or recurrence of the symptoms and signs. Treatment success was defined as cure or improvement.

Global assessment was evaluated by using a visual analogue scale (VAS) to measure overall improvement in symptoms, patients rating from 100% (severe symptoms) to 0% (no symptoms).

The safety of Sinupret® was assessed with regard to adverse drug reactions. All adverse events, either observed by the investigators or reported by the patients, were recorded at each visit and evaluated by the investigators with regard to severity, onset, duration and whether a causal relationship to the study drug existed.

Statistical Analysis

The percentage of patients who had the three main symptoms and abnormal endoscopic findings were compared between visits, using the McNemar Test. The mean VAS before and after treatment were compared using Paired t-test. A significance level of 0.05 was used.

RESULTS

A total of 39 patients (14 males and 25 females) with a mean age of 39.7 ± 14.1 years (range 16-75) were included in the study. The diagnosis was acute sinusitis in 16 patients and chronic sinusitis or acute exacerbation on chronic sinusitis in 23 patients. The duration of symptoms in the acute group was 21.3 ± 9.4 days (7-30 days), and that of the chronic group was 16.4 ± 25.6 months (1-96 months).

At V1 (before treatment), 34 patients (87.2%) had nasal discharge, 26 patients (66.7%) had nasal obstruction, and 25 patients (64.1%) had sinus headache. After 2 weeks treatment (V2) the percentages of patients who had symptoms decreased to 74.4%, 48.7%, and 33.3%, and after 3 weeks treatment (V3), these percentages were significantly decreased to 64.1%, 41.0%, and 38.5% for nasal discharge, nasal obstruction, and sinus headache respectively (Table 1).

At V1, 35 patients (89.7%) had nasal mucosal swelling, and 39 patients (100%) had secretions in the nasal cavity or middle meatus. After treatment, the percentages of patients who had mucosal swelling and nasal secretion were significantly decreased to 59.0% and 79.5% at the second visit (V2), and to 59.0% and 69.2% at the third visit (V3) respectively (Table 2). The radiological findings before treatment were abnormal in 100% of patients (air–fluid level 28.2%, opacification 35.9%, and mucosal thickening 35.9%). After 3 weeks treatment, 33.3% of the sinus plain films were normal. An air-fluid level and opacification were found in only 2.6% and 12.8% respectively. The total improvement of pathology seen on the plain films was 61.5% (33.3% normal, 28.2% improvement) and no change in the pathology

Table 1. Percentage of patients who had symptoms at each visit.

Symptoms	No. of patients (%)			P value	
	Visit 1	Visit 2	Visit 3	V1-V2	V1-V3
Nasal discharge	34 (87.2)	29 (74.4)	25 (64.1)	0.219	0.006*
Nasal obstruction	26 (66.7)	19 (48.7)	16 (41.0)	0.146	0.021*
Sinus headache	25 (64.1)	13 (33.3)	15 (38.5)	0.021*	0.021*

*Significance level $p < 0.05$

Table 2. Percentage of patients who had abnormal endoscopic findings at each visit.

Findings	No. of patients (%)			P value	
	Visit 1	Visit 2	Visit 3	V1-V2	V1-V3
Mucosal swelling	35 (89.7)	23 (59.0)	23 (59.0)	0.008*	0.008*
Nasal secretion	39 (100.0)	31 (79.5)	27 (69.2)	0.001*	0.000*
- mucopurulent	21 (53.8)	3 (7.7)	7 (17.9)		
- mucoid	18 (46.2)	28 (71.8)	20 (51.3)		

*Significance level $p < 0.05$

Table 3. Changes in pathology seen on a plain film of the sinuses after 3 weeks treatment with herbal preparation.

Before treatment	After 3 weeks treatment	No. of cases	%
Air-fluid level	Mucosal thickening	6	15.38
Air-fluid level	Clear	5	12.82
Opacification	Mucosal thickening	6	15.38
Opacification	Clear	2	5.12
Mucosal thickening	Clear	5	12.82
Total improvement		24	61.5
Opacification	Opacification	5	12.82
Air-fluid level	Air-fluid level	1	2.56
Mucosal thickening	Mucosal thickening	9	23.07
Total no change		15	38.5

was found in 38.5% of patients (Table 3).

The mean VAS before treatment was 84.7 ± 19.9, which significantly decreased to 49.1 ± 23.0 and 28.2 ± 20.7 at V2 and V3 respectively.

A satisfactory clinical response to herbal secretolytic preparation treatment was recorded in 31 out of 39 patients (79.4%), i.e., cure in 9 (23.0%) and improvement in 22 (56.4%) patients. Four patients (10.3%) had clinical improvement at V2 but the clinical symptoms relapsed at the end of V3. The other four patients (10.3%) were considered treatment failures; one with acute sinusitis and three with chronic sinusitis (Table 4).

Adverse events were reported in 4 patients (10.3%) which were mild and resolved spontaneously without premature cessation of treatment in all cases. The adverse events were dizziness, swelling of the lip, diarrhea and weakness.

Table 4. Clinical response after 14 days (V2) and 21 days (V3) of treatment.

Clinical response	Acute rhinosinusitis No. of cases (%)		Chronic rhinosinusitis No. of cases (%)		Total cases No. of cases (%)	
	V2	V3	V2	V3	V2	V3
Cure*	3 (18.8)	6 (37.5)	0 (0)	3 (13.0)	3 (7.7)	9 (23.00)
Improvement*	12 (75.0)	8 (50.0)	17 (73.9)	14 (61.0)	29 (74.4)	22 (56.4)
Failure	1 (6.2)	1 (6.3)	6 (26.1)	3 (13.0)	7 (17.9)	4 (10.3)
Relapse	0 (0)	1 (6.3)	0 (0)	3 (13.0)	0 (0)	4 (10.3)
Total no. of patients	16	16	23	23	39	39

*Satisfactory clinical response = cure + improvement

DISCUSSION

This study demonstrated a satisfactory clinical response in 79.4% of patients (23% cure and 56.4% improvement). This was supported by the significant decrease in the percentage of patients who had symptoms at the end of treatment (Table 1), and a significant improvement in nasal endoscopic findings at both 2 weeks and 3 weeks of treatment (Table 2), and also significant improvement in the mean VAS at both V2 and V3. If the patients in the study were separated into acute and chronic sinusitis groups, a satisfactory clinical response in those with acute sinusitis was obtained in 87.5% (37.5% cure and 50% improvement) and in those with chronic sinusitis 74.0% (13% cure and 61% improvement). These figures are comparable to other studies using Sinupret® in treating sinusitis, i.e., Low[16] (94.5% good success in children age 2-7 years and 71.9% good success in children age 8-14 years), Richstein, et al[17] (75% clinical success in chronic sinusitis), Khan[18] (86% very good response), Goroll[19] (95% clinical success in acute sinusitis, 87% clinical success in chronic sinusitis).

The weakness of this study was that it was not a double-blind placebo controlled study, and also bacterial culture was not performed. However, in a double blind study comparing Sinupret® vs. placebo in the treatment of chronic sinusitis, clinical success was obtained in 75% (Sinupret®) vs. 40% (placebo).[17]

Ferguson[22] has summarized series of clinical studies of antibiotic therapy in patients with acute sinusitis, showing efficacies ranging from 74% to 95%. The clinical response rates of Sinupret® in the treatment of acute (87.5%) and chronic sinusitis (74.0%) are about the same as antibiotic therapy. A recent, well designed, randomised placebo-controlled trial of antibiotic treatment in acute maxillary sinusitis, using 7-days amoxycillin versus placebo, with adjunctive treatment (xylometazoline 0.1% steam inhalation), demonstrated equal efficacy (83%

amxycillin vs 77% placebo, p = 0.20).[13] This raises the question of the use of antibiotic in the treatment of acute, uncomplicated maxillary sinusitis, and proves the efficacy of adjunctive treatment, which may alone be enough in the treatment of acute, uncomplicated sinusitis.

However, if we take a look in detail of the clinical success of antibiotic therapy[13,23] in the treatment of acute sinusitis, the cure rate is higher than that of Sinupret® (more than 50% cure in antibiotic therapy vs. only 37.5% cure in our study). In our opinion, if patients receive this herbal secretolytic agent for a longer period such as 4 to 6 weeks, the clinical response, especially the cure rate may be higher. One of the objective of treatment of sinusitis is to promote ventilation and drainage of the nose and paranasal sinuses. This can be achieved by decongestion of the nasal and sinus mucous membrane as well as decreasing the viscosity of the secretions. This herbal secretolytic agent acts by decongesting the nasal mucous membrane and reducing the viscosity of secretions.[18] Also the secretolysis makes it possible for the ciliated epithelium to remove infected secretions by mucociliary transport.[19]

Concerning adverse reactions of Sinupret®, the rate of adverse reactions reported in the literature[21] is 0.8%, which is lower than ambroxol (1.0%), acetylcysteine (4.3%), myrtol (5.8%), and other herbs (11.1%); and is comparable to our study (10.3%).

Sinusitis is a common disease which appears to be increasing in frequency in the clinical practice of both general practitioners and specialists, i.e., otolaryngologists, pediatricians, allergists and family physicians. The incidence of sinusitis is 14.7% in the United States general population.[24] In the United States alone, there were more than 13 million antibiotic prescriptions for sinusitis per year, which cost about $ 375 million.[25] In 1997, the annual cost of sinusitis in the United States was estimated to be about $ 6.1 billion.[26] Thus, sinusitis is an expensive disease and has a major impact on individual patients and also the health care system. The traditional treatment for sinusitis such as aromatherapy with essential oils, hydrotherapy with sulphur water, breathing steaming spa water, and herbal medicines, can be an alternative treatment or complementary to conventional treatment of sinusitis.[15] These treatments are offered to patients who do not get good results from conventional or surgical treatment, or those who do not really need antibiotics, and can thus reduce the cost of treatment of sinusitis.

In conclusion, this study has demonstrated the efficacy and safety of a 3-week course of herbal secretolytic preparation (Sinupret®) as a sole therapy in the treatment of acute or chronic sinusitis. A satisfactory clinical response was obtained in 87.5% (acute sinusitis) and 79.4% (chronic sinusitis). Radiological findings were normal in 30.8%, showed improvement in 30.7% and no change in 38.5% of patients. Adverse events were reported in 10.3% of patients which were mild and resolved spontaneously. The use of this treatment as sole therapy may be useful in most cases of uncomplicated sinusitis, and decrease the risk of adverse drug reactions from antibiotic therapy, and also reduce the cost of treatment.

ACKNOWLEDGEMENT

The authors would like to thank Miss Anchalee Tongsima for her help with statistical analysis, and Miss Tippawan Inchukul for her assistance in preparing the manuscript. We also thank Bionorica Company (Germany) for providing the herbal secretolytic agent used in the study and Dr. Jane Hardy for editing the manuscript.

REFERENCES

1. Gwaltney JM Jr, Jones JG, Kennedy DW. Medical management of sinusitis : Educational goals and management guidelines. The International Conference on Sinus Disease. Ann Otol Rhinol Laryngol 1995; **167 (Suppl):** 22-30.
2. Low DE, Desrosiers M, McSherry J, et al. A practical guide for the diagnosis and treatment of acute sinusitis. CMAJ 1997; **156 (Suppl 6):** S1-S14.
3. Spector SL, Bernstein IL, Li JT, et al. Parameters for the diagnosis and management of sinusitis. J Allergy Clin Immunol 1998; **102 (6 pt 2):** S107-S144.

4. Rachelefsky GS. National guideline needed to manage rhinitis and prevent complications. Ann Allergy Asthma Immunol 1999; **82:** 269-305.
5. Chan KH, Winslow CP, Levin MJ, et al. Clinical practice guidelines for the management of chronic sinusitis in children. Otolaryngol Head Neck Surg 1999; **120:** 238-43.
6. Stalman W, van Essen GA, van der Graaf Y, et al. Maxillary sinusitis in adults : An evaluation of placebo-controlled double-blind trials. Fam Pract 1997; **14:** 124-29.
7. Gwaltney JM Jr, Scheld WM, Sande MA, Sydnor A. The microbial etiology and antimicrobial therapy of adult with community-acquired sinusitis : a fifteen-year experience at the University of Virginia and view of other selected studies. J Allergy Clin Immunol 1992; **90:** 457-62.
8. Penttila M, Savolainen S, Kiukaanniemi H, et al. Bacterial findings in acute maxillary sinusitis-European Study. Acta Otolaryngol (Stockh) 1997; **529:** 165-68.
9. Wald ER. Microbiology of acute and chronic sinusitis in children and adults. Am J Med Sci 1998; **316:** 13-20.
10. Vogan JC, Bolger WE, Keyes AS. Endoscopically guided sinunasal cultures : a direct comparison with maxillary sinus aspirate cultures. Otolaryngol Head Neck Surg 2000; **122:** 370-73.
11. Kongkaew T, Prakunhungsit S, Kulpraditharom B. Bacteriologic study of acute and subacute maxillary sinusitis at Ramathibodi Hospital. Thai J Otolaryngol H&N Surg 2000; **1:** 21-26.
12. Jareoncharsri P, Bunnag C, Tunsuriyawong P, et al. Bacteriologic profile of acute and chronic maxillary sinusitis. J Infect Dis Antimicrob Agents 2001; **18:** 96-102.
13. van Buchem FL, Knottnerus JA, Schrijnemaekers VJ, et al. Primary-care-based randomised placebo-controlled trial of antibiotic treatment in acute maxillary sinusitis. Lancet 1997; **349:** 683-87.
14. Stalman W, van Essen GA, van der Graaf Y, et al. The end of antibiotic treatment in adults with acute sinusitis-like complaints in general practice? A placebo-controlled double-blind randomized doxycycline trial. Br J Gen Pract 1997; **47:** 794-99.
15. Woodham A, Peters D. Treating ailments : The respiratory system. In : Woodhan A, Peters D, eds. Encyclopedia of natural healing. Dorling Kindersley, London, 1997: 224-25.
16. Löw J. Experience in pediatric practice with a mucosally active sinal agent-Sinupret®. Therapiewoche 1975; **25:** 7220-28.
17. Richstein A, Mann A. On treating chronic sinusitis with Sinupret®. Therapie der Gegenwart 1980; **119:** 1055-60.
18. Khan NA. Sinupret® for the treatment of diseases in the ENT-area. Therapiewoche 1982; **32:** 1811-14.
19. Goroll M, Stehle W. Inflammation of the nasal sinuses and its medicational therapy with Sinupret®. Therapie der Gegenwart 1982; **121:** 21-25.
20. Zimmer M. Specific conservative therapy of acute sinusitis in the ENT practice. Therapiewoche 1985; **35:** 2024-28.
21. Ernst E, Sieder CH, März R. Adverse drug reactions to herbal and synthetic expectorants. Int J Risk & Safety Med 1995; **7:** 219-25.
22. Ferguson BJ. Acute and chronic sinusitis. How to ease symptoms and locate the cause? Postgrad Med 1995; **97:** 45-57.
23. Adelglass J, DeAbate A, McElvaine P, et al. Comparison of effectiveness of levofloxacin and amoxicillin clavulanate for the treatment of acute sinusitis in adults. Otolaryngol Head Neck Surg 1999; **120:** 320-27.
24. Kaliner MA. Rhinosinusitis-the role of the allergist in diagnosis and treatment. ACI International 1998; **10:** 141-48.
25. Kaliner MA, Osguthorpe JD, Fireman P, et al. Sinusitis: Bench to bedside. J Allergy Clin Immunol 1997; **99:** S829-48.
26. Ray N, Rinehart C, Thamer M, et al. The cost of sinusitis: Estimation by the Delphi consensus method. J Allergy Clin Immunol 1998; **107:** S177.