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An Open-Label, Non-Comparative Phase IIIb Study of Oral Gatifloxacin in the Treatment of Acute, Uncomplicated Bacterial Sinusitis in Thai Patients

Perapun Jareoncharsri, M.D.*
Chaweewan Bunnag, M.D.*
Prayuth Tunsuriyawong, M.D.*
Sanguansak Thanaviratananich, M.D.**
Suthee Kraitakul, M.D.**
Jongrak Phromchairak, M.D.***
Chavalit Rodsutthi, M.D.***
Siriporn Voraprayoon, B.Ed.****
Chertsak Dhirabutra, M.D.****

Abstract : **This was an open-label, non-comparative phase IIIb study of oral gatifloxacin in the treatment of acute, uncomplicated bacterial sinusitis in Thai patients. The study was conducted at three otolaryngologic centers in Thailand, i.e. Siriraj Hospital, Srinakarind Hospital, and Bhumipol Hospital, during the period of November 1999 through October 2000. Thirty patients with symptoms and signs of acute maxillary sinusitis, which were confirmed by abnormal radiological findings, were included. Documentation of infection was made by pre- and post-therapy culture and susceptibility testing. All patients received gatifloxacin 400 mg tablet orally once daily for 10 days. Symptoms and signs were evaluated on four occasions, i.e. before treatment started (day 0, V1), day 3-5 (V2), the third (V3) on day 11-14 (V3), and day 21-28 (V4). Primary outcome measures were the changes in the percentage of patients who had general clinical symptoms (i.e. fever, malaise, chill, sore throat, headache, cough, and halitosis), and also the clinical symptoms and signs of sinusitis (i.e. sinus pain, sinus tenderness, purulent nasal discharge, facial pressure, nasal congestion, postnasal drip, and anosmia). The clinical responses were classified as**

*Rhinology Division, Department of Otolaryngology, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand. **Department of Otolaryngology, Srinakarind Hospital, Khonkaen University, Khonkaen, Thailand. ***Department of Otolaryngology, Bhumipol Hospital, Bangkok, Thailand. ****Department of Microbiology, Faculty of Medicine Siriraj Hospital, Bangkok 10700, Thailand.

cure, improvement, relapse or failure at the end of treatment (V3) and at follow up (V4). Treatment success was defined as cure or improvement. The safety of gatifloxacin was assessed from vital signs, general physical examination, hemato-biochemical parameters, and adverse events reported.

There were 13 males and 17 females, with a mean age of 34.7 ± 12.2 years (range 21-70). The mean duration of symptoms was 2.4 ± 8.8 weeks. At V1, 23 patients (76.7%) had headache, 19 patients (63.3%) had cough, and 14 patients (46.7%) had halitosis. At V3 and V4 all these symptoms had resolved, except in 1 patient who still had cough. The percentages of patients who had symptoms and signs of sinusitis at V1 were as follows : purulent nasal discharge 90%, nasal congestion 86.7%, postnasal drip 86.7%, sinus pain 80%, facial pain 66.7%, and sinus tenderness 63.6%. After 3-5 days of treatment (V2), the percentages of patients who had symptoms and signs of sinusitis decreased significantly for every symptom and sign. The same was true at V3 and V4.

The total percent improvement in radiological findings was 83.4% (41.7% resolution, 41.7% improvement). Pretreatment cultures were positive in 23 out of 30 patients (76.7%). The most common pathogens were *Hemophilus influenzae* (18.4%), *Streptococcus pneumoniae* (9.4%), other *Streptococcus* species (9.4%), *Klebsiella pneumoniae* (6.3%) and coagulase negative *Staphylococcus* (6.3%). The anaerobes found were *Peptostreptococcus prevotii* (9.4%), *Fusobacterium nucleatum* (9.4%), *Bacteroides* species (6.1%) and *Prevotella* species (3.1%). Bacteriological responses at V3 were 30.4% eradication, 65.2% presumed eradication, and 4.4% persistence. Clinical responses at V4 were 88.9% cured, 7.4% relapsed, and 3.7% failed. Adverse events were found in 4 patients (13.3%) which were transient and resolved spontaneously. Adverse events found were nausea, vomiting, dry mouth, constipation, agitation and tremor.

This study showed the efficacy and safety of a 10-day course of oral gatifloxacin 400 mg once daily in the treatment of acute uncomplicated bacterial sinusitis. 88.9% of patients experienced a cure, and bacteriological eradication was achieved in 95.6%. The excellent profile of gatifloxacin makes it suitable for the treatment of community acquired acute bacterial sinusitis. The once daily regimen enhances patient compliance.

Key words : Gatifloxacin, acute bacterial sinusitis, acute maxillary sinusitis, antral aspiration cultures.

เรื่องย่อ : การศึกษาแบบเปิดในการใช้ยากาติฟล็อกซาซินรักษาผู้ป่วยโรคไซนัสอักเสบเฉียบพลันที่เกิดจากเชื้อแบคทีเรีย

พีรพันธ์ เจริญชาศรี พ.บ.*, ฉวีวรรณ บุนนาค พ.บ.*, ประยุทธ ตันสุริยวงษ์ พ.บ.*, สงวนศักดิ์ ธนาวิรัตนานิจ พ.บ.**, สุธี ไกรตระกูล พ.บ.**, จงรักษ์ พรหมใจรักษ์ พ.บ.***, ชวลิต รอดสุทธิ พ.บ.***, ศิริพร วรประยูร ค.บ.****, เชิดศักดิ์ ธีระบุตร พ.บ.****

*ภาควิชาโสต นาสิก ลาริงซ์วิทยา, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กรุงเทพมหานคร. **ภาควิชาโสต ศอ นาสิก ลาริงซ์วิทยา, คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น, ขอนแก่น. ***กองโสต ศอ นาสิกกรรม, โรงพยาบาลภูมิพล, กรุงเทพมหานคร. ****ภาควิชาจุลชีววิทยา, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กรุงเทพมหานคร.

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ได้ศึกษาการใช้ยากาติฟล็อกซาซินชนิดกินในการรักษาผู้ป่วยโรคไซนัสอักเสบเฉียบพลันที่เกิดจากเชื้อแบคทีเรีย ที่ภาควิชาโสต นาสิก ลาริงซ์วิทยา โรงพยาบาลศิริราช, โรงพยาบาลศรีนครินทร์ ขอนแก่น และโรงพยาบาลภูมิพล ระหว่างเดือนพฤศจิกายน 2542 – ตุลาคม 2543 ผู้ป่วยที่ได้รับการวินิจฉัยว่าเป็นโพรงอากาศแม็กซิลล่าอักเสบเฉียบพลันที่ได้รับการคัดเลือกเข้าทำการศึกษาจะได้รับยากาติฟอล็กซาซินชนิดเม็ด 400 มิลลิกรัม วันละครั้ง เป็นเวลา 10 วัน ผลการศึกษาประเมินจากการเปลี่ยนแปลงของร้อยละของจำนวนผู้ป่วยที่มีอาการและอาการแสดงของไซนัสอักเสบ ภาพถ่ายรังสีก่อนและหลังการรักษา และผลการเพาะเชื้อจากตัวอย่างหนองที่ได้จากไซนัสโดยวิธีการเจาะดูดหนองจากโพรงอากาศแม็กซิลล่า ทั้งก่อนและหลังการรักษา ความปลอดภัยของการศึกษาประเมินจากอาการข้างเคียงที่เกิดขึ้น การตรวจร่างกายทั่วไป และการเจาะเลือดตรวจทางห้องปฏิบัติการจำนวนผู้ป่วยที่ศึกษาทั้งสิ้น 30 ราย เป็นชาย 13 ราย หญิง 17 ราย อายุเฉลี่ย 34.7 ± 12.2 ปี (21 – 70 ปี) ระยะเวลาที่มีอาการเฉลี่ย 2.4 ± 8.8 สัปดาห์ ก่อนการรักษาผู้ป่วยมีอาการปวดศีรษะ (ร้อยละ 76.7), อาการไอ (ร้อยละ 63.3), ลมหายใจมีกลิ่นเหม็น (ร้อยละ 46.7), น้ำมูกเหลืองเขียว (ร้อยละ 90), คัดจมูก (ร้อยละ 86.7), เสมหะไหลลงคอ (ร้อยละ 86.7), ปวดบริเวณโพรงอากาศ (ร้อยละ 80), ปวดบริเวณใบหน้า (ร้อยละ 66.7) และกดเจ็บบริเวณโพรงอากาศ (ร้อยละ 63.6) หลังการรักษา จำนวนร้อยละของผู้ป่วยที่มีอาการและอาการแสดงเหล่านี้ลดลงอย่างมีนัยสำคัญเมื่อเทียบกับก่อนการรักษา ภาพถ่ายรังสีก่อนการรักษาพบมีความผิดปกติร้อยละ 100 (โพรงอากาศแม็กซิลล่าทึบ ร้อยละ 23.3, เห็นระดับน้ำร้อยละ 33.4 และเยื่อบุหนาร้อยละ 43.3) หลังการรักษาพบว่าภาพถ่ายรังสีเป็นปกติหรือดีขึ้นร้อยละ 83.4 (ปกติร้อยละ 41.7, ดีขึ้นร้อยละ 41.7) ผลการเพาะเชื้อก่อนการรักษาพบเชื้อแบคทีเรียร้อยละ 76.7 (ให้ผลบวก 23 จาก 30 ราย) เชื้อที่พบบ่อยได้แก่ *Hemophilus influenzae* ร้อยละ 18.4, *Streptococcus pneumoniae* ร้อยละ 9.4, เชื้อ *Streptococcus* ชนิดอื่นๆ ร้อยละ 9.4, *Klebsiella pneumoniae* ร้อยละ 6.3, coagulase negative *Staphylococcus* ร้อยละ 6.3 นอกจากนี้ยังพบเชื้อ anaerobes ซึ่งได้แก่ *Peptostreptococcus prevotii* ร้อยละ 9.4, *Fusobacterium nucleatum* ร้อยละ 9.4, *Bacteroides* species ร้อยละ 6.1 และ *Prevotella* species ร้อยละ 3.1 การเพาะเชื้อหลังการรักษาไม่พบเชื้อ (กำจัดเชื้อหมด) ร้อยละ 95.6 และพบเชื้อแบคทีเรีย ร้อยละ 4.4 การประเมินประสิทธิภาพของการรักษาหลังสิ้นสุดการศึกษา พบว่าผู้ป่วยหายร้อยละ 88.9 กลับเป็นซ้ำใหม่ร้อยละ 7.4 และ ไม่ได้ผลร้อยละ 3.7 ผลข้างเคียงที่เกิดจากการรักษาพบร้อยละ 13.3 อาการข้างเคียงที่พบได้แก่ คลื่นไส้ อาเจียน ปากแห้ง ท้องผูก ใจสั่น และมือสั่น อาการเหล่านี้เป็นชั่วคราว ไม่รุนแรง และหายไปได้เองโดยไม่ต้องให้การรักษา ผลการศึกษาครั้งนี้แสดงว่ายากาติฟล็อกซาซินชนิดเม็ดขนาด 400 มิลลิกรัม วันละครั้ง ให้เป็นเวลา 10 วัน มีประสิทธิภาพและปลอดภัยในการใช้รักษาผู้ป่วยโรคไซนัสอักเสบเฉียบพลัน มีฤทธิ์ในการกำจัดเชื้อแบคทีเรียในโพรงอากาศสูง และการใช้ยาวันละครั้งทำให้เกิดความสะดวกแก่ผู้ป่วยและผู้ป่วยร่วมมือในการรักษาดีขึ้น

INTRODUCTION

Gatifloxacin is a third generation, 8-methoxy fluoroquinolone. It has broad spectrum activity against gram-positive and gram-negative organisms, especially those found in patients with acute sinusitis, i.e. *Streptococcus pneumoniae (S. pneumoniae)*, including penicillin-resistant strains; *Hemophilus influenzae (H. influenzae)* and *Moraxella catarrhalis (M.catarrhalis)*, including beta-lactamase producing strains.[1] It also possesses an in vitro activity against anaerobic organisms which are implicated in acute, uncomplicated sinusitis and acute exacerbations of chronic sinusitis, i.e. *Peptostreptococcus* species, *Fusobacterium* species, and *Bacteroides* species.[2,3]

Gatifloxacin is recommended as an initial treatment of patients with moderate sinusitis who had beta-lactam allergy or intolerance.[4] Antimicrobial therapy for patient with acute sinusitis is usually empiric because the identification of the causative organism requires maxillary antral puncture or middle meatus sampling and a few days delay to obtain a report of culture from the microbiological laboratory. So, an antimicrobial agent which covers all the likely pathogens, including those with penicillin-resistant and beta-lactamase producing strains, is needed.

The objective of this study was to assess the clinical efficacy, bacteriological efficacy, and safety profile of oral gatifloxacin 400 mg once daily in the treatment of acute, uncomplicated bacterial sinusitis.

Patients and methods

This was an open, non-comparative, phase IIIb study, conducted at three otolaryngologic centers in Thailand, i.e. Siriraj Hospital, Bangkok; Srinakarind Hospital, Khonkaen ; and Bhumipol Hospital, Bangkok, during the period of November 1999 through October 2000. The study was approved by the Ethical Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Siriraj Hospital, Mahidol Univerisity, Khonkaen Univerisity, and Bhumipol Hospital.

Out-patient adult males and females aged 18 years or older with acute maxillary sinusitis were included. The diagnosis was established on the basis of clinical history and physical examination i.e. facial pain and/or tenderness over one or both maxillary areas, and mucopurulent discharge either in the nasal cavity or from maxillary ostium or mucopurulent postnasal discharge. The diagnosis was confirmed by radiological findings of either opacification or an air-fluid level, or mucosal thickening of more than 5 mm of one or both maxillary sinuses. Documentation of infection was made by pre- and post-therapy cultures and susceptibility testing. Written informed consent was obtained from all patients.

Patients were excluded from the study if they had chronic or complicated sinusitis, an endonasal anatomical abnormality which might impair ventilation and drainage of the maxillary sinus ostium, nosocomial sinusitis and recent sinus surgery (within 3 months). Patients who had received antimicrobial therapy within two weeks prior to enrollment, unless there was documented failure of the previous therapy, were also excluded. Evidence or a history of chronic diarrheal disease, any other gastrointestinal conditions that might affect drug absorption, the presence of terminal illness, severe life threatening infection, or other conditions that would interfere with the study drug treatment and its evaluation, were all additional criteria for exclusion. Pregnant or lactating women and patients with a known history of hypersensitivity to fluoroquinolone compounds were also excluded from the study.

Those who fulfilled the inclusion criteria, received gatifloxacin 400 mg tablet, given as a single daily dose for ten days, and might be taken without regard to food. Patient compliance was measured by counting the remaining tablets at the third visit, and checking the medication diary card which was recorded by all patients indicating the date and time of each dosage.

Clinical symptoms were evaluated on four occasions, i.e.before the treatment started (day 0, V1, day 3-5 (V2), day 11-14 (V3), and day 21-28 (V4).

The changes in the percentage of patients who had general clinical symptoms such as fever, malaise, chills, sore throat, headache, cough, and halitosis, and also the clinical symptoms and signs of sinusitis, i.e. sinus pain, sinus tenderness, purulent nasal discharge, facial pressure, nasal congestion, postnasal drip, and anosmia, were recorded by physicians.

The clinical responses were classified as cure, improvement, relapse, and failure at the end of treatment (V3) and at follow up (post - treatment, V4). Cure was defined as complete resolution of symptoms and signs with no radiological evidence of disease; improvement if there was incomplete resolution of symptoms and signs together with improvement of radiological findings; relapse if an initial improvement or cure was followed by worsening or recurrence of symptoms and signs; and failure if there was neither clinical nor radiological improvement. Treatment success was defined as cure or improvement.

Radiological studies using plain film sinuses (Waters' and Caldwell's view) were done at inclusion (V1) and then again at the end of therapy (V3). Radiological evaluations were assessed as resolution, improvement, unchanged, or worse.

Specimens for bacteriological study were collected before treatment (V1) and at V3 by maxillary antral aspiration using a sterile technique. All specimens were sent for both aerobic and anaerobic cultures. Microorganisms were isolated and identified according to standard bacteriological methods.[3] The bacteriological response was graded as follows : eradication if all the pathogens presented at baseline were eliminated or no material was available for follow up culture; persistence if the baseline pathogens were isolated on the second sample (V3) and new infection if new pathogens causing clinical symptoms of infection were isolated on the second sample (V3).

The safety of gatifloxacin was assessed from vital signs, general physical examination, hemato-biochemical parameters, and adverse events reported, which were performed at V1 and V3. All the adverse events, either observed by the investigators or reported by the patients, were recorded at each visit and evaluated by the investigators for severity, onset, duration and causal relationship to the study drug. Hemato-biochemical parameters included a complete blood count, liver function tests, fasting blood sugar, blood urea nitrogen and creatinine.

Statistical analysis

All numerical data were expressed as mean ± standard deviation. ANOVA test was used to compare the vital sign measurements and hemato-biochemical parameters before and after treatment. The percentages of patients who had general clinical symptoms, and symptoms and signs of sinusitis were compared between visits, using the McNemar test. A p value < 0.05 was considered to be a significant difference.

RESULTS

A total of 30 patients was included. The mean age was 34.7 ± 12.2 (range 21-70) years. There were 13 males and 17 females. The mean duration of symptom was 2.4 ± 8.8 weeks. The demographic characteristics of the patients are shown in Table 1. Approximately one-third of the patients had a history of allergy, sinusitis or upper respiratory tract infection within the past 3 months.

General clinical symptoms

At inclusion (V1), the general clinical symptoms found were headache (23 patients, 76.7%), cough (19 patients, 63.3%), and halitosis (14 patients, 46.7%). Other symptoms found in minority of patients were sore throat (13.3%), malaise (10.0%), chill (6.7%), and fever (6.7%). At the end of treatment (V3) and at the follow up study (V4), all these symptoms had resolved, except in 1 patient who still had cough (Table 2).

Symptoms and signs of sinusitis

The most common symptoms and signs of sinusitis presented at V1 were purulent nasal discharge (90%), nasal congestion (86.7%), postnasal drip (86.7%), sinus pain (80%), facial pain (66.7%), and sinus tenderness (63.3%). After 3-5 days of treatment (at V2), the percentage of patients who had symptoms and signs of sinusitis decreased significantly for every symptom and sign. The same was true at V3 and V4. At the end of treatment (V3), only 1 patient (3.4%) had nasal congestion, 1 patient (3.4%) had postnasal drip, and another had hyposmia. At follow up (V4), 3 patients (11%) had nasal congestion, 2 patients (7.4%) had postnasal drip, and 1 patient (3.7%) had sinus pain (Table 3).

Radiological findings

Radiological findings were abnormal in all 30 patients. Twenty two patients had bilateral maxillary sinusitis, and 8 patients had unilateral disease. The X-ray findings were as follows; opacification in 7 patients (23.3%), an air fluid level in 10 patients (33.4%), and mucosal thickening in 13 patients (43.3%). After 10 days treatment with gatifloxacin (at V3), 24 patients were evaluated radiologically and the X-ray findings were normal in 10 patients (41.7%), opacification in 3 patients (12.5%), an air fluid level in 1 patient (4.1%), and mucosal thickening in 10 patients (41.7%) (Table 4). The total improvement in radiological findings was 83.4% (41.7% resolution, 41.7% improvement).

Table 1. Demographic characteristics of patients.

Number of patients	30
Male : Female	13 : 17
Mean age (years)	34.7 ± 12.2
Duration of symptoms (weeks)	2.4 ± 8.8
Height (cm)	161.1 ± 9.0
Weight (kg)	59.8 ± 12.7
History of nasal allergy (%)	9 (30.0)
History of URI in the past 3 months (%)	9 (30.0)
Episodes of sinusitis in the past 12 months (0 : 1 : 2)	25 : 3 : 2

Table 2. Percentages of patients who had general clinical symptoms at each visit.

	Number of patients who had symptoms (%)			
Symptoms	**Visit 1 (day 0) n = 30**	**Visit 2 (day 3-5) n = 28**	**Visit 3 (day 11-14) n = 25**	**Visit 4 (day 21-28) n = 27**
Headache	23 (76.7)	2 (7.1)	0 (0)	0 (0)
Cough	19 (63.3)	4 (14.3)	1 (4.0)	1 (3.7)
Halitosis	14 (46.7)	1 (3.6)	0 (0)	0 (0)
Sore throat	4 (13.3)	0 (0)	0 (0)	0 (0)
Malaise	3 (10.0)	0 (0)	0 (0)	0 (0)
Chills	2 (6.7)	0 (0)	0 (0)	0 (0)
Fever ≥ 38° C	2 (6.7)	0 (0)	0 (0)	0 (0)

Table 3. Percentages of patients who had symptoms and signs of sinusitis at each visit.

	Number of patients who had symptoms (%)			
Symptoms	**Visit 1 (day 0) n = 30**	**Visit 2 (day 3-5) n = 28**	**Visit 3 (day 11-14) n = 25**	**Visit 4 (day 21-28) n = 27**
Purulent nasal discharge	27 (90.0)	3 (10.7)	0 (0)	0 (0)
Nasal congestion	26 (86.7)	2 (7.1)	1 (4.0)	3 (11.1)
Post nasal drip	26 (86.7)	3 (10.7)	1 (4.0)	2 (7.4)
Sinus pain	24 (80.0)	2 (7.1)	0 (0)	1 (3.7)
Facial pain	20 (66.7)	2 (7.1)	0 (0)	0 (0)
Sinus tenderness	19 (63.3)	2 (7.1)	0 (0)	0 (0)
Facial pressure	17 (56.7)	2 (7.1)	0 (0)	0 (0)
Dental pain	12 (40.0)	1 (3.6)	0 (0)	0 (0)
Hyposmia	10 (33.3)	1 (3.6)	1 (4.0)	0 (0)

Table 4. Radiological findings at visit 1 and visit 3.

	Visit 1 (day 0), n = 30	Visit 3 (day 11-14), n = 24
	n (%)	n (%)
Normal	0 (0)	10 (41.7)
Opacification	7 (23.3)	3 (12.5)
Air-fluid level	10 (33.4)	1 (4.1)
Mucosal thickening	13 (43.3)	10 (41.7)

Table 5. Results of pretreatment maxillary sinus cultures.

Total number of patients	30 (100)
Positive culture (%)	23 (76.7)
Aerobes (%)	19 (63.3)
Anaerobes (%)	3 (10.0)
Mixed aerobes + anaerobes (%)	1 (3.3)
No growth	7 (23.3)
Total number of bacteria isolated (%)	32 (100)
No. of bacteria isolated / No. of positive culture	1.4
Aerobes (%)	23 (71.9)
H. influenzae BL - ve*	3 (9.4)
H. influenzae BL + ve*	3 (9.4)
S. pneumoniae	3 (9.4)
Klebsiella pneumoniae	2 (6.3)
Coagulase negative *Staphylococcus*	2 (6.3)
Enterobacter species	2 (6.3)
α - *Haemolytic streptococci* (non group D)	1 (3.1)
Streptococcus viridans	1 (3.1)
Group D *Streptococcus*	1 (3.1)
Staphylococcus aureus	1 (3.1)
Non-fermentative gram negative rod	1 (3.1)
H. parainfluenzae	1 (3.1)
Diphtheroid species	1 (3.1)
Propionibacterium acne	1 (3.1)
Anaerobes (%)	9 (28.1)
Peptostreptococcus prevotii	3 (9.4)
Fusobacterium nucleatum	3 (9.4)
Prevotella melaninogenica	1 (3.1)
Bacteroides fragilis	1 (3.1)
Bacteroides melaninogenicus	1 (3.1)

*BL + ve = betalactamase producing strains, BL - ve = non-betalactamase producing strains.

Bacteriological findings

Pretreatment cultures were positive in 23 out of 30 specimens (76.7%); 19 specimens (63.3%) grew pure aerobes, 3 (10.0%) grew pure anaerobes, and 1 culture (3.3%) grew a mixture of aerobe and anaerobe. The most common pathogen was *H. influenzae* which accounted for 18.4% of all bacterial isolates. Other pathogens were *S. pneumoniae* (9.4%), other *Streptococcus* species (9.4%), *Klebsiella pneumoniae (K. pneumoniae)* (6.3%), coagulase negative *Staphylococcus* (6.3%) and some other pathogens as shown in Table 5. Anaerobes were found in 28.1% of all bacterial isolates, i.e. *Peptostreptococcus prevotii* (9.4%), *Fusobacterium nucleatum* (9.4%), *Prevotella melaninogenica* (3.1%), *Bacteroides fragilis* (3.1%), and *Bacteroides melaninogenicus* (3.1%). The bacteriological responses after 10 days treatment with oral gatifloxacin in the 23 bacteriological evaluable patients were eradication in 7 patients (30.4%), presumed eradication in 15 patients (65.2%), and persistence in 1 patient (4.4%).

The persistent bacteria in one patient were multiple anaerobes, i.e. *Bacteroides melaninogenicus, Peptostreptococcus prevotii*, and *Fusobacterium nucleatum*, and the MIC_{90} for these anaerobes against gatifloxacin were higher than 32, 0.094, and 0.064 µg/ml respectively.

Clinical response

One patient reported was pregnant after receiving one dose of gatifloxacin, so she was excluded. Two patients were withdrawn due to adverse events. Two patients missed the evaluation at the end of treatment but came back for follow up at the end of study. So, there were 25 patients and 27 patients for clinical evaluation at the end of treatment (V3) and at the end of the study (V4) respectively. Clinical responses at V3 were cure in 18 patients (72.0%), improvement in 3 patients (12.0%), and failure in 4 patients (16.0%). At V4, 24 patients (88.9%) were cured, 2 patients (7.4%) were clinically relapsed and 1 patient (3.7%) was failed.

Safety of oral gatifloxacin

There were no significant changes ($p > 0.05$) in vital sign measurements, general physical examination, or hemato-biochemical parameters at the end of treatment (V3) as compared to baseline values. Adverse events were found in 4 patients (13.3%).

One patient had agitation and tremor, and was withdrawn after 2 days of treatment. Another patient had anorexia, nausea, constipation and dry mouth, he was withdrawn after 3 days of treatment. Another two patients had mild nausea and vomiting after the first two days of treatment, both continued the treatment without problem until the end of the study. All the symptoms were either transient and resolved spontaneously or disappeared after continuing the treatment.

DISCUSSION

This study demonstrated a satisfactory clinical response in 84.0% of patients (72.0% cure, 12.0% improvement) 10 days after treatment (V3, day 11-14) with oral gatifloxacin, and this increased to a 88.9% cure rate at follow up (V4, day 21-28). The percentages of patients who had general clinical symptoms, and the symptoms and signs of sinusitis decreased significantly as early as three days after treatment began (V2, day 3-5), and also at V3 and V4 (Table 3-4). Eradication of the baseline pathogens was found in 95.6% of patients (30.4% eradication, 65.2% presumed eradication). All the major pathogens of acute sinusitis, i.e. *H. influenzae*, including beta-lactamase producing strains, *S. pneumoniae* and other *Streptococcus* species, were 100% eradicated. Anaerobes were found in 9 out of 32 bacterial isolates (28.1%), and the eradication rate of gatifloxacin for these anaerobes was 66.7% (6 out of 9 anaerobes).

The clinical cure rate and bacteriological eradication rate were comparable to other studies using gatifloxacin in the treatment of acute sinusitis, viz. Fogarty et al[5] (93% clinical cure) and Lopez-Sisniega et al [6] (95% clinical success, with an eradication rate of 97%, 100%, 100% and 90% for *S. pneumoniae, H. influenzae, M. catarrhalis* and *Staplylococcus aureus* (respectively).

Although there are some arguments about the necessity of antibiotics for the treatment of acute uncomplicated sinusitis,[7,8] most guidelines recommend antibiotics as the first line of therapy.[4,9-13] In recent guidelines, gatifloxacin and other new generation quinolones were the recommended antibiotic of choice for adult acute bacterial rhinosinu-

sitis in many situations, i.e. 1) mild sinusitis, using as switch therapy after 72 hours of treatment with initial empiric antibiotics with no improvement or worsening, 2) moderate sinusitis with beta-lactam allergy, 3) moderate sinusitis with a history of prior antibiotic therapy in the past 4-6 weeks.

Gatifloxacin is well absorbed from the gastrointestinal tract and is extensively distributed throughout body tissues and fluids. It achieves high concentration in the target respiratory tissue, often exceeding serum level by 2 to 4 folds. This high penetration coupled with its excellent bacteriologic profile indicate that gatifloxacin is an ideal agent for the treatment of community-acquired respiratory tract infections. In a recent respiratory surveillance study of the incidence of pathogens and antimicrobial susceptibility of community-acquired respiratory tract infection[16], high level resistances to penicillin (2 μg/ml or greater; 16% overall) and to macrolides (32 to 35%) were found among *S. pneumoniae*, and beta-lactamase-mediated resistance to ampicillin among *H. influenzae* ranged from 15 to 32%. The fluoroquinolones were highly active against pathogens isolated from community-acquired respiratory tract infections, with more than 99% of all *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* strains being susceptible to gatifloxacin (MIC_{90} = 0.5 μg/ml) and levofloxacin (MIC_{90} = 2 μg/ml). This surveillance study concluded that the extended-spectrum fluoroquinolones appeared to be well suited for community-acquired respiratory tract infection therapy. However, increased use of fluoroquinolones for treatment of rhinosinusitis and other community-acquired respiratory infections may result in increased bacterial resistance. Two recent studies reported the incidence of *S. pneumoniae* resistance to fluoroquinolones to be 1.7%[14] and 12.1%.[15]

So, the choice of antibiotic therapy for acute uncomplicated bacterial sinusitis should be a stepwise approach, i.e. empirical antibiotics for new cases with no previous antimicrobial therpay, oral cephalosporins in cases of prior antimicrobial therapy with no improvement or worsening, and the newer fluoroquinolones for patients with beta-lactam allergy. In cases where culture materials are available, antimicrobial agents should be selected according to the results of culture and sensitivity.

CONCLUSION

This study demonstrates the clinical and bacteriological efficacy, and the safety 10-day oral gatifloxacin 400 mg once daily in the treatment of acute, uncomplicated bacterial sinusitis. Eradication of all baseline pathogens was found in 95.6% of patients. The eradication rate for all major pathogens of acute sinusitis was 100%, and for the anaerobes was 66.7%. The once daily dosage is convenient for patients and produces better compliance.

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REFERENCES

1. Fish DN, North DS. Gatifloxacin, an advanced 8-methoxy fluoroquinolone. Pharmacotherapy 2001; **21:** 35-59.
2. Ednie LM, Jacobs MR, et al. Activities of gatifloxacin compared to those of seven other agents against anaerobic organisms. Antimicrob Agents Chemother 1998; **42:** 2459-62.
3. 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.
4. Sinus and Allergy Health Partnership. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. Otolaryngology Head and Neck Surgery 2000; **123(1 Part 2):** S1-S32.
5. Fogarty C, McAdoo MA, Paster RZ, et al. Gatifloxacin vs. clarithromycin in the management of acute sinusitis. J Respir Dis 1999; **20(Suppl):** S17-S22.
6. Lopez-Sisniega JA, Belalcazar V, Mascareno A, et al. Gatifloxacin in the treatment of acute bacterial sinusitis. J Resp Dis 1999; **20(Suppl):** S11-S16.

7. Van Buchem FL, Knottnerus JA, Schrijemaekers VJJ, Peeters MF. Primary-care-based randomised placebo-controlled trial of antibiotic treatment in acute maxillary sinusitis. Lancet 1997; **349:** 983-87.
8. Poole MD. Antimicrobial therapy for sinusitis. Otolaryngol Clin North Am 1997; **30:** 311-19.
9. Gwaltney JM Jr, Jones JG, Kennedy DW. Medical management of sinusitis : Educational goals and management guideline. The International Conference on Sinus Disease. Ann Otol Rhinol Laryngol 1995; **167(Suppl):** S22-S30.
10. Low DE, Desrosiers M, McSherry J, et al. A practical guide for the diagnosis and treatment of acute sinusitis. CMAJ 1997; **156:** 1-14.
11. Spector SL, Bernstein IL, Li JT, et al. Parameters for the diagnosis and management of sinusitis. J Allergy Clin Immunol 1998; **102:** S107-S144.
12. Rachelefsky GS. National guideline needed to manage rhinitis and prevent complications. Ann Allergy Asthma Immunol 1999; **82:** 269-305.
13. Chan KH, Winslow CP, Levin MJ, et al. Clinical practice guideline for the management of chronic sinusitis in children. Otolaryngol Head Neck Surg 1999; **120:** 238-43.
14. Ho PL, Oue TL, Tsang DNC, et al. Emergence of fluoroquinolone resistance among multiply resistant strains of Streptococcus pneumoniae in Hong Kong. Antimicrob Agents Chemother 1999; **43:** 1310-13.
15. Chen DK, McGeer A, DeAzavedo JC, Low DE. Decreased susceptibility of Streptococcus pneumoniae to fluoroquinolones in Canada. N Engl J Med 1999; **341:** 233-39.
16. Pfaller MA, Ehrharat AF, Jone RN. Frequency of pathogen occurrence and antimicrobial susceptibility among community-acquired respiratory tract infections in the respiratory surveillance program study : microbiology from the medical office practice environment. Am J Med 2001; **111:** 4S-12S.