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An open label, randomized comparative study of levofloxacin and amoxicillin / clavulanic acid in the treatment of purulent sinusitis in adult Thai patients*

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SUMMARY

The objective of the study was to compare the clinical efficacy and bacteriological response of levofloxacin and amoxicillin / clavulanic acid (co-amoxiclav) in the treatment of purulent maxillary sinusitis. Sixty patients randomly received either levofloxacin 300 mg orally once daily (LEV group) or co-amoxiclav 625 mg three times a day (COA group) for 14 days. Thirty four patients were in the LEV group and 26 patients were in the COA group. The mean total symptom score was significantly decreased after treatment and was comparable between both groups. Radiological improvement was 61.8% in the LEV group (41.2% resolution, 20.6% improvement) and 61.5% in the COA group (26.9% resolution, 34.6% improvement).

Pretreatment maxillary antral aspiration cultures were positive in 28 patients (82.4%) in the LEV group and 20 patients (76.9%) in the COA group. Bacteriological eradication was 78.5% in the LEV group and 70.0% in the COA group, which was not significantly different. In the LEV group, the eradication rate for major pathogens of acute sinusitis was 100% for H. influenzae (both betalactamase +ve and -ve), 100% for S. pneumoniae and S. aureus, 100% for Neisseria species, and 66.7% for P. aeruginosa. The eradication rate in the COA group was 75% for H. influenzae (both betalactamase + ve and -ve), 100% for S. pnumoniae and S. aureus, 50% for Neisseria species, and 0% for P. aeruginosa.

There were no significant changes in vital sign measurements or hemato-biochemical parameters at the end of treatment as compared to baseline values, in both groups. Adverse events were found in 8.8% of patient in the LEV group and in 7.7% of patients in the COA group. Adverse events included nausea, abdominal pain, and diarrhea. All the adverse events in both groups were mild and resolved spontaneously.

This study demonstrated that levofloxacin 300 mg orally once daily was as effective and safe as amoxicillin / clavulanic acid 625 mg three times a day in the treatment of maxillary sinusitis, either acute or acute exacerbation. Both drugs showed bacteriological efficacy that was not significantly different. The once daily dosage regimen is more applicable, convenience and has better compliance.

Key words: Levofloxacin, amoxicillin / clavulanic acid, acute maxillary sinusitis, acute exacerbation of chronic sinusitis, antral aspiration culture

INTRODUCTION

Sinusitis is a common disease that has significant impact both on the individual health and also on society. Sinusitis is the most frequently reported chronic disease, affecting 14.7% of the population in the United States (Benson et al., 1998; Spector et al., 1998). It is also the fifth leading disease in the United States that needs antimicrobial therapy, which amounts to 13 million antibiotic prescriptions per year (McCaig et al.,

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1995).

Antimicrobial drugs are the first line therapy for the treatment of acute sinusitis and acute exacerbation of chronic sinusitis. Empirical antibiotics (i.e. amoxycillin, co-trimoxazole, erythromycin and doxycycline) are usually the drugs of choice, because the identification of organisms requires antral aspiration or nasal endoscopy in order to obtain specimen for culture. So empirical antimicrobial therapy is usually started without microbiological confirmation. A primary problem associated with this empirical approach of treatment is the increasing incidence of betalactamase-producing strains of *H. influenzae* and *M. catarrhalis* (Jousimies-Somer et al., 1988; Penttila et al., 1997; Wald, 1998; Kongkaew et al., 2000; Jareoncharsri et al., 2001). Another important problem is the increasing incidence of penicillin-resistant strains of *S. pneumoniae*, which also often shows multidrug resistance. So, more effective antimicrobial agents that have a broad spectrum of activity against these resistant strains of common micro-organisms causing sinusitis are needed.

Levofloxacin, the *l*-isomer of the racemic ofloxacin, is the third generation fluoroquinolone. It has been shown to be at least twice as effective as ofloxacin, while still maintaining the excellent safety profile of its parent compound (Davis et al., 1994). The excellent pharmacokinetics with high level of penetration into the tissues throughout the body, together with the broad spectrum antimicrobial activity, and the ability to use it with a once-daily dosage schedule are important qualities of levofloxacin (Davis et al., 1994). The bacteriological strong points of levofloxacin include its excellent spectrum with better gram-positive coverage than previous fluoroquinolones, which is two to four times more active against *Staphylococci* and *Streptococci* than ciprofloxacin; it is effective against the majority of bacteria that cause upper respiratory tract infection, especially sinusitis; it is effective against drug-resistant *S. pneumoniae* and beta-lactamase producing strains (BL) of *H. influenzae* (Davis et al., 1994; Gootz et al., 1994). The objective of this study was to compare the efficacy, safety and antimicrobial activity of levofloxacin with amoxicillin / clavulanic acid (co-amoxiclav) in the treatment of purulent sinusitis in adult Thai patients.

MATERIALS AND METHODS

This study was an open, randomised, comparative and parallel design study conducted at two Otolaryngologic centers in Thailand: Siriraj Hospital, Bangkok and Chiang Mai University Hospital, Chiang Mai, during the period June 1998 through December 1999. The study was approved by the Ethical Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Siriraj Hospital, Mahidol University and Maharaj Hospital, Chiang Mai University.

Out-patient males and females age 16 years or older with acute or acute exacerbation of chronic sinusitis were included in the study. Diagnosis was established on the basis of clinical symptoms and signs, i.e. nasal obstruction, purulent nasal discharge or postnasal drip, impairment of sense of smell, foul smell and headache. Acute sinusitis is defined as having a sudden onset, with symptoms lasting less than 4 weeks. The acute worsening of symptoms in individuals with chronic sinusitis (history of symptoms longer than 12 weeks) is the definition of acute exacerbation of a chronic condition (Lanza et al., 1997). The diagnosis was confirmed by the finding of mucopurulent discharge in the middle meatus or maxillary ostium as seen by nasal endoscopy, and abnormal radiological findings. Documentation of bacterial infection was made using pre-and post-therapy antral aspiration cultures and susceptibility testing. Informed consent was obtained from all patients. All patients were randomly allocated to receive either levofloxacin 300 mg/ day, once daily (LEV group) or co-amoxiclav 625 mg, three times a day (COA group) for 14 days. Symptoms and signs were evaluated at four visits i.e., the first visit (day 0, V1) before the treatment started, the second visit (V2) on day 7, the third visit (V3) on day 14, and the fourth visit (V4) on day 21. Changes in clinical symptoms and signs were recorded by the investigators using a 4-point scale (0 = no symptom, 1 = mild, 2 = moderate, 3 = severe). The clinical response was classified as cure, improved, relapse or failure at the fourth visit or 21 days after the start of treatment. Cure was defined as complete resolution of symptoms and signs with no radiological evidence of remaining disease; improvement meant incomplete resolution of symptoms and signs and improvement of radiological findings; relapse if an initial improvement or cure was followed by worsening or recurrence of symptoms and signs; failure if neither clinical nor radiological improvement was seen. Treatment success was defined as cure and improvement. Radiological studies using plain film of the sinuses (Waters' and Caldwell view) were done at inclusion and again at the end of therapy (V3). Radiological evaluations were assessed as resolution, improved, unchanged, or worsened.

Specimens for bacteriological study were collected, before treatment and at the third visit, by maxillary antral aspiration using sterile technique. All specimens were sent for both aerobic and anaerobic cultures. The details of the techniques used for bacterial culture, isolation, identification and susceptibility test are described elsewhere (NCCLS., 1999; Jareoncharsri et al., 2001). 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 repeatedly isolated; eradication / re-infection if there was reappearance of the baseline pathogens after eradication, with clinical symptoms of infection; eradication / colonization if new organisms were isolated on repeated cultures and not related to clinical symptoms of infection; and super-infection if there was isolation of new pathogens on repeated culture, causing clinical symptoms of infection.

The safety of the study drug was assessed according to incidence of adverse drug reactions, laboratory tests and vital sign measurements, which were performed at the first and third

visit. All the adverse events, either observed by the investigator or reported by the patient, were recorded at each visit and evaluated by the investigator for the severity, onset, duration and its causal relationship to the study drugs. Laboratory tests included complete blood count, urinalysis, liver function test, blood urea nitrogen and creatinine analysis.

Statistical analysis

Statistical analysis was carried out using SPSS for window. All numerical data were expressed as the mean ± standard deviation. Student's t-test was used to compare the data within one individual group and the unpaired t-test was used to compare the data between the two groups. Analysis of the difference of discrete data was done using the Chi-square test.

RESULTS

A total of 60 patients were included, having a mean age of 35.5±13.1 (range 17-68) years, and male: female ratio was 23 : 37 (1 : 1.6). The diagnoses were acute maxillary sinusitis (AMS) in 48 patients (80%) and acute exacerbation of chronic sinusitis (AECS) in 12 patients. Thirty four patients received levofloxacin (LEV group) and 26 patients received co-amoxiclav (COA group). The demographic characteristics of both groups were statistically comparable for all parameters, except for concomitant allergy which were found more frequent in the LEV group than in the COA group (35.3% vs. 23.1%, p=0.04). The distribution of patients with AMS and AECS in both groups was similar. Other associated sinus inflammation i.e. ethmoid and frontal sinusitis was at the same prevalence. Bilateral involvement was found in 17 patients (50.0%) of the LEV group, and in 10 patients (38.5%) of the COA group.

Mean total symptom score (TSS) gradually decreased after treatment, which could be noted as early as the 3rd day of treatment, in both groups (Table 1). The percentage of decrease in symptom score was comparable between both groups in all visits (V2: 55.4% vs. 54.2%, V3: 65.1% vs. 67.7%, V4: 68.7% vs. 69.8%, for LEV group vs. COA group).

Radiological findings

The distribution of x-ray findings before treatment in both groups was comparable i.e. in the LEV group: air-fluid level 20.6%, opacification 70.6%, mucosal thickening 8.8% and in the COA group: air-fluid level 15.4%, opacification 69.3%, mucosal thickening 15.3%. After 14 days of treatment, radiological improvement was 61.8% in the LEV group (41.2% resolution, 20.6% improvement) and 61.5% in the COA group (26.9% resolution, 34.6% improvement).

Bacteriological responses

Pretreatment cultures were positive in 28 patients (82.4%) in the LEV group and in 20 patients (76.9%) in the COA group. The percentage of aerobes and anaerobes in both groups were quite similar (Table 2). After 2 weeks of treatment, eradication of the pretreatment pathogens were found in 78.5% of the patients in the LEV group and 70.0% of the patients in the COA group, which was not significantly different ($p > 0.05$). Persistence of pretreatment pathogens was noted in 21.5% of the patients of the LEV group and 30.0% of the patients of the COA group. Bacteriological responses of the various types of bacteria are shown in Table 3.

Clinical efficacy

Levofloxacin treatment resulted in 91.2% clinical success (cure 44.1%, improvement 47.1%), and the co-amoxiclav treatment resulted in 84.7% clinical success (cure 38.5%, improvement 46.2%). The failure and relapse rate in the LEV group was 5.8% and in the COA group was 15.4%.

Safety

There were no significant changes in vital sign measurements or laboratory tests at the end of treatment (V3) as compared with baseline values, in both groups.

Table 1. Mean individual symptom score and total symptom score of patients in both groups in each visit.

	V 1 (day 0)		**Day 3 (Telephone)**		**V2 (day 7)**		**V 3 (day 14)**		**V 4 (day 21)**	
Symptoms	LEV	COA	LEV	COA	LEV	COA	LEV	COA	LEV	COA
Nasal obstruction	1.5	1.9	0.9	0.9	0.4	0.8	0.6	0.6	0.6	0.6
Nasal discharge	1.7	1.8	1.1	1.6	0.7	1.1	0.7	0.6	0.5	0.9
Post nasal drip	2.1	1.9	1.4	1.4	1.4	1.2	1.1	1.2	0.8	0.8
Smell disturbance	0.9	1.1	0.5	0.9	0.5	0.4	0.4	0.2	0.3	0.3
Foul smell	0.9	1.1	0.4	0.0	0.2	0.2	0.3	0.1	0.1	0.1
Headache	1.3	1.8	0.5	0.3	0.6	0.6	0.2	0.3	0.3	0.3
Total symptom score	8.3	9.6	4.7	5.0	3.7	4.4	2.9	3.1	2.6	2.9
p value LEV vs. COA	0.09		0.23		0.19		0.29		0.35	

LEV = Levofloxacin group
COA = Co-amoxiclav group

Table 2. Results of pre-treatment maxillary antral aspiration cultures of patients in both groups.

	Levofloxacin N = 34 (%)	**Co-amoxiclav N = 26 (%)**
Positive culture	28 (82.4)	20 (76.9)
Aerobes	23 (67.7)	17 (65.4)
Anaerobes	1 (2.9)	2 (7.7)
Mixed aerobes+anaerobes	4 (11.8)	1 (3.8)
No growth	6 (17.6)	6 (23.1)
Total no. of bacteria isolates	59 (100)	41(100)
No. of bacteria isolate / No. of positive culture	2.1	2.1
Aerobes	46 (78.0)	29 (70.7)
Gram + ve organisms	23 (39.0)	11 (26.8)
α- *Streptococci*	6 (10.2)	3 (7.3)
S. pneumoniae	4 (6.8)	2 (4.9)
S. aureus	3 (5.1)	1 (2.4)
S. coagulase negative	2 (3.4)	1 (2.4)
γ- *Streptococci*	2 (3.4)	-
Corynbacterium species	2 (3.4)	-
Diphtheroid species	1 (1.7)	1 (2.4)
Other *Streptococcus* species	3 (5.1)	3 (7.3)
Gram – ve organisms	23 (39.0)	18 (43.9)
H .influenzae BL-ve*	9 (15.3)	4 (9.8)
H .influenzae BL+ve*	1 (1.7)	4 (9.8)
Neisseria species	4 (6.8)	2 (4.9)
P. aeruginosa	6 (10.2)	2 (4.9)
K. pneumoniae	3 (5.1)	1 (2.4)
H. parainfluenzae	-	1 (2.4)
Proteus mirabilis	-	1 (2.4)
E. coli	-	1 (2.4)
Enterobacteria species	-	2 (4.9)
Anaerobes	13 (22.0)	12 (29.3)
Fusobacterium species	3 (5.1)	5 (12.2)
Peptostreptococcus species	3 (5.1)	2 (4.9)
Prevotella species	3 (5.1)	-
Staphylococcus saccha.	2 (3.4)	-
Porphyromonas	1 (1.7)	1 (2.4)
Unidentified GNR**	1 (1.7)	-
Tissierella species	-	2 (4.9)
Bacteroides species	-	2 (4.9)

* BL = betalactamase.

** Unidentified gram negative rod.

Adverse events were found in 8.8% (3 in 34 patients) of the LEV group, and in 7.7% (2 in 26 patients) of the COA group. Drug – related adverse events in the LEV group included nausea, dizziness, abdominal pain and diarrhea, and those found in the COA group were nausea, palpitation, acute urticaria and bronchospasm. All the adverse events in both groups were mild and resolved spontaneously.

DISCUSSION

This study demonstrated that administration of levofloxacin 300 mg once daily was as effective as co-amoxiclav 500/125 mg three times daily in the 14-day treatment of adult purulent sinusitis. The clinical success rate (cure or improvement) was slightly higher in the LEV group (91.2%) than in the COA group (84.7%). The clinical success rate of levofloxacin in this study was comparable to other levofloxacin studies done by Adelglass et al. (1999), 88.4%; Sydnor et al. (1998), 88.0% and Lasko et al. (1998), 93.9%. These success rates were correlated with the efficacy results from sinusitis studies with other oral antimicrobial agents reviewed by Ferguson (1995), which ranged from 74% to 95%.

The improvement of sinusitis symptoms was noted as early as the third day of treatment in both groups, the mean individual symptom score and TSS at V3 were significantly decreased when compared to the baseline value. Patients in both groups still had some nasal symptoms at the end of study (V4, day 21). This might be from the concomitant allergic rhinitis (LEV gr. 35.3% and COA gr. 23.1%, p=0.04) or associated inflammation in ethmoid and frontal sinuses (23.6% in LEV gr. and 19.2% in COA gr.).

The use of plain x-rays sinuses in the diagnosis of bacterial rhinosinusitis has moderate sensitivity (76 percent) and specificity (79 percent) compared with the sensitivity and specificity of sinus aspiration culture (Kuusela et al., 1982; Laine et al., 1998). In this study we used the maxillary antral puncture and aspiration culture to prove for the presence of pre- and post-treatment pathogens.

The eradication rate for major pathogens of acute sinusitis in the LEV group was 100% for *S. pneumoniae*, *H. influenzae* (both BL +ve and -ve), and *S. aureus*, which is comparable to other levofloxacin study. *M. cattarrhalis* was not found in the present study.

The eradication rate for the bacteria found in AECR in the LEV group was as follows: *H. influenzae* (100%), *P. aeruginosa* (66.7%), *K. pneumoniae* (100%), other *Streptococcus* spp. (0%), *Fusobacterium* spp. (33.3%), *Peptostreptococcus* spp. (33.3%), and *Prevotella* spp. (0%) (Table 3). These figures showed that there was some levofloxacin resistance in these bacterial strains. The increased use of fluoroquinolones for the treatment of rhinosinusitis and other community-acquired respiratory infections may result in increased *S. pneumoniae*-resistance which was reported to be 1.7% - 12.1%. (Chen et al., 1999; Ho et al., 1999).

The total eradication rate for gram-positive bacteria (57.5%) and anaerobes (30.8%) in our study (Table 3) was different from another levofloxacin study of patients with acute sinusitis, which reported eradication rates of 93% for gram-positive bacteria, and 100% for anaerobes . These differences might be due to the fact that the patients included in our study were a mixture of acute maxillary sinusitis (AMS) and acute exacerbation of chronic sinusitis (AECS) cases in which the bacteria found in case of AECS were more resistant than in AMS. So if

Table 3. Bacteriological responses by types of bacteria in patients with bacteriological evaluable in both groups.

Type of bacteria	Levofloxacin group Number of bacteria isolates (%)			Co-amoxiclav group Number of bacteria isolates (%)		
	Before treatment	Persistence	Eradication	Before treatment	Persistence	Eradication
Gram +ve organisms						
α -*Streptococci*	6	3 (50.0)	3 (50.0)	3	2 (66.7)	1 (33.3)
S. pneumoniae	4	0	4 (100.0)	2	0	2 (100.0)
S. aureus	3	0	3 (100.0)	1	0	1 (100.0)
Other *streptococcus* spp.	3	3 (100.0)	0	3	1 (33.2)	2 (66.7)
S. coagulase negative	2	2 (100.0)	0	1	0	1 (100.0)
γ-*Streptococci*	2	1 (50.0)	1 (50.0)	-	-	-
Corynbacterium spp.	2	1 (50.0)	1 (50.0)	-	-	-
Diphtheroid spp.	1	0	1 (100.0)	1	0	1 (100.0)
Total Gram +ve	**23**	**10 (42.5)**	**13 (57.5)**	**11**	**3 (27.3)**	**8 (72.7)**
Gram –ve organism						
H. influenzae BL -ve	9	0	9 (100.0)	4	1 (25.0)	3 (75.0)
H. influenzae BL +ve	1	0	1 (100.0)	4	1 (25.0)	3 (75.0)
Neisseria sp.	4	0	4 (100.0)	2	1 (50.0)	2 (50.0)
P. aeruginosa	6	2 (33.3)	4 (66.7)	2	2 (100.0)	0
K. pneumoniae	3	0	3 (100.0)	1	1 (100.0)	0
H. parainfluenzae	-	-	-	1	0	1 (100.0)
Proteus mirabialis	-	-	-	1	0	1 (100.0)
E. coli	-	-	-	1	0	1 (100.0)
Enterobacteria spp.	-	-	-	2	0	1 (100.0)
Total Gram –ve	**23**	**2 (8.7)**	**21 (91.3)**	**18**	**6 (33.7)**	**12 (66.7)**
Anaerobes						
Fusobacterium spp.	3	2 (66.7)	1 (33.3)	5	2 (40.0)	3 (60.0)
Peptostreptococcus spp.	3	2 (66.7)	1 (33.3)	2	1 (50.0)	1 (50.0)
Prevotella spp.	3	3 (100.0)	0	-	-	-
Staphylococcus sacch.	2	0	2 (100.0)	-	-	-
Porphyromonas	1	1 (100.0)	0	1	1 (100.0)	0
Unidentified GNR	1	1 (100.0)	0	-	-	-
Tissierella spp.	-	-	-	2	0	1 (100.0)
Bacteroides spp.	-	-	-	2	1 (50.0)	1 (50.0)
Total anaerobes	**13**	**9 (69.2)**	**4 (30.8)**	**12**	**5 (41.7)**	**7 (58.3)**

we subgrouped our patients into AMS and AECR, the eradication rate of levofloxacin in patients with AMS was 90.5% and that of co-amoxiclav was 68.8%. (Table 4). The common persistent bacteria of both groups are shown in Table 3.

However, the number of each type of bacteria isolates in this study was too small to conclude the true figure of the eradication rate and resistance rate of these bacteria in both the LEV group and COA groups (Table 3).

In cases of AECS, the clinical features were more likely to be chronic in nature than acute. The diagnosis of chronic sinusitis depends on the duration of infection (more than 12 weeks). Acute sinusitis is typically of viral or bacterial etiology. This is different from the chronic sinusitis which is more of a mucosal disease, often with osteomeatal complex obstruction and sometimes endonasal structural abnormalities. Therefore, for the management of chronic sinusitis, in addition to antimicrobial therapy, surgical procedures are needed to promote the ventilation and drainage of the nose and sinuses. A comparison of the clinical success rate between AMS and AECR in both the LEV and COA groups is shown in Table 5.

Drug-related adverse events were noted in 8.8% of the patients in the LEV group, which was comparable to that of the COA

Table 4. Comparison of bacteriological response rate in patients with bacteriological evaluable between AMS* and AECS* in both groups.

Bacteriological response	LEV group n = 28		COA group n = 20	
	AMS n = 21	AECS n = 7	AMS n = 16	AECS n = 4
1.Eradicatiom	13 (61.9%)	1 (14.3%)	7 (43.8%)	-
2.Presumed eradication	4 (19.1%)	2 (28.6%)	4 (25.0%)	3 (75.0%)
3.Eradication/colonization	2 (9.5%)	-	-	-
4.Persistence	2 (9.5%)	4 (57.1%)	5 (31.2%)	1 (25.0%)
Total	**21 (100%)**	**7 (100%)**	**16. (100%)**	**4 (100%)**
Total eradication (1+2+3)	**19 (90.5%)**	**3 (42.9%)**	**11 (68.8%)**	**3 (75.0%)**

* AMS = acute maxillary sinusitis
* AECS = acute exacerbation of chronic sinusitis

Table 5. Comparison of clinical success rate between AMS* and AECS* in both groups.

Clinical response	LEV group N = 34		COA group N = 26	
	AMS n = 27 (%)	AECS n = 7 (%)	AMS n = 21 (%)	AECS n = 5 (%)
Cure	15 (55.6)	-	8 (38.1)	2 (40.0)
Improvement	9 (33.3)	7 (100.0)	10 (47.6)	2 (40.0)
Failure	1 (3.7)	-	1 (4.8)	1 (20.0)
Relapse	1 (3.7)	-	2 (9.5)	-
Withdrawn	1 (3.7)	-	-	-
Clinical success (Cure + improvement)	88.9%	100%	85.7%	80.0%

* AMS = acute maxillary sinusitis
* AECS = acute exacerbation of chronic sinusitis

group (7.7%) and was comparable to other levofloxacin studies, which ranged from 7.4-22.5% (Lasko et al., 1998; Sydnor et al., 1998; Adelglass et al., 1999). Common adverse events were nausea, diarrhea, abdominal pain and dizziness. In an another comparative study, drug-related gastrointestinal side effects were found to be more common with the amoxicillin-clavulanate treatment than with levofloxacin (Adelglass et al., 1999). The results of this study show that oral levofloxacin 300 mg once-daily is as effective and safe as amoxicillin-clavulanate 625 mg three times daily in the 14-day treatment of adult purulent sinusitis. Both drugs showed bacteriological efficacy that was not significantly different. The once daily dosage regimen is convenient for patients and produces better compliance.

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SOCIETY NEWS

CALL FOR PAPERS

RESEARCH PRIZES 2004 of the EUROPEAN RHINOLOGIC SOCIETY

The European Rhinologic Society biennial awards two Research Prizes; one prize is awarded for original basic research, and the second for an original clinical research in the field of Rhinology. In 2004 again, these prizes will be awarded, and therefore ENT Residents and Fellows are kindly requested to apply. Entries will have to meet the following conditions:

- Entries are to be submitted in the form of a scientific paper. Papers that have been accepted for publication by an international scientific journal will also be considered. Scientific papers – as well as supplements and Ph.D.-theses – that have already been published are excluded from competition.

- The research paper submitted is either the result of individual research activities or resulting from a team effort. In the latter case the first author will be considered as the nominee.

- Each applicant is allowed one entry. The author indicates whether the paper is a basic research or a clinical study. (We define clinical research as studies that deal with patients or normal subjects in a clinical set-up, whereas basic research refers to studies performed with either animals or tissues taken from patients or normal subjects).

- Only candidates below the age of 40 years can apply.

- The executive Committee of the European Rhinologic Society, supported by a number of invited expert referees, will act as the jury and will select both prize winners.

- The prizes, each of which amounts to Euro 1,500.- will be awarded during the Opening Ceremony of the forthcoming ERS Congress at Istanbul (Turkey), June 19- June 23, 2004. The prize winners will be invited to attend the congress, free of charge. The prize-winning entries will be given priority when submitted to the Journal Rhinology.

Applications together with five copies of the submitted papers, should be directed before May 1, 2004, to the Editor-in-Chief of the Journal Rhinology, Prof. Dr. E.H. Huizing at the following address: Department of Otorhinolaryngology, University Hospital Utrecht, Heidelberglaan 100, NL-3584 CX Utrecht, Room G05.127, The Netherlands.