

# Low dose sultamicillin in acute sinusitis

## **Sultamicillina a basse dosi per il trattamento della sinusite acuta**

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### ■ INTRODUCTION

The combination of ampicillin with sulbactam (prodrug sultamicillin) expands the spectrum of the former to include beta-lactamase producing microorganisms, such as *Haemophilus influenzae* and *Moraxella catarrhalis* [1, 2]. The plasma levels of ampicillin and sulbactam, when given as sultamicillin, are two to three times higher than with an equivalent dose of either drug alone [3].

The clinical efficacy and safety of the generally recommended daily dose of sultamicillin, 50 mg/kg administered in the treatment of children, and 1500 mg in the treatment of adults, have been established by numerous studies [4, 5, 6, 7, 8]. In Turkey, the recommended daily dose of sultamicillin is 25 mg/kg in the treatment of children, and 750 mg in the treatment of adults. We have found some studies, reporting the efficacy of low dose administration [4, 9, 10, 11], but none of them were comparative.

The aim of this clinical study was to evaluate the efficacy and safety of orally administered sultamicillin (Pfizer), marketed in low doses in Turkey, and compare it with orally administered amoxicillin (ABFAR, a Turkish company) in the treatment of acute sinusitis

### ■ METHODS

**Patients:** One hundred and twenty-five patients (58 male and 67 female), between the ages of 16-63 (mean 36.2), suffering from acute sinusitis, took part in the trial. All patients were outpatients and self-referrals. The diagnosis of infection was based on medical history, physical examination, conventional radiographic evalua-

tion and leukocyte count. Most of the patients complained of prolonged common cold, despite having symptomatic therapy. At the beginning, they had watery discharge, changing to purulent in the following week.

Signs and symptoms of the infection (purulent postnasal or nasal discharge; nasal inflammation; frontal/maxillary tenderness or pain; headache) were assessed and graded (0: absent, 1: mild, 2: moderate, 3: severe) before, during (five days after the first dose of study drugs), and at the end of therapy (10 days after the first dose of study drugs), and 20 days after the last dose (follow-up). A physician indicated chemotherapy, and another physician who was blind randomly prescribed study drugs. The first physician carried out control evaluations.

Exclusion criteria for the study were:

- 1) treatment with another antimicrobial agent within one week prior to enrolment, or receiving prophylactic antimicrobial agent;
- 2) symptoms no longer than a week that may be attributed to a common cold;
- 3) known hypersensitivity to any beta-lactam antibiotic;
- 4) infections requiring treatment with another antimicrobial agent;
- 5) terminal illness, immune deficiency or other disease that precluding evaluation of the study drug therapy;
- 6) pregnancy.

Each patient or patient's parent gave informed consent.

**Treatment and evaluation:** At the beginning, the patients were randomized to receive daily, oral dose of sultamicillin and amoxicillin, 2x375mg and 3x500mg respectively. At the end,

the remaining 25 patients received sultamicillin. Demographic data, severity grade of patients, by treatment, are shown in table 1.

In both treatment groups patients were treated for ten days. The first control was made 5 days after the first dose of study drugs. A patient was considered clinically cured when all pre-treatment signs and symptoms of infection were eliminated. Clinical improvement was defined as partial disappearance of pretreatment signs and symptoms. In either result study drugs were reconstituted for 5 additional days. Failure was defined as no change or worsening of signs and symptoms; and the study drug was changed. Relapse was defined as improvement or cure with subsequent reappearance of signs and symptoms at the follow-up assessment. A patient who was either cured or improved was considered a clinical success. No other concomitant medications were allowed, except for a few patients who received acetaminophen.

Independent-Samples T test was used to compare demographic information such as age. The chi-square test was employed to compare the sex distribution of patients and the rates of adverse events according to treatment. The Wilcoxon two-sample test was used to compare the distribution of clinical efficacy and signs/symptoms between two treatment groups. The level of significance was set at 0.05.

## RESULTS

One hundred and eight patients, 46 male and 62 female, between the ages of 16-56 (mean 32.8), came to their control visits regularly. There were 66 patients in the sultamicillin group, 42 in amoxicillin group. The age, weight and sex of patients were comparable in treatment groups.

The clinical success (improvement+cure) rate was (17+11)/42 (66.6%) and (28+21)/66 (74.2%) for amoxicillin and sultamicillin respectively, at the first control, as shown in table 2. All improved patients were cured at the second control. The side effects were seen in two patients (3.0%) in the sultamicillin group and in five (11.9%) in the amoxicillin group. All side effects were in the gastrointestinal system. Treatment was discontinued in no patient for adverse drug reaction. Relapses were observed in four patients (6.0%) in the sultamicillin group and three (7.1%) in the amoxicillin group.

Responses to both treatments were similar and there were no significant differences between the treatment groups with respect to resolution of symptoms, side effects and relapse ( $p>0.05$ ).

## DISCUSSION

Pharmacokinetic studies have established that ampicillin peak plasma concentrations achieved after oral administration of sultamicillin are approximately three times those obtained with equimolar dose of oral ampicillin [3]. Although the elimination half-lives of ampicillin and sulbactam are each approximately 1 hour, the high serum concentrations achieved, coupled with their synergistic bactericidal activity, permit twice-daily dosing [3]. However, although the proposed daily dose of sultamicillin is 50 mg/kg in the treatment of children and 1500 mg in the treatment of adults [4, 5, 6, 7], in Turkey it has been marketed in low (25 mg/kg for children, 750 mg for adults) and twice-daily dose form for more than 10 years.

There are some studies reporting similar clinical and bacteriological cure rates in the treat-

**Table 1 - Demographic data by treatment (age, gender, severity grade of sinusitis).**

Treatment	Mean age	Male/female	Mild n (%)	Moderate n (%)	Severe n (%)
Sultamicillin	37.1	37/38	17 (22.6)	51 (68.0)	7 (9.3)
Amoxicillin	35.4	21/29	9 (18.0)	37 (74.0)	4 (8.0)

**Table 2 - Numbers and percentages of cures, improvements and failures by treatment and disease severity (I: Improvement, C: Cure, F: Failure). The percentages show success rates.**

Treatment	Mild n (%)	Moderate n (%)	Severe n (%)
Sultamicillin I/C/F	5/9/3 (82.3)	13/24/14 (72.5)	3/1/3 (57.1)
Amoxicillin I/C/F	2/5/2 (77.7)	7/21/9 (75.6)	2/0/2 (50.0)

ment of mild to moderate community-acquired, acute ear-nose-throat infections, using a low and twice-daily dosage of sultamicillin [4, 9, 10, 13]. In such studies, overall clinical and bacteriological cure rates were high (94-99%). However, none of them was comparative. The only comparative study that we found was held in Turkey. In that study, only 24 acute maxillary sinusitis patients were involved; and success rate was 83.3% for sultamicillin and 66.6 % for amoxicillin ( $P>0.05$ ) [14]. Our cure rates were not as high as in preceding studies. We consider that comparative studies are more reliable.

In this study, although some patients were cured by five-day treatment, the duration of the treatment should be at least ten days in order to obtain a cure for improved patients and pre-

vent relapses. Though not significant, sultamicillin was found to be more effective than amoxicillin. The beta lactamase-producing organisms may be an explanation of that result. It is well known that there are some beta lactamase-producing organisms in acute sinusitis [12,15].

The side-effects of low-dose sultamicillin were considerably lower than the generally accepted dose, 4-8% [9, 10, 13] and 7-65% [5, 7, 8] respectively. The low incidence of side effects with low dosage of sultamicillin is confirmed in the present study. This finding requires further investigation. The treatment cost of sultamicillin was higher than that of amoxicillin.

*Key words:* amoxicillin, sultamicillin, acute sinusitis.

## SUMMARY

*Objectives:* to study the effectiveness of low dose sultamicillin in the treatment of acute sinusitis.

*Methods:* a total of 108 patients, between 16-56 years of age (mean 32.8), suffering from acute sinusitis took part in the trial. Patients received orally 2x375 mg sultamicillin, and compared with patients receiving 3x500 mg amoxicillin. The first control was made between the 5th and 7th days. A patient was considered clinically cured when all pretreatment signs and symptoms of infection were eliminated. Clinical improvement was defined as the partial disappearance of pretreatment signs and symptoms. In either result, study drugs were reconstituted for additional 5 days. Failure was defined as no change or worsening of signs

and symptoms; and study drug was changed. The second control was made between 10-12th days, and the third was four weeks later.

*Results:* The clinical success (improvement + cure) rate was (17+11)/42 (66.6%) and (28+21)/66 (74.2%) for amoxicillin and sultamicillin respectively, at first control. All improved patients were cured at the second control. No significant side-effects were noted in either amoxicillin or sultamicillin treated patients. All side effects were gastrointestinal, 11.9% and 3.0% in the same order.

*Conclusions:* Low dose sultamicillin was comparable to amoxicillin; sultamicillin has fewer side effects than amoxicillin ( $p>0.05$ ).

## RIASSUNTO

*Obiettivi:* studiare l'efficacia terapeutica della sultamicillina a basso dosaggio nel trattamento della sinusite acuta.

*Metodi:* 108 pazienti di età compresa tra 16 e 56 anni (media 32.8) affetti da sinusite acuta sono stati arruolati nel presente studio. I pazienti suddivisi in due gruppi sono stati sottoposti a trattamento orale con sultamicillina (2x375 mg) o con amoxicillina (3x500 mg). Il primo controllo clinico è stato effettuato tra il 5° e il 7° giorno dall'inizio della terapia. La guarigione clinica è stata definita sulla base

della scomparsa di tutti i segni e sintomi dell'infezione precedenti l'inizio del trattamento. Miglioramento clinico è stato definito come parziale scomparsa dei segni clinici. Nel caso di mancata guarigione o miglioramento il trattamento con i farmaci in studio è stato proseguito per ulteriori 5 giorni. Il fallimento è stato definito come nessuna variazione o peggioramento dei segni e sintomi. Il secondo controllo clinico è stato effettuato tra il 10° e il 12° giorno; il terzo controllo dopo 4 settimane.

**Risultati:** al primo controllo è stato osservato successo clinico (miglioramento + guarigione) in (17+11)/42 (66.6%) ed in (28 + 21)/66 (74.2%) pazienti rispettivamente trattati con amoxicillina e sultamicillina; al secondo controllo tutti i pazienti migliorati sono risultati guariti. Si è osservata una differenza statisticamente significativa nell'incidenza di effetti

collaterali (prevalentemente gastrointestinali) nei due gruppi di trattamento (11.9% per amoxicillina, 3% per sultamicillina) ( $P>0.05$ ).

**Conclusioni:** i risultati terapeutici ottenuti con sultamicillina a basse dosi sono stati paragonabili a quelli dell'amoxicillina. La sultamicillina ha mostrato minori effetti collaterali.

## ■ REFERENCES

- [1] Friedel H.A., Campoli-Richards D.M., Goa K.L. Sultamicillin: A review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 37, 491-522, 1989.
- [2] Stefani S., Russo G., Pellegrino M.B., Mezzatesta M.L., Cocuzza C., Nicoletti G. In-vitro activity of ampicillin/sulbactam and other antibiotics against clinical isolates of haemophilus sp. and Branhamella catarrhalis. *J Chemother.* 2(1):26-30, 1990.
- [3] Lode H., Hampel B., Bruckner G., Koeppe P. The pharmacokinetics of sultamicillin. *Acta Pathol., Microbiol. Immunol. Scand.* 97 (suppl.5) 23-34, 1989.
- [4] Alvarit R. An open multicentre study to compare the efficacy and safety of sultamicillin with that of cefuroxime axetil in acute ear nose and throat infections in adults. *J. Intern. Med. Res.* 20, Suppl 1, 53-61, 1992.
- [5] Bluestone CD. The role of sulbactam/ampicillin and of sultamicillin in the treatment of bacterial infections of respiratory tract of children. *Acta Pathol. Microbiol. Immunol. Scand.* 97 (suppl 5), 35-40, 1989.
- [6] Jones S., Yu V.L., Johnson J.T., Wagner R.L., Kim H.K.C. Pharmacokinetic and therapeutic trial of sultamicillin in acute sinusitis. *Antimicrob. Agents Chemother.* 28, 832-833, 1985.
- [7] Kaleida P.H., Bluestone C.D., Blatter M.M., Reisinger K.S., Wucher F.P., Fall P.A. Sultamicillin (ampicillin-sulbactam) in the treatment of acute otitis media in children. *Ped. Infect. Dis. Journal* 5, 33-37, 1986.
- [8] Rodriguez W.J., Khan W.H., Sait T., Chhabra O.P., Guarinello A., Smith A.W. Sultamicillin (ampicillin-sulbactam) versus amoxicillin in the treatment of acute otitis media in children. *J. Intern. Med. Res;* 18 (suppl 4), 78-84, 1990.
- [9] Arguello A. An open non-comparative pilot study of the safety and efficacy of oral sultamicillin in the treatment of mild to moderate upper respiratory tract infections in children. *J. Intern. Med. Res.* 20 (Suppl 1), 24-30, 1992.
- [10] Raillard P., Kose G., Ozkan H., Hasanoglu A., Firat S., Feiner C. Low-dose sultamicillin oral suspension in the treatment of mild to moderate pediatric infections in Turkey. *J. Intern. Med. Res.* 20 (Suppl 1) 12-23, 1992.
- [11] Wandstrat T.L., Kaplan B. Pharmacoeconomic impact of factors affecting compliance with antibiotic regimens in the treatment of acute otitis media. *Ped. Infect. Dis. Journal.*; 16 (Suppl. 2), 27-29, 1997
- [12] Edelstein D.R., Avner S.E., Chow J.M., Duerksen R.L., Johnson J., Ronis M. Once-a-day therapy for sinusitis: a comparison study of cefixime and amoxicillin. *Laryngoscope* 103, 33-41, 1993.
- [13] Raillard P., Feiner C., Ott V., Treadway G., Wang Y., Hawkey P.M. Worldwide pediatric experience with low-dose sultamicillin oral suspension. *Curr. Ther. Res.* 55, 334-347, 1994.
- [14] Dalçık E., Özçelik H.S., Aktan E., Özer M.A., Çelikoğlu M.M., Şenvar A. The comparison of sultamicillin with amoxicillin in the treatment of acute maxillary sinusitis. *In Proceedings Books of Twenty-First National Congress of Turkish Otolaryngology Society* Antalya: 1991; 846-849
- [15] Gwaltney J.M. Sinusitis. In *Principles and Practice of Infectious Disease* (Mandell G.L., Bennett E., Dolin R. eds.). 1995, pp 585-90 Churchill Livingstone.