A Comparative Efficacy and Safety Study of Clarithromycin, Roxithromycin and Erythromycin Stearate in Mild Pneumonia

Osman Nuri Hatipoglu[1] and Yucel Tasan[2]

———— Abstract ————

The efficacy and safety of clarithromycin, roxithromycin and erythromycin stearate in mild pneumonia were compared in an open randomized trial. Eighty-six male patients, doing their obligatory military service, ranging between 19 and 24 years of age (mean 20), were randomly treated: 29 with clarithromycin 500 mg 12-hourly, 30 with roxithromycin 150 mg 12-hourly, and 27 with erythromycin stearate 500 mg 6-hourly, each course being administered for 10 days. Seventy-eight patients were able to be evaluated for efficacy, 28 receiving clarithromycin, 28 roxithromycin, and 22 erythromycin stearate. There were no significant differences among the groups in terms of clinical success rates (clinical cure or improvement: 89% for clarithromycin, 82% for roxithromycin, and 73% for erythromycin stearate, p=0.32). However, we found that there were significant differences among the groups in terms of clinical cure rates (75% for clarithromycin, 64% for roxithromycin, and 41% for erythromycin stearate, p=0.04). Adverse events, mostly gastrointestinal, caused discontinuation of treatment in 3.4% of the patients in the clarithromycin group, in 6.6% of the patients in the roxithromycin group, and in 18.5% of the patients in the erythromycin stearate group. The results indicate that there were no statistically significant differences among the three treatment groups in terms of clinical success rates, but that clarithromycin and roxithromycin were better tolerated.

Key Words: Clarithromycin, erythromycin stearate, roxithromycin, pneumonia

INTRODUCTION

According to the guidelines issued by the American Thoracic Society,[1] European Respiratory Society,[2] British Thoracic Society,[3] Infectious Diseases Society of America[4] and Turkish Thoracic Society,[5] macrolides are recommended for the treatment of adults with mild community-acquired pneumonia (CAP) either as a first-line therapy, or as an acceptable alternative. The aim of this study was to determine which macrolide represents the best therapy for the treatment of mild pneumonia. In the present clinical trial, the efficacy and safety of clarithromycin, roxithromycin and erythromycin stearate in the treatment of mild pneu-

monia were studied.

MATERIALS AND METHODS

We prospectively studied patients with mild pneumonia not requiring hospitalization or i.v. antibiotic treatment in an open randomized trial at Etimesgut Army Hospital from April 1997 to May 1998.

Eligibility criteria

Eligible patients were male soldiers 18 years of age or older, doing their obligatory military service. Informed consent was obtained from all patients. A clinical diagnosis of mild pneumonia was required for study entry. Pneumonia was diagnosed by the presence of the following two criteria: (1) an acute pulmonary infiltrate that was evident on the chest radiographs and that was consistent with pneumonia, and (2) compatible clinical symptoms and signs. Among the patients with pneumonia, mild community-acquired pneumonia cases (not requiring hospi-

talization or initial treatment with i.v. antibiotics) were selected according to the criteria of the American Thoracic Society.[1]

Exclusion criteria

Exclusion criteria included a history of hypersensitive reaction to macrolide antibiotics, severe renal or hepatic dysfunction, pneumonia suspected Legionella or active tuberculosis, a history of pneumonia unsuccessfully treated with macrolide antibiotics within four weeks of study entry, the presence of symptoms/signs indicating clinical improvement in condition due to the use of a systemic antibiotic that had been started before study entry, or the use of a systemic antibiotic three days prior to study entry.

Treatment and assessment

At entry, a complete history, physical examination, and a chest x-ray were performed on each patient. Symptoms of pneumonia (cough, dyspnea, sputum, fever, and auscultatory findings) were recorded. The following information was collected from participants by means of standardized methods: age, smoking habit, coexisting illnesses, previous use of antibiotics and the recording/measurement of various laboratory values (complete blood counts, hepatic enzymes, BUN, creatinin). A specimen of sputum, if available, was obtained before the initiation of therapy. Chest X-rays were repeated at the complete end of therapy, and if necessary at the follow-up evaluation.

One of the following three antibiotics was randomly administered to the eligible patients: Oral clarithromycin 500 mg 12-hourly, oral roxithromycin 150 mg 12-hourly, and oral erythromycin stearate 500 mg 6-hourly, each administered for 10 days.

The patients were hospitalized and observed during the treatment period. The patients were visited every day, and any adverse effects resulting from the course of antibiotic treatment were recorded. The antibiotic regimen was stopped with the appearance of any severe adverse effects.

Efficacy analysis

Treatment efficacy was evaluated by observing/recording variations in clinical symptoms and signs within 48 hrs (post-treatment evaluation) and 15 to 45 days (follow-up evaluation) of the last dose, and was rated as cure (elimination of signs and symptoms of infection with no recurrence in the follow-up period); improvement (partial but not complete resolution of signs and symptoms of infection); success (cure or improvement); relapse (deterioration of signs and symptoms of infection after initial improvement) or failure (no improvement). Similarly, radiographic response was graded as resolution, improvement, success (resolution or improvement), or failure (unchanged or worsened). Patients who were withdrawn prematurely from the trial because of serious adverse effects were not included for efficacy analysis.

Safety analysis

All patients who received at least one dose of medication were included in the safety analysis. Adverse events were recorded with respect to the incidence, type, and severity of the events.

Statistical analysis

The three treatment regimens were compared at the baseline with respect to sex, history of smoking, coexisting illnesses and previous use of antibiotic by the chi-square method and with respect to age by one-way analysis of variance techniques. The efficacy of the three treatment groups was assessed by both clinical and radiographic variables including: clinical cure rate, clinical success rate, and radiographic success rate. As we had nominal data and three independent groups making 2×3 contingency tables, we used the 'chi-square test of independence with more than two groups' to analyze the responses of the patients able to be evaluated.[6]

First, the safety of the three treatment groups was assessed by considering the number of all adverse effects, and then considering only the serious ones. All adverse effects seen in the treatment groups were compared using the chi-square test. As more than 20% of the expected frequencies were less than 5, we combined the serious adverse effects occurring due to the clarithromycin therapy with those occurring due to the roxithromycin therapy, and compared the combined results with those of erythromycin stearate using Fisher's exact test (two-tailed).[6] Significance was defined as $p < 0.05$.

RESULTS

Patients characteristics

Eighty-six patients were entered into the study. No patient died either during the treatment or within a post-treatment follow-up period of 15 to 45 days after last dose. Twenty-nine patients received clarithromycin, 30 roxithromycin and 27 erythromycin stearate. For the three groups of patients there were no statistically significant differences among the groups with respect to age, smoking history and coexisting illnesses (Table 1). Although there was a numerical difference among the groups in terms of previous antibiotic use, this was not statistically significant.

Table 1. Patient Characteristics

Characteristic	Clarithromycin (n=29)	Roxithromyicn (n=30)	Erythromycin (n=27)
Sex, M/F	29/0	30/0	27/0
Mean age, yr	22.2	21.1	21.2
Positive smoking history, %	62	53	55
Previous antibiotic use, %	28	13	12
Coexisting illness, %	10	10	15

p > 0.05 for all comparisons.

Table 2. Clinical Efficacy and Safety of Study Drugs at the Post-treatment Evaluation

	Clarithro-mycin	Roxithro-mycin	Erythro-mycin	p value
Clinical cure*, %	75	64	41	0.04
Clinical success, %	89	82	73	0.32
Radiographic success, %	86	82	77	0.74
Total adverse effect, %	10	13	26	0.75
Serious adverse effect, %	3.4	6.6	18.5	0.10

* statistically significant (by using 'chi-square test independence with more than two groups').
Clinical success=clinical cure + clinical improvement.

Clinical evaluation

Seventy-eight patients were able to be evaluated for efficacy, 28 receiving clarithromycin, 28 roxithromycin, and 22 erythromycin stearate. Table 2 shows the clinical efficacy and safety of the study drugs at the post-treatment evaluation. There were no significant differences among the three treatment groups in terms of clinical success rates (clinical cure and improvement: 89% for clarithromycin, 82% for roxithromycin, and 73% for erythromycin stearate, p=0.32). However, there were significant differences among the three treatment groups in terms of clinical cure rates (75% for clarithromycin, 64% for roxithromycin, and 41% for erythromycin stearate, p=0.04). Fig. 1 shows the clinical cure and success rates at the post-treatment evaluation within 48 hrs after last dose. Sixty of the 64 who improved or were cured, were evaluated within 15 to 45 days after the last dose and no relapse occurred.

Radiological evaluation

Chest X-rays after treatment showed resolution or improvement in 86% of patients given clarithromycin, 82% of those given roxithromycin, and 77% those given erythromycin stearate (p=0.74). The radiographic success rate mirrored the clinical success rate for all but two patients. One of these patients was given erythromycin stearate and showed radiographic improvement but no clinical improvement, whereas the other patient, given clarithromycin, showed clinical improvement but no radiographic improve-
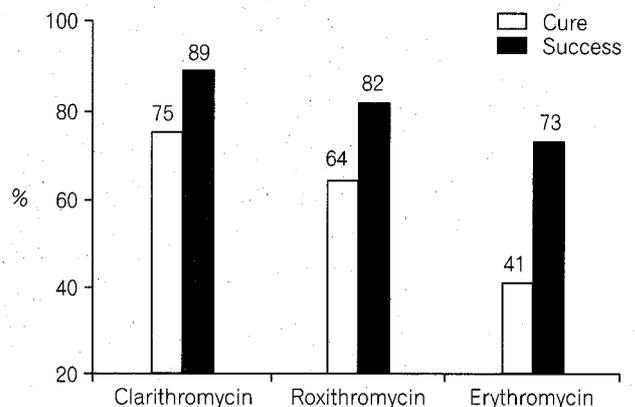

Fig. 1. Clinical cure and success rates at the post-treatment evaluation. Success=clinical cure +clinical improvement.

ment within 48 hrs of the end of treatment.

Microbiological evaluation

Seven target pathogens were isolated before the start of treatment, one from blood and six from sputum: Streptococcus pneumoniae,[6] Haemophilus influenzae.[1]

In total, one patient was bacteriologically able to be evaluated in the clarithromycin group, one patient in the roxithromycin group, and two patients in the erythromycin stearate group. All of the pathogens were eradicated except for one case of S. pneumoniae persisting in one patient in the erythromycin stearate group.

Adverse events

The number of the total number of adverse events and the number of serious ones that required discontinuation of the therapy were respectively 3 and 1 in the clarithromycin group, 4 and 2 in the roxithromycin group, and 7 and 5 in the erythromycin group (Table 3). The most frequent side effects in all treatment groups were gastrointestinal including nausea, vomiting and diarrhea. The only nervous system side effect observed was dizziness in 3 patients, all in the erythromycin group. The only patient who showed a rash as a dermatologic side effect was in the roxithromycin group. There were no statistically significant differences among the three treatment groups with respect to total adverse events (p=0.75) and serious adverse events (p=0.10).

Table 3. Summary of Adverse Events

	Clarithro-mycin		Roxithro-mycin		Erythro-mycin	
	mild*	serious†	mild	serious	mild	serious
Gastrointestinal	2	1	2	1	1	3
Nervous	—	—	—	—	1	2
Skin	—	—	—	1	—	—
Overall	3		4		7	

* mild: adverse events not requiring discontinuation of therapy.
† serious: adverse events requiring discontinuation of therapy.

DISCUSSION

Clarithromycin and roxithromycin are two new macrolide antibiotics derived from erythromycin. Although both agents are better tolerated than erythromycin because of their improved pharmacokinetic profile, the clinical efficacies of clarithromycin, roxithromycin and erythromycin are similar.

In a clinical trial performed by Anderson et al.,[7] clarithromycin was compared with erythromycin stearate in the treatment of 108 evaluable inpatients with CAP. They found that there was no significant difference between the two groups with respect to clinical cure or clinical success, radiological response, or adverse events. In a comparative multicentre clinical trial,[8] the efficacy and safety of clarithromycin and roxithromycin were compared and the clinical cure rates for clarithromycin and roxithromycin were 76% and 81%, respectively.

In the present study, we found that there were no significant differences among the three treatment groups in terms of post-treatment and follow-up clinical success rates. However, we found that clarithromycin and roxithromycin are more effective in achieving a rapid cure rate than erythromycin stearate. Even though previous antibiotic use rate was higher in the clarithromycin group than the roxithromycin group, clinical success and cure rates were higher in the clarithromycin group. Serious adverse events occurred in more patients who received erythromycin stearate (18.5%) than in those who received roxithromycin (6.6%) and clarithromycin (3.4%) although the incidences were not statistically different.

It can be concluded that there were no statistically significant differences among the three treatment groups in terms of clinical success, but that early clinical cure and better tolerance were obtained with clarithromycin and roxithromycin.

REFERENCES

1. Niederman MS, Bass JB Jr, Campbell GD, Fein AM, Grossman RF, Mandell LA, et al. Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy: American Thoracic Society, Medical Section of the American Lung Association. Am Rev Respir Dis 1993;148:1418-26.
2. European Study on Community-acquired Pneumonia (ESOCAP)

Committee. Guidelines for management of adult community-acquired lower respiratory tract infections. Eur Respir J 1998;11:986-91.

3. BTS (The British Thoracic Society). Guidelines for the management of community-acquired pneumonia in adults admitted to hospital. Br J Hosp Med 1993;49:346-50.

4. Bartlett JG, Breiman RF, Mandell LA, File TM Jr. Community-acquired pneumonia in adults: Guidelines for management. Clin Infect Dis 1998;26:811-38.

5. Ekim N, Kokturk O, Arseven O, Eraksoy H, Koksal F, Unal S, et al. Toplum Kokenli Pnomoni-Tani ve Tedavi Rehberi. Toraks Bulteni 1998;3:2-15.

6. Dawson-Saunders B, Trapp RG. Estimating and comparing proportions. In: Basic & Clinical Biostatistics. 2nd ed. Connecticut: Appleton & Lange; 1994. p.143-61.

7. Anderson G, Esmonde TS, Coles S, Macklin J, Carnegie C. A comparative safety and efficacy study of clarithromycin and erythromycin stearate in community-acquired pneumonia. J Antimicrob Chemother 1991;27 Suppl A: 117-24.

8. Poirier R. Comparative study of clarithromycin and roxithromycin in the treatment of community-acquired pneumonia. J Antimicrob Chemother 1991;27 Suppl A:109-16.