Clarithromycin vs Combined Cefuroxime and Erythromycin in the Treatment of Hospitalised Community-Acquired Pneumonia Patients - Intravenous Followed by Oral Therapy


1 Pulmologisches Zentrum der Stadt Wien, Vienna, Austria
2 Abbott International Ltd, Chicago, Illinois, USA
3 Beaumont Hospital, Dublin, Republic of Ireland
4 Dumfries and Galloway Royal Infirmary, Dumfries, Scotland
5 Institut Central des Hôpitaux Valaisans, Division de Microbiologie et des Maladies Infectieuses, Sion, Switzerland
6 Servicio de Neumología, Hospital Txagorritzu, Vitoria, Alava, Spain
7 Landeskrankenhaus, Abteilung für Lungenkrankheiten, Graz, Austria
8 AO Krankenhaus der Elisabethinen, Lungenerhebung, Linz, Austria
9 Servicio de Medicina Interna, Hospital La Paz, Madrid, Spain
10 Sir Mortimer B. Davis Jewish General Hospital, Montreal, Canada
11 Kings Cross Hospital, Dundee, Scotland

Summary

This study compared intravenous followed by oral clarithromycin (500mg twice daily; manufactured by Abbott Laboratories) with intravenous followed by oral erythromycin and cefuroxime (1g erythromycin three times daily, 1.5g cefuroxime three times daily intravenously, 500mg erythromycin, 500mg cefuroxime axetil orally) in the treatment of patients admitted to hospital with community-acquired pneumonia in 21 centres in Europe and Canada. 235 patients were enrolled for the study, of whom 169 (88 clarithromycin and 81 erythromycin/cefuroxime) were clinically evaluable and 47 (24 clarithromycin and 23 erythromycin/cefuroxime) were bacteriologically evaluable. All clinically evaluable patients received intravenous therapy for between 2 and 5 days. No significant differences between the treatment groups were seen regarding age, underlying disease, extent of chest x-ray shadowing and other indices of severity of pneumonia. A satisfactory clinical response was observed in 91 and 88% of clinically evaluable patients and 71 and 66% of all patients (intent-to-treat analysis) in the clarithromycin and erythromycin/cefuroxime groups, respectively, and similar bacterial cure rates were obtained (67 and 70%, respectively). There were no significant differences in the clinical and bacterial response rates between the two treatment groups. There was a significantly greater number of patients experiencing drug-related adverse events in the erythromycin/cefuroxime group (65%) than in the clarithromycin group (49%; p = 0.018), with significantly less nausea, vomiting, diarrhoea and abdominal pain occurring in the clarithromycin group. We concluded that clarithromycin is a suitable monotherapy for patients with community-acquired pneumonia who require intravenous treatment, and is associated with significantly fewer adverse effects than the combination of erythromycin and cefuroxime.
Community-acquired pneumonia (CAP) is a common reason for admission to hospital in Western societies, and it has been estimated that 1 in 1000 of the adult population is admitted to hospital annually for this reason.\(^1\) The mortality rates in studies of such patients have varied widely from 5 to 24%.\(^2\) An audit of patients with a diagnosis of pneumonia admitted to hospital in Scotland found a mortality of 24% and an average length of stay of 14 days,\(^3\) indicating that this disease not only carries a high mortality, but consumes significant hospital resource.

The microbial aetiology of CAP has been established by a number of studies in recent years.\(^4\) The majority of cases are associated with infections caused by Streptococcus pneumoniae, with smaller proportions being due to Mycoplasma pneumoniae, Haemophilus influenzae, Legionella and Chlamydia organisms, respiratory viruses, and occasionally other organisms. However, it is extremely rare for the causative pathogen to be identified when the choice of initial antibiotic treatment is made, so it is appropriate to use antimicrobial chemotherapy that is effective against the major pathogens.

β-Lactams and macrolides are the most common antibiotic classes used in the treatment of pneumonia. β-Lactams are inadequate treatment for pathogens such as Mycoplasma, Legionella and Chlamydia, whereas erythromycin has limited activity against H. influenzae.\(^5\) Newer macrolides such as clarithromycin have better activity against H. influenzae,\(^6\) and are effective against the majority of pathogens causing CAP.\(^7\) Oral clarithromycin has been shown to be effective in the treatment of lower respiratory tract infections including pneumonia in patients with relatively mild disease.\(^8\)

Patients with more severe disease are usually admitted to hospital and treated with intravenous antibiotics. An audit of patients admitted to hospital with CAP\(^9\) showed that over 60% of 319 patients received intravenous antibiotics. Accordingly, an intravenous preparation of clarithromycin has been developed and in this study was compared with intravenous cefuroxime and erythromycin, recommended as a routine treatment for patients with severe CAP admitted to hospital.\(^10\)

### Patients and Methods

#### Study Participants

This open-label, randomised, multicentre study compared the efficacy of two 10-day treatment regimens for pneumonia: (a) intravenous clarithromycin 500mg twice daily for 2 to 5 days followed by oral clarithromycin 500mg twice daily, and (b) combined therapy with intravenous erythromycin and cefuroxime sodium (1g three times daily and 1.5g three times daily, respectively), for 2 to 5 days followed by oral erythromycin base and cefuroxime axetil (500mg four times daily and 500mg twice daily, respectively). The study was approved by the ethics committees of the institutions involved, and conducted in accordance with Good Clinical Practice procedures.\(^11\)

Patients aged 18 years or older were enrolled in the study if they required admission to hospital for CAP (or had already been admitted to hospital) and, in the opinion of the investigator, required intravenous antibiotic treatment. All patients provided written informed consent before taking part in the study. Diagnosis of CAP was based upon radiological evidence together with clinical signs and symptoms consistent with CAP, including at least two of the following: cough, sputum colour or consistency indicative of an acute bacterial infection, pyrexia, development of or increase in chest discomfort/congestion, dyspnoea, crackles, wheeze or cyanosis.

Patients were excluded from the study if any of the following criteria existed: evidence of active tuberculosis; they were immunocompromised; an infection that necessitated the use of a concomitant antibacterial agent; history of hypersensitivity to macrolide or cephalosporin antibiotics; treatment with an investigational drug within 4 weeks prior to study drug administration; history of severe renal or hepatic impairment or disease; previous treatment in the study; pregnancy, risk of pregnancy, or lactation; any condition that would inter-