Clinical and Bacteriological Efficacy and Tolerability of FCE 22891 in Patients with Exacerbations of Chronic Obstructive Pulmonary Disease

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A β-lactamase-stable antibiotic, the oral penem FCE 22891 (ritipenem acoxil), was investigated for use in exacerbations of chronic obstructive pulmonary disease (COPD). Thirteen of the 15 COPD patients had a proven lower respiratory tract infection. Symptom scores and forced expiratory volume in 1 s significantly improved during therapy with FCE 22891 in combination with bronchodilators and intravenous corticosteroids. Conversion of representative sputum to nonrepresentative sputum or eradication of the original pathogen in representative sputum was effected in 12 patients. Resistance to FCE 22891 was observed in three cases with Haemophilus influenzae. Gastrointestinal disturbances, of which one was severe, were experienced by eight patients. Although FCE 22891 has some beneficial effect in exacerbations of COPD, there are reservations about its use because of adverse effects and potential inefficacy in the treatment of infection with H. influenzae.

Exacerbations of chronic obstructive pulmonary disease (COPD) are often caused by viral and bacterial infections, which are the most common causes of death in patients with this disease (5). The three major pathogens isolated from sputum specimens from COPD patients during an exacerbation are Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis. In the past decade an increasing resistance to ampicillin due to production of β-lactamase has been recorded for H. influenzae (15 to 30%) (10, 11, 13) and M. catarrhalis (up to 85%) (8, 10, 22). When the choice of treatment is empiric, especially in seriously ill patients, the agent should be directed against these β-lactamase-producing bacteria (17).

The penem FCE 22891 (ritipenem acoxil) can be orally administered and is hydrolyzed in the intestine into its active moiety, FCE 22101 (7). FCE 22101 is active against staphylococci (including methicillin-resistant Staphylococcus aureus strains), streptococci, anaerobes (including Bacteroides species), and gram-negative aerobic bacteria, particularly the β-lactamase-producing strains (17, 18, 24), but it has little or no activity against Pseudomonas aeruginosa (24). The aim of this study was to investigate the clinical and bacteriological efficacy and tolerability of FCE 22891 (Farmitalia Carlo Erba, Milan, Italy) in patients with exacerbations of COPD. The study was performed according to an open noncontrolled design.

Fifteen COPD patients (2) (aged >40 years) were enrolled in the study during an episode of exacerbation (increase in dyspnea, cough, sputum production, and/or purulence of sputum). Patients were included if the forced expiratory volume in 1 s (FEV1) was within the range of 30 to 80% of the predicted value during a stable phase of their illness. Exclusion criteria were an infiltrate on the chest X ray, pretreatment with antibiotics during the week preceding admission to the hospital, sputum culture yielding Pseudomonas species, allergy or hypersensitivity to β-lactam antibiotics, severe renal or liver disease, and pregnancy or breast-feeding.

All patients were treated according to standardized therapy. Prednisolone (60 mg/24 h, tapering dosage) and theophylline (500 to 800 mg/24 h) was administered intravenously, salbutamol (2,500 μg) and ipratropium bromide (500 μg) were administered via a nebulizer four times a day, and FCE 22891 (2 tablets of 500 mg three times a day) was given orally with a meal for 10 days. This was the maximum dosage which was tolerated well when given to healthy individuals in multiple administrations. Moreover, pharmacokinetic studies showed an acceptable bioavailability after a single oral administration of 1 g of FCE 22891 (20).

Symptoms were assessed before, during (days 4 and 8), and after (day 11) treatment and during follow-up (day 18) by the same investigator (S.P.). The severity of symptoms (dyspnea, cough, rales, signs of bronchial obstruction, and sputum production) was scaled from 0 to 2 (absent, mild, and severe). Sputum samples were examined and given a score of 0 (absent), 1 (mucous), 2 (mucopurulent), or 3 (purulent) (maximal symptom score, 13). Clinical efficacy was expressed as follows: cure, all symptoms and signs subsided with treatment; marked improvement, a >50% reduction in symptom score; slight improvement, a <50% reduction in symptom score; failure, no change in or worsening of clinical symptoms.

On days 0, 4, 8, 11, and 18, inspiratory vital capacity and FEV1 were measured with a calibrated water-sealed spirometer according to standardized guidelines (19). The highest of three reproducible values was used for the analysis. FEV1 was expressed as a percentage of the predicted value.

Sputum was collected in a sterile jar and washed three times in physiological saline (15). The resulting purulent fragments were used for microscopic examination (Gram staining) and semiquantitative culture. Only representative sputum specimens (>50 leukocytes and ≤5 squamous epithelial cells at a magnification of ×100) were used for the bacteriological
assessment. In the Gram-stained smears, characteristic morphologies of one or more respiratory pathogens were seen in combination with clusters of leukocytes. All other sputum specimens were considered nonrepresentative. Susceptibility to FCE 22101 (FCE 22891 is the prodrug) was tested by the disk diffusion technique with disks containing 10 µg of FCE 22101. Antibiogram results for aerobic bacteria (excluding *Haemophilus* species) were categorized as follows: susceptible, zone diameter of ≤17 mm (MIC for 90% of the strains, ≤4 mg/liter); intermediate, zone diameter of 14 to 16 mm (MIC for 90% of the strains, >4 and ≤8 mg/liter); and resistant, zone diameter of >13 mm (MIC for 90% of the strains, >8 mg/liter). The zone diameters for *Haemophilus* species were ≥27, 23 to 26, and ≥22 mm. Bacteriological efficacy at the end of treatment and during follow-up was defined as follows: eradication, absence of bacteria in representative sputum or absence of representative sputum; reinfection, isolation of bacteria different from those originally isolated; and persistence, recurrence of the same bacteria originally isolated.

During treatment and follow-up potentially adverse events were recorded.

Symptom scores and FEV₁, expressed as percentages of the predicted value, are presented as means and standard errors of the means. The differences in symptom scores and FEV₁ measured on different days were tested for significance by the paired Student *t* test. A *P* value of <0.05 was considered statistically significant.

With the administration of multiple-drug treatment, the semiquantitative symptom scores of 15 COPD patients (11 males and 4 females; mean age, 65.1 years [range, 44 to 74 years]) decreased, especially during the first 4 days of treatment (Fig. 1). Cure or marked improvement (reduction in ≥50% of the symptoms) was observed in eight patients (53%) by the end of treatment (day 11) and in six patients (40%) during follow-up (day 18). None of the patients were assessed as treatment failures.

All patients had a moderate to severe bronchial obstruction on admission; the FEV₁ was 37.5 ± 4.3% (mean ± standard error of the mean). During antibiotic treatment (day 0 to day 11), the FEV₁ did not improve significantly (*P* = 0.10), in contrast to the FEV₁ (*P* = 0.02) between the start of treatment and follow-up (day 18) (Fig. 2).

In the case of two patients (patients 2 and 14) the sputum specimen of day 0 either was not representative or yielded no pathogens. In the pretreatment cultures from the other 13 patients, *M. catarrhalis* and *H. influenzae* were most frequently isolated (Table 1). All pretreatment isolates were susceptible to FCE 22101, except for three of the five *H. influenzae* strains. After the completion of antibiotic treatment (day 11), representative sputum was replaced by nonrepresentative sputum in most patients. The original pathogen was eradicated in 12 of 13 patients and persisted in all sputum cultures only in the case of patient 3 (*Klebsiella ozaenae*). Reinfection with a different respiratory pathogen (*S. pneumoniae*) was observed in patient 13 during follow-up. Five patients (patients 3 to 7) were treated with an alternative antibiotic drug during follow-up; this was started 2 to 7 days after completing treatment with FCE 22891. One patient received a different antibiotic therapy because purulent sputum persisted; the unsatisfactory respiratory improvement in the other four patients caused clinicians to treat them with another antibiotic.

Adverse effects were observed in 8 of 15 patients, most of whom had mild gastrointestinal complaints (diarrhea). In one individual (patient 10) diarrhea was so severe that antibiotic treatment was terminated on day 6. This patient's feces did not contain *Clostridium difficile* or its toxin. Dysuria was reported by one patient.

The role of antibiotics in managing exacerbations of COPD is still controversial, because a spectrum of infectious and noninfectious agents may be involved in the pathogenesis of these exacerbations (3). Yet it seems unjustified to withhold antibiotics in COPD patients with severe or moderately severe exacerbations, especially since insufficient data on this issue are available (16).

During the past decade a number of new antibiotics with activity against β-lactamase-producing bacteria have been developed. One of these, FCE 22101, and its oral prodrug FCE 22891 have excellent activities against respiratory pathogens producing β-lactamases, except for *P. aeruginosa* (4, 6, 9).

In the present study, symptom scores and lung function improved especially during the first days of treatment. Whether the beneficial effect was due to FCE 22891 can only be speculated upon, since all COPD patients were concomitantly using bronchodilators and anti-inflammatory drugs.

Speculation is emphasized by the observation that the recovery

FIG. 1. Symptom score assessment before, during, and after multiple-drug treatment including FCE 22891 in 15 patients with exacerbations of COPD.

FIG. 2. FEV₁ as a percentage of the predicted value before, during, and after multiple-drug treatment including FCE 22891.
of three patients infected with *H. influenzae* resistant to FCE 22891 was not different from that of the other patients. Our rate of reduction (53%) of at least 50% of the symptoms was much lower than those (up to 98%) found by others and may be explained by both patient selection and inclusion criteria (12, 14). A significant increase in FEV₁ was measured between days 0 and 18 in our patients, with the greatest improvement during the first week. The reason why symptom scores and FEV₁ did not completely normalize is related to the nature and severity of COPD. No lung function data are available from other reports of studies of FCE 22891 as a treatment for lower respiratory tract infection (14, 21, 23).

By the end of treatment and during follow-up the original pathogens, including resistant *H. influenzae* strains, were eradicated in 11 of 13 patients. In other studies, bacteriological efficacy was found in 76 to 100% of the cases (12, 14, 21). Not all patients included in these studies had a positive sputum culture yielding respiratory pathogens (12, 14, 21). Nevertheless, for diverse clinical reasons the treating physicians (non-investigators) in this study prescribed another antibiotic in five cases. In these cases the comedication was not changed. Sputum cultures of both representative and nonrepresentative specimens from four of these patients yielded no pathogens prior to the institution of alternative antibiotic treatment. The high frequency of occurrence of FCE 22101-resistant *H. influenzae* strains was remarkable and has been recorded in only one other in vitro activity study (9).

The adverse effect most frequently registered was gastrointestinal disturbance; in one patient this was so severe that the antibiotic had to be discontinued. Such gastrointestinal symptoms were also recorded in studies with both healthy volunteers and COPD patients (1). These gastrointestinal disturbances are probably not dose related, because no difference in adverse effects was found in patients using 250 mg three times a day and those using 1,000 mg three times a day (14). These symptoms may be due to the effect of FCE 22891 on the intestinal flora. From this study it can be concluded that FCE 22891 has only a moderate efficacy in treating bacterial exacerbations in COPD patients and that the drug causes gastrointestinal symptoms with a high degree of frequency.

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**REFERENCES**


