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Clinical response to ertapenem in severe community-acquired pneumonia: a retrospective series in an elderly population

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Abstract

To evaluate in routine hospital practice the clinical response to ertapenem in comparison with other parenteral antibiotics in the treatment of community-acquired pneumonia (CAP), clinical records from patients with severe CAP treated with ertapenem from July 2002 to June 2006 in seven Spanish hospitals were retrospectively reviewed. Patients were classified according to the Pneumonia Severity Index (PSI). Each ertapenem-treated patient was matched with two patients in the same hospital treated with other antibiotics, according to age (difference ≤5 years), same PSI class and whether or not resident in a nursing home. Seventy-one patients treated with ertapenem and 131 matched controls were identified; 71 of the 202 patients came from nursing homes. A larger (p 0.0002) number of patients were treated with monotherapy in the ertapenem group. In total, 174 patients (86.1%) belonged to PSI classes IV–V; a higher (p <0.0001) PSI score was found in patients from nursing homes. The mean age was 80.5 years (75% of patients >76 years). Comorbidities were present in 193 patients (95.5%). No differences were found in median hospital stay (7 days for ertapenem vs. 10 days for comparators, p 0.066). A slightly higher clinical response rate was obtained for ertapenem vs. comparators (88.7% vs. 77.1%; p 0.0465; OR 2.25; 95% CI 0.99–5.12), with significant differences in clinical response in patients coming from nursing homes (95.8% ertapenem vs. 63.8% comparators; p 0.0034) but not in non-institutionalized patients (85.4% ertapenem vs. 84.5% comparators; p 0.929). The higher clinical response to ertapenem vs. comparators in severe CAP was due to its significantly higher efficacy in healthcare-associated CAP in patients coming from nursing homes.

Keywords: CAP, elderly, ertapenem, hospital practice, nursing homes, retrospective study
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Introduction

The incidence of community-acquired pneumonia (CAP) in Spain ranges from 1.8 to 8.8 cases per 1000 inhabitants [1–3], with 20–35% of the patients requiring hospital treatment [4]. Whereas the mortality of CAP in domiciliary patients is <1%, it is 12–14% in hospital-treated patients and 30–40% in those with bacteraemia [5,6]. Correct empirical choice of antibiotic treatment and initial therapeutic interventions is essential in minimizing the morbidity and mortality associated with this condition [7]. The prevalence of multiresistant bacteria in CAP has increased, probably owing to the wide use of antibiotics in respiratory tract infections, to early discharge from acute care facilities, to invasive medical services in nursing homes and rehabilitation facilities, and to the shift of healthcare from institutional to home-based services [7,8]. Ertapenem in Europe is licensed for diabetic foot, skin and skin-structure infections, intra-abdominal infections, acute gynaecological infections and CAP [9]. Its *in vitro* activity against respiratory pathogens [10,11], together with the

pharmacokinetic profile of total and free drug [10,12] and the consequent adequate pharmacodynamic coverage, suggest its use in severe CAP, where ceftriaxone is the standard therapy in many countries. Two CAP clinical trials [13,14] have been performed using ceftriaxone as standard comparator. In a pooled analysis of those two trials [15] clinical cure rates for ertapenem and ceftriaxone were 92.0% and 91.8%, respectively, in clinically evaluable patients, and clinical cure rates in the subgroup of patients with isolation of *Streptococcus pneumoniae* in pre-treatment cultures were also around 90%.

The aim of this study was to assess the efficacy of ertapenem in the treatment of CAP in daily practice by retrospectively reviewing data from patients admitted to hospital with a diagnosis of CAP and treated with ertapenem in a 4-year period after the introduction of ertapenem in Spain.

Materials and Methods

The clinical records of patients, ≥18 years of age, admitted to seven Spanish hospitals with a diagnosis of CAP, requiring hospitalization and parenteral treatment, who had been treated with ertapenem 1 g once a day, from July 2002 to June 2006, were retrospectively reviewed. Each ertapenem-treated patient was matched with two patients from the same hospital treated with other parenteral antibiotics, except in those cases where it was not possible to find two matching patients and only one was used. Matching criteria were: similar age (difference ≤5 years), same category Pneumonia Severity Index (PSI) [16] and whether or not resident in a nursing home. The study protocol was approved by the Ethical Review Board of Hospital Central de la Defensa (Madrid).

Medical records were reviewed to obtain demographic, clinical and analytical data, including those data necessary to classify patients according to PSI category [16]. Data recorded comprised: (i) demographic data: age, gender, nursing home residence, previous antibiotic treatment; (ii) comorbidities: malignancies, liver, renal, metabolic, endocrinological, heart or vascular disease, chronic obstructive pulmonary disease; (iii) clinical, radiological and analytical data for CAP diagnosis: fever, cough, sputum characteristics, pleuritic chest pain, auscultatory findings, dyspnoea or tachypnoea, total peripheral white blood cell count, PO_2 or oxygen saturation by pulse oximetry, chest radiograph; (iv) microbiological tests performed; (v) initial antibiotic parenteral treatment and duration, and (vi) length of hospital stay and outcome.

Patients were excluded if they had received parenteral antibiotic treatment for >24 h within the 72 h prior to hospital admission and/or if they had a diagnosis of tuberculosis, ventilator-associated pneumonia, nosocomial pneumonia, shock, immunosuppression, cystic fibrosis, neutropenia, bronchiectasis, primary lung cancer or lung metastasis, meningitis and/or HIV (<200 CD4/mm^3).

Patients were assessed at the end of parenteral treatment and until hospital discharge or death. Clinical response was considered as resolution or improvement of baseline signs or symptoms together with absence of progressive infiltration on chest X-ray. Clinical failure was defined as: death, persistence or worsening of baseline signs or symptoms, emergence of new signs or symptoms, or requirement of additional antibiotics different from those empirically prescribed.

Comparison of proportions was performed by Chi square test. Confidence intervals of median values were used when appropriate. Chi square for trends was used to compare trends. Significance level was established at $p \leq 0.05$. The Cochran–Mantel–Haenszel statistic was used to control for variations between patient groups and the Breslow–Day test was used to assess the homogeneity of the ORs.

Results

Seventy-one patients treated with ertapenem and 131 matched controls treated with other parenteral antibiotics, complying with the inclusion criteria, were identified in the study period. A total of 41 patients (20.3%) of the total population (202 patients) were receiving oral antibiotic treatment on admission (12 with amoxicillin-clavulanate, ten with macrolides, nine with quinolones, two with oral cephalosporins and eight with antibiotic combinations).

A significantly (p 0.0002) higher number of patients were treated with monotherapy in the ertapenem group than in the control group (other parenteral antibiotics) (83.1% vs. 57.2%). Of the 71 patients in the ertapenem group, 59 (83.1%) were treated with monotherapy while the 12 remaining patients were concomitantly treated with a macrolide (n = 8), a quinolone (n = 3) or ceftazidime (n = 1). Among the 131 controls treated with other antibiotics, 75 (57.2%) patients were treated with monotherapy (31 with a quinolone, 20 with a third-generation cephalosporin, 16 with amoxicillin-clavulanate, five with piperacillin-tazobactam and three with other antibiotics), and 56 with antibiotic combinations (26 with β-lactam + quinolone combination, 19 with β-lactam + macrolide combination, six with two β-lactams and five with other combinations).

One hundred and twenty-nine patients (63.9%) were male: 60.6% and 65.6% for ertapenem and controls, respectively.

TABLE 1. Patient matching criteria (age, residence and PSI) and comorbidities (%) present in more than 5% of the study population

	Total (*n* = 202)	Ertapenem (*n* = 71)	Controls (*n* = 131)
Age (years, mean ± SD)	80.5 ± 11.8	80.2 ± 11.7	80.2 ± 11.9
Residence in nursing home *n* (%)	71 (35.1)	24 (33.8)	47 (35.9)
PSI-II *n* (%)	6 (3.0)	2 (2.8)	4 (3.1)
PSI-III *n* (%)	22 (10.9)	8 (11.3)	14 (10.7)
PSI-IV *n* (%)	97 (48.0)	34 (47.9)	63 (48.1)
PSI-V *n* (%)	77 (38.1)	27 (38.0)	50 (38.2)
Cardiovascular disorders	124 (61.4)	45 (63.4)	79 (60.3)
Neurological disorders	107 (53.0)	37 (52.1)	70 (53.4)
Metabolic disorders	77 (38.1)	28 (39.4)	49 (37.4)
Respiratory disorders	45 (22.3)	15 (21.1)	30 (22.9)
Urogenital disorders	39 (19.3)	15 (21.1)	24 (18.3)
Gastrointestinal	29 (14.4)	11 (15.5)	18 (13.7)
Cancer	21 (10.4)	10 (14.1)	11 (8.4)
Hepatic disorders	17 (8.4)	9 (12.7)	8 (6.1)
Haematological disorders	12 (5.9)	7 (9.9)	5 (3.8)

PSI, Pneumonia Severity Index.

Table 1 shows the matching criteria (age, residence in nursing homes and PSI) for the whole population and both treatment groups. One hundred and seventy-four patients (86.1%) belonged to classes IV–V of the severity score. Three patients were treated in the intensive care unit. Six patients were class II, and hospitalized because of comorbidities (diabetes, toxic hepatitis or previous lung resection).

Seventy-one of the 202 patients (35.1%) came from nursing homes. A significantly (p <0.0001) higher PSI score was found in patients coming from nursing homes (22.5% class IV and 77.5% class V) than in those not institutionalized (23.4% class II–III, 61.8% class IV and 16.8% class V).

The mean age of the study population was 80.5 ± 11.8 years, with 75% of patients over 76 years. One hundred and ninety-three patients (95.5%) presented comorbidities, which are shown for the whole population and both treatment groups in Table 1. Cardiovascular (mainly hypertension, congestive heart disease, ischaemia and fibrillation) and neurological (mainly dementia and stroke) disorders were present in >50% of patients, metabolic disorders (mainly diabetes) in 38.1%, respiratory disorders in 22.3%, urogenital disorders (mainly renal impairment and prostatic disorders) in 19.3% and gastrointestinal disorders (mainly ulcers) in 14.4%. Malignancies were present in 10.4% of the study population.

Treatment duration, length of hospital stay, outcome and mortality are shown in Table 2. The mean treatment duration was similar in both treatment groups (9.9 ± 4.3 days for ertapenem and 10.1 ± 4.4 days for controls). No significant differences were found in median length of hospital stay (7 days for ertapenem vs. 10 days for controls, p 0.066). The clinical response was rather better for ertapenem treatment

TABLE 2. Treatment duration, hospital stay, outcome and mortality

	Ertapenem (*n* = 71)	Controls (*n* = 131)
Parenteral treatment duration (days, mean ± SD)	9.9 ± 4.3	10.1 ± 4.4
Hospital stay, median days (95% CI)	7 (4–10)	10 (6–13)
Clinical response, *n* (%)	63 (88.7)	101 (77.1)
Mortality, *n* (%)	6 (8.5)	10 (7.6)

than for other antibiotics (88.7% vs. 77.1%; p 0.0465; OR 2.25, 95% CI 0.99–5.12). Mortality during hospitalization was 4.5% (one patient out of 22) in PSI-III class (the patient suffered amyotrophic lateral sclerosis), 4.1% (four out of 97) in PSI-IV class, and 14.3% (11 out of 77) in PSI-V class, a significantly (p 0.028 Chi square for trends) higher mortality rate than in classes PSI-III and PSI-IV. No differences in mortality rates were found between treatment groups (8.5% for ertapenem group vs. 7.6% for controls).

A poorer clinical response was obtained in those patients coming from nursing homes than in those not institutionalized (74.6% vs. 84.7%), but differences did not reach statistical significance (p 0.080). No difference (p 0.929) in clinical response was found in non-institutionalized patients between ertapenem (85.4% response rate) and control (84.5%) treatments. On the other hand, in the subgroup of patients coming from nursing homes the response rate with ertapenem (95.8%) was significantly higher than in controls (63.8%) (p 0.0034; OR 13.03, 95% CI 1.61–105.23).

Pre-therapy positive bacteriological cultures were obtained from specimens from 29 patients (14.4%): 21 were respiratory samples and eight were blood cultures. Bacterial species identified were *S. pneumoniae* in ten patients (six blood cultures), *Haemophilus influenzae* in ten patients (one blood culture), *Escherichia coli* in four patients (one blood culture), *Klebsiella pneumoniae* in three patients, and *Serratia marcescens* and *Moraxella catarrhalis* in one patient each. In the ertapenem group *S. pneumoniae* was isolated in six patients (four of them with bacteraemia) and all patients showed a clinical response. In the control group *S. pneumoniae* was isolated in four patients (two of them with bacteraemia), and two of them showed clinical failure (one with bacteraemia) during treatment with levofloxacin plus ceftriaxone. Nine of the ten positive cultures for *H. influenzae* corresponded to patients in the control group, with clinical response in all patients with *H. influenzae* isolates except one patient in the control group. The patient with a positive culture for *Serratia marcescens* was treated with ertapenem and classified as clinical failure after 11 days of monotherapy. Eight out of nine Gram-negative bacilli were isolated in patients in the control

group, with four failures (three *E. coli* and one *K. pneumoniae*).

Positive urine pneumococcal antigen was identified in the clinical records of 11 patients: three in the ertapenem group (all of them with clinical response) and eight in the control group (with one failure).

Discussion

In a previous pooled analysis of two clinical trials comparing ertapenem with ceftriaxone [15], and showing equivalence, around 50% patients belonged to PSI I–II class, 20–25% to PSI III–IV class, with only 4% patients in the PSI-V class. In addition, only 36% patients included could be considered elderly (>65 years) and the mean age was 57 years. The ertapenem clinical response in elderly patients was similar to that in the overall population regardless of the PSI score [15,17].

To our knowledge, this is the first study to assess the efficacy of ertapenem in the treatment of CAP in the uncontrolled setting of daily medical practice. The study was retrospective (by reviewing clinical records of CAP patients treated with ertapenem during 4 years just after licensure) and included only seven Spanish hospitals, two facts that limit the strength of the conclusions. However, it provides valuable data from daily practice about the potential of ertapenem in the treatment of hospitalized CAP patients. The results of this study indicate that, at least in these centres, ertapenem is administered in daily practice as treatment of CAP-hospitalized patients mainly in the very elderly and when patients present comorbidities. The study population can be clearly considered a very old population (mean age 80.5 years; 91.6% patients >65 years, and 75% >76 years) with the comorbidities associated with this aged setting (with 61.4% population with cardiovascular disorders, 53.0% with neurological disorders, 38.1% with metabolic disorders and 10.4% with malignancies) and a severe pneumonia picture (86.1% of patients classified as PSI IV–V). In this population the clinical response with ertapenem was higher (p 0.0465) than that obtained with pooled comparators used in clinical practice (88.7% vs. 77.1%). This could influence length of hospitalization, since hospital stay was shorter for ertapenem (median values of 7 days for ertapenem vs. 10 days for comparators) although, since the difference did not reach statistical significance (p 0.066), no definitive conclusions can be drawn.

Moreover, 35.1% patients in the current study came from nursing homes and thus can be considered patients with healthcare-associated pneumonia (HCAP), a condition that may be associated with multi-resistance, thus influencing empirical treatment [7]. Patients with HCAP had more severe pneumonia (as defined by the PSI index) as previously described [7]. In this subgroup of patients, ertapenem showed significantly higher clinical response than did the antibiotics used as controls (95.8% vs. 63.8%; p 0.0034; OR 13.03, 95% CI 1.61–105.23). Although the higher clinical response of ertapenem vs. comparators in the global population was in the limit of significance (p 0.0465), and this fact together with the retrospective nature of the study suggest that the results should be taken with caution, in the subgroup of institutionalized patients with HCAP differences favouring ertapenem were evident. This could be important, because this subgroup of patients presented more severe pneumonia (significantly higher PSI score).

In addition to the retrospective nature of the study, a potential criticism is the absence of *Legionella* coverage by the ertapenem treatment of severe pneumonia. In a country such as Spain where *Legionella* outbreaks or sporadic cases are kept in mind by the physicians when managing severe pneumonia, testing for *Legionella* antigen in urine is widely used, and if the possibility of this aetiology cannot be excluded, appropriate coverage with a macrolide can be provided.

In summary, the results of this retrospective study analysing data from daily practice suggest that ertapenem administered as 1 g once a day was equivalent to comparator for non-institutionalized severe CAP in elderly patients (where CAP incidence is much higher than the 2–10 cases per 1000 inhabitants described for the general population) [5,18] with associated comorbidities, but showed significant superiority in the more severe CAP in patients from nursing homes. These results obtained in daily practice indicate the adequacy of ertapenem monotherapy (once *Legionella* has been excluded) as hospital treatment of severe HCAP in institutionalized patients.

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Transparency Declaration

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