Original

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The use of ertapenem for the treatment of community-acquired pneumonia in routine hospital practice: a matched cohort study

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ABSTRACT

Background. The clinical response to ertapenem in community-acquired pneumonia (CAP) at the setting of routine hospital practice has been scarcely evaluated.

Methods. We retrospectively compared CAP cases treated with ertapenem or with other standard antimicrobials (controls) at a tertiary 1,434-bed center from 2005 to 2014.

Results. Out of 6,145 patients hospitalized with CAP, 64 (1%) ertapenem-treated and 128 controls were studied (PSI IV-V 72%, mean age 73 years.). A significant higher proportion of bedridden patients (41% vs. 21%), residence in nursing homes (19% vs. 7%), previous use of antibiotics (39% vs. 29%) and necrotizing (13% vs. 1%) or complicated (36% vs. 19%) pneumonia, was observed in the ertapenem vs. non-ertapenem patients. Initial treatment with ertapenem was independently associated with an earlier resolution of signs of infection. In patients aged 65 or older the independent risks factors for mortality were: PSI score (7.0, 95%CI 1.8-27.7), bedridden status (4.6, 95%CI 1.1-20.9) and Health Care Associated Pneumonia (HCAP) (4.6, 95%CI 1.3-16.5). First-line treatment with ertapenem was an independent protector factor in this subgroup of patients (0.1, 95%CI 0.1-0.7).

Conclusions. Ertapenem showed a superior clinical response in frail elderly patients with complicated community-acquired pneumonia, and it may be considered as a first-line therapeutic regimen in this setting.

Key Words: Community-acquired pneumonia, ertapenem, elderly, aspiration, time-to-clinical-stability.

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Uso de ertapenem en la neumonía adquirida en la comunidad en la práctica clínica diaria: estudio de cohortes pareadas

RESUMEN

Introducción. La respuesta clínica a ertapenem en la neumonía adquirida en la comunidad (NAC) en el contexto de la práctica clínica diaria ha sido evaluada de forma insuficiente.

Material y Métodos. Estudio retrospectivo, comparativo de pacientes con NAC tratados con ertapenem o con otros antimicrobianos en un hospital terciario de 1.434 camas en el período 2005-2014.

Resultados. De los 6.145 pacientes hospitalizados con NAC, 64 (1%) tratados con ertapenem y 128 controles fueron incluidos en el estudio (PSI IV-V 72%, edad media 73 años). Se observó una proporción significativamente mayor de pacientes encamados (41% vs. 21%), institucionalizados (19% vs. 7%), con antibioterapia previa (39% vs. 29%) y con neumonías necrotizantes (13% vs. 1%) o complicadas (36% vs. 19%) en el grupo de ertapenem vs. no-ertapenem. El tratamiento inicial con ertapenem se asoció de forma independiente con una resolución más temprana de los signos de infección. En el subgrupo de pacientes con 65 años o más, los factores independientes de riesgo de mortalidad fueron: PSI score (7,0 IC95% 1,8-27,7), encamamiento (4,6 IC95% 1,1-20,9) y la Neumonía Asociada a Cuidados Sanitarios (NACS) (4,6 IC95% 1,3-16,5). El tratamiento en primera línea con ertapenem fue un factor protector independiente en este grupo de pacientes (0,1 IC95% 0,1-0,7).

Conclusiones. El tratamiento con ertapenem se asoció a una respuesta clínica superior en el paciente anciano frágil con NAC complicada y se podría considerar como un régimen terapéutico de primera línea en este contexto.

Palabras clave: Neumonía adquirida en la comunidad (NAC), ertapenem, anciano, broncoaspiración, tiempo hasta la estabilidad clínica.

INTRODUCTION

The incidence of community-acquired pneumonia in adults in Spain is 3-8 cases per 1000 inhabitants/year[1] and at least 20% of the patients require hospitalization. The mortality of CAP in hospital-treated patients is 10-25% and it significantly increases if adequate antimicrobial treatment is delayed[2].

Ceftriaxone, co-amoxiclav (associated to a macrolide) and levofloxacin are the standard empirical treatment of CAP in adults, in accordance with The American Thoracic Society and the Infectious Diseases Society of America (ATS/IDSA) consensus guidelines[3]. However, the increase of beta-lactamase producing Enterobacteriaceae and the changing global resistance patterns of gram-negative organisms, may compromise the efficacy of standard agents in at-risk CAP patients. Ertapenem has been licensed in Europe for the treatment of CAP since 2002 and it is recommended by ATS/IDSA guidelines for the treatment of CAP in selected cases. Nevertheless, guidelines lack detailed clinical profile recommendations. The efficacy of ertapenem in aspiration pneumonia or empyema has not been systematically evaluated to date, and reported experience with this agent in the uncontrolled setting of clinical practice has been limited.

The aim of the study was to compare the clinical response to ertapenem with other antimicrobials among patients admitted to hospital with CAP in routine clinical practice.

METHODS

Setting, participants, and study design. This retrospective observational follow-up study, with a control group, was performed in a 1,434 - bed tertiary university teaching public hospital (providing universal free care to the whole population) in Spain from January 1, 2005 to December 31, 2014.

All adults (18 years or older) hospitalized for CAP and treated with ertapenem during at least 3 days were included in the study. Each ertapenem-treated patient was matched with two controls treated with other parenteral antibiotics. Matching criteria: same PSI risk category[4], according to the chronological order of admission, ± 2 calendar years. Patients were excluded in the case of nosocomial pneumonia (onset ≥2 days after hospital admission), or if they had a diagnosis of lung cancer, bronchiectasias, cystic fibrosis, severe immunosuppression, neutropenia, HIV infection (<200 CD4) or tuberculosis.

Medical records were reviewed to obtain the data. The following groups of variables were recorded: demographic data, co-morbidities, severity, clinical signs, radiological and analytical data, microbiologic studies, antimicrobial treatment, the indication of ertapenem (as first-line, rescue therapy or others), and outcomes. Outcome variables analyzed were time to clinical stability, ICU admission, length of stay, case-fatality rates, and readmission for pneumonia within 30 days. Ethical review board approval was obtained (Registry code CEIC Galicia: 2013/259).

Definitions. Hospitalization criteria have been previously described[5]. Pneumonia was defined as a new infiltrate on chest X-rays and one or more of the following symptoms or signs of acute lower respiratory tract infection: cough, chest pain, fever >38°C, temperature <35°C, and dyspnoea within the previous 24 h[6]. Patients were classified as having HCAP if they acquired pneumonia outside the hospital but fulfilled any of the criteria described in ATS/IDSA guidelines[7]. Criteria for aspiration pneumonia and sepsis were described elsewhere[8, 9]. Complicated pneumonia was defined if at least one of the following were present: respiratory insufficiency, multi-lobar affection, pleural effusion/empyema, bacteraemia or necrotizing pneumonia. Time to clinical stability was calculated as the number of days needed to reach threshold values for all of the following: T^a (≤37.8), heart rate (≤ 100/min), respiratory rate (≤24/min), systolic blood pressure (≥90 mm Hg), and oxygen saturation (≥90 %)[10]. Rescue therapy was defined as the requirement of broader spectrum antibiotics due to persistence or worsening of baseline signs or symptoms or the emergence of new ones. Clinical response was considered if no death or rescue therapy occurred during the episode of pneumonia. Length of stay (LOS) was measured in days and was calculated as the time from admission to the date of hospital discharge. The overall case-fatality rate was considered as death from any cause within 30 days of hospitalization and hospital readmission was evaluated within 30 days after hospital discharge.

Statistical analysis. Qualitative variables were described as frequencies and percentages, and quantitative variables as means ±standard deviation. Associations between variables were studied with the non-parametric Mantel-Haenszel test for paired samples and the chi-squared test or the Fisher's exact test for independent samples. Odds ratio values were also computed. Paired means were compared using the nonparametric Friedman test. For independent samples the Mann-Whitney U test was performed. Variables independently associated with a more prolonged time to reach clinical stability were analyzed by means of a generalized linear model with Poisson response variable, using the log-link function. Statistical analysis was performed with IBM-SPSS software, release 19 (IBM, Armonk, NY, USA), R software v3.2.1 (The R Foundation for Statistical Computing) and Epidat v3.1 (Dirección Xeral de Innovación e Xestión da Saúde Pública, Xunta de Galicia y Organización Panamericana de la Salud (OPS-OMS)). Bilateral p-values <0.05 were considered as statistically significant.

RESULTS

Out of 6,145 patients hospitalized with CAP during the period of the study, 64 (1.0%) who were treated with ertapenem and 128 matched controls, complied with the inclusion criteria. Most patients were male (62.5%) with a mean age of 72.9 years (71.4% of patients >65 yrs. and 23.4% of patients >85 yrs.), and 71.9% of the total population belonged to PSI IV-V risk categories.

Ertapenem was used mainly in monotherapy (58, 90.6%) or concomitantly with a macrolide (3) or a quinolone (3). Ertape-

Table 1 **Clinical and epidemiological characteristics of CAP patients in ertapenem and non-ertapenem treatment groups.**

Variables	Total (n=192)	Ertapenem (n=64)	Controls (n=128)		
	mean±sd	mean±sd	mean±sd	p (Friedman)	
Age (years)	72.9 ± 16.3	70.1 ± 16.6	74.4 ± 16.0	0.716	
Charlson-Index	2.26±1.9	1.8 ±1.6	2.5±1.9	0.050	
	n(%)	n(%)	n(%)	p (Mantel-Hanzel)	OR (IC95%)
Sex (male)	120 (62.5)	46 (71.9)	74 (57.8)	<0.001	1.857 (1.347-2.561)
Previous hospitalization	98 (54.7)	22 (37.3)	76 (63.3)	0.788	0.340 (0.000-489.226)
Cardiac disorder	43 (22.4)	10 (15.6)	33 (25.8)	0.157	0.581 (0.145-2.319)
Vascular disorder	19 (9.9)	2 (3.1)	17 (13.3)	0.049	0.235 (0.087-0.636)
Stroke	29 (15.1)	8 (12.5)	21 (16.4)	0.613	0.722 (0.015-34.963)
Dementia	57 (29.7)	23 (35.9)	34 (26.6)	0.022	1.600 (0.682-3.754)
Respiratory disorder	63 (32.8)	16 (25.0)	47 (36.7)	0.413	0.559 (0.051-6.130)
Peptic Ulcer	15 (7.8)	7 (10.9)	8 (6.3)	0.395	1.857 (0.185-18.610)
Hepatic disorders	16 (8.3)	5 (7.8)	11 (8.6)	0.925	0.900 (0-inf)
Diabetes mellitus	53 (27.6)	17 (26.6)	36 (28.1)	0.954	0.929 (0-inf)
Renal insufficiency	4 (2.1)	1 (1.6)	3 (2.3)	0.596	0.400 (0.010-16.110)
Neoplasia	16 (8.3)	4 (40.6)	12 (9.4)	0.648	0.667 (0.010-48.842)
Bedridden status	53 (27.6)	26 (40.6)	27 (21.1)	<0.001	2.786 (1.682-4.614)
Swallowing disorders	77 (40.1)	28 (43.8)	49 (38.3)	<0.001	1.350 (0.856-2.128)
Residence in nursing home	21 (10.9)	12 (18.8)	9 (7.0)	0.017	4.750 (2.089-10.799)
Current smoker	30 (15.6)	9 (14.1)	21 (16.4)	0.829	0.833 (0.000-7117.875)
Alcohol abuse	25 (13.0)	16 (25.0)	9 (7.0)	<0.001	5.600 (3.146-9.967)
Previous Antibiotics	62 (32.3)	25 (39.1)	37 (28.9)	0.020	1.722 (0.740-4.007)
<1 week	40 (20.8)	17 (26.6)	23 (18.0)	0.235	1.611 (0.309-8.393)
1week-2 months	37 (19.3)	19 (29.7)	18 (14.1)	0.019	2.667 (1158-6.141)
HCAP	54 (28.1)	24 (37.5)	30 (23.4)	0.023	2.125 (0.895-5.045)
Complicated pneumonia	136 (70.8)	51 (79.7)	85 (66.4)	<0.001	2.133 (1.702-2.675)
PSI risk classes					
I	6 (3.1)	2 (3.1)	4 (3.1)		
II	21 (10.9)	7 (10.9)	14 (10.9)		
III	27 (14.1)	9 (14.1)	18 (14.1)		
IV	81 (42.2)	27 (42.2)	54 (42.2)		
V	57 (29.7)	19 (29.7)	38 (29.7)		
Multi-lobar CAP	43 (22.4)	20 (31.3)	23 (18.0)	0.053	2.308 (0.839-6.346)
Empyema	10 (5.2)	7 (10.9)	3 (2.3)	0.025	6.500 (2.709-15.597)
Abscess/Necrotizing CAP	9 (4.7)	8 (12.5)	1 (0.8)	0.002	16.000 (8.642-29.623)

HCAP: health care associated pneumonia, CAP: community acquired pneumonia.

nem was used as first-line agent (31, 48.4%), as rescue therapy (23, 35.9%) and for other indications (10, 15.6%). Among the 128 controls, patients were treated as follows: levofloxacin (39, 30.5%), ceftriaxone + azithromycin (35, 27.3%), co-amoxclav (25, 19.5%), piperacillin-tazobactam (10, 7.8%), co-amoxclav + azithromycin (5, 3.9%), and others (14, 10.9%).

In the ertapenem vs. non-ertapenem group, a significantly higher proportion of bedridden patients (40.6% vs. 21.1%), dementia (35.9% vs. 26.6%), swallowing disorders (43.8% vs. 38.3%), residence in nursing homes (18.8% vs. 7.0%), and antibiotic therapy in the previous 2 months (39.1% vs. 28.9%) was observed. Necrotizing pneumonia and pulmonary abscess (12.5% vs. 0.8%), multilobar pneumonia with ≥2 lobes involved (31.3% vs. 18.0%) or the presence of pleural effusion/empyema (10.9% vs. 2.3%), were present also more frequently in the ertapenem than the non-ertapenem group, respectively (table 1).

An etiologic diagnosis was made in 39 (20.3%) patients, with no differences between groups. Blood cultures were obtained more often in patients who received ertapenem (50, 79.4% vs. 72, 56.3%; p=0.002). Bacteraemia was detected in 3 (6.0%) and 7 (9.7%) patients in ertapenem and controls, respectively (p=0.351). Testing for *Legionella* antigenuria was done similarly between groups (52, 81.3% ertapenem-patients vs. 98, 76.6% controls; p=0.459). The most-frequent microorganisms causing CAP were *S. pneumoniae* (22, 56.4%) and *Enterobacteriaceae* (8, 20.5%), with no significant differences between ertapenem and non-ertapenem treated patients.

In the univariate analysis, no differences in time to clinical stability (2.9±4.3 vs. 2.3±3.2; p=0.250), ICU admission (4.7% vs. 3.1%; p=0.586), 30 day-mortality (12.5% vs. 8.6%; p=0.393) and readmission rates (5.4% vs. 4.3%; p=760), were observed between the ertapenem and non-ertapenem treatment groups. A longer hospital stay was observed in the ertapenem-group (18.0±12.1 vs. 9.3±6.2; p<0.001).

A more prolonged time to reach clinical stability was associated in a multivariate analysis model with PSI-V category, sex (male), dementia and multilobar pneumonia; while, initial treatment with ertapenem was independently associated with an earlier resolution of signs of infection (table 2).

Overall, the independent risk factors for mortality were a PSI-V risk class (5.6, 95%CI 1.7-7.8; p=0.004) and HCAP (3.4, 95%CI 1.1-11.2; p=0.044). In the subgroup of patients aged 65 years or older (n=137), mortality was associated with a bedridden status (4.6, 95%CI 1.1-20.9), PSI score (7.0, 95%CI 1.8-27.7) and HCAP (4.6, 95%CI 1.3-16.5). In this subgroup, a first-line treatment with ertapenem was an independent protector factor for mortality (0.1, 95%CI 0.1-0.7) (table 3).

Table 2 **Variables associated with time to clinical stability. Multivariate analysis.**

Variables	Estimate	Standard error	Z value	*P*
PSI-V category	0.2310	0.1022	2.260	**0.023821**
Sex (male)	0.3218	0.1038	3.101	**0.001932**
Dementia	0.3524	0.1048	3.364	**0.000769**
Pleural efflux/empyema	0.1581	0.1233	1.282	0.199757
Multilobar pneumonia	0.2838	0.1053	2.696	**0.007010**
Necrotizing pneumonia	0.1897	0.2225	0.853	0.393896
Initial treatment with ertapenem	-0.2932	0.1329	-2.207	**0.027337**

Table 3 **Risk factors associated with mortality**

Variables	Overall Population (n=192)			Patients ≥65 years old (n=137)		
	OR	95% IC	p	OR	95% IC	p
Dementia	0.067	0.156-2.853	0.585	0.695	0.141-3.426	0.655
Bedridden status	3.155	0.783-12.716	0.106	4.583	1.004-20.925	**0.049**
Swallowing disorder	2.400	0.577-9.977	0.229	1.761	0.379-8.171	0.470
HCAP	3.405	1.036-11.187	**0.044**	4.551	1.250-16.527	**0.022**
Multilobar pneumonia	0.862	0.227-3.275	0.827	0.949	0.228-3.957	0.943
PSI score	5.571	1.748-7.761	**0.004**	7.002	1.770-27.705	**0.006**
Initial ertapenem treatment	0.214	0.037-1.237	**0.085**	0.071	0.007-0.706	**0.024**

HCAP: health care associated pneumonia

DISCUSSION

In this observational study of clinical practice, ertapenem was used mainly to treat a severely ill elderly population with a poor functional status, at increased risk of aspiration, and in the presence of complicated pneumonia. Bedridden status and severity were also significant risk factors for mortality. A superior clinical response to ertapenem was observed in this scenario, underscoring conditions to use this agent as a first-line antimicrobial treatment.

Ertapenem was licensed in Europe for the treatment of CAP in 2002 based on the results of two clinical trials that compared this drug with ceftriaxone, showing similar efficacy[11,12]. More than a decade afterwards, only a few studies reported the clinical experience with ertapenem in the uncontrolled setting of daily practice[13].

The present observational study included a high proportion of seriously ill patients with complicated pneumonia and a range of clinical presentations (e.g., empyema) that were not captured in the phase III clinical trials. In a previous pooled analysis of the two trials that compared ertapenem with ceftriaxone, the mean age of patients was 57 years and only 25% and 4% of patients belonged to PSI-IV and V categories, respectively[11]. This contrasts with the findings of the present study where the mean age was 73 years and the 42% and 30% of the total population belonged to PSI-IV and V categories, respectively.

Significant differences in demographics and disease characteristics were observed among patients who received ertapenem or standard treatment. In daily practice, clinicians considered ertapenem to treat elderly patients with frailty criteria; particularly, at the suspicion of causing drug-resistant gram-negative bacteria or at the occurrence of complicated or aspiration pneumonia (polymicrobial infections) or failure of previous antimicrobial therapy. This specific approach is in accordance with the recommendations recently published in the Spanish consensus guidelines for the management of community-acquired pneumonia in the elderly patient[14].

A favourable clinical overall response to ertapenem was observed in this setting, consistent with previous findings. Murcia et al. concluded in a retrospective comparative multicenter study that ertapenem was equivalent to the comparator for non-institutionalized elderly patients with severe CAP, and showed significant superiority in patients from nursing homes[13].

In the present study hospital stay was longer in the ertapenem group than in the comparator, which the higher number of abscesses and necrotizing pneumonia cases included in the former, may partially explain. Moreover, ertapenem was indicated as rescue therapy in a significant proportion of cases, which may also have influenced the length of hospitalization. After taking into account the potential confounders, it was observed that patients initially treated with ertapenem presented a faster resolution of signs of infection in the multivariate analysis.

The microbiological diagnosis was reached in only 20% of the episodes, reflecting the difficulty in reaching a microbiological diagnosis when routine hospital testing is performed. *Enterobacteriaceae* was isolated in a quarter of cases. The high proportion on gram-negative bacteria among the isolates is congruent with the characteristics of the described population[15].

Ideally, CAP patients should be treated with antimicrobials guided by microbiological results. However, since the etiological microorganisms are often unknown, clinicians must base their prescribing decisions on the recommendations of treatment guidelines taking into account the local epidemiology. Alternative treatments are recommended if particular risk factors are present. Nevertheless, the particular risk factors for harbouring resistant bacteria are not completely understood.

The treatment failure of CAP has been associated in literature with host-related factors (61%) and resistant pathogens (16%)[16]. Functional status has been cited as an independent predictor for short- and long-term mortality in hospitalized patients[17]. Some authors consider that functional limitations and aspiration pneumonia are key factors impacting decisions about empirical treatment and have not been adequately recognized, although the increasing number of patients in whom those characteristics are present is an obvious change in pneumonia epidemiology, as previously stated by Ewing et al[18].

Bedridden status was an independent risk factor for mortality in this study in patients aged 65 and older, but not in the overall study population. A possible explanation for this finding is that specific underlying pathways of infection may be present in the elderly, differing from pathophysiological mechanisms in younger adults with the same infection.

In this scenario, first-line treatment of CAP with ertapenem led to a superior clinical response in terms of time to reach clinical stability and mortality, compared with standard therapy. The data presented showed subset superiority in the over 65 aspiration patients probably because of the drug's activity against a wide range of both aerobic and anaerobic bacteria. Our usual CAP empiric regimens are active against some oral anaerobic bacteria but are far less potent and have a narrower spectrum than ertapenem. The present study, representative of clinical practice, confirmed the predictions made by Grau et al. in a decision analytic model incorporating current antimicrobial susceptibilities. The authors concluded that treatment with ertapenem compared with ceftriaxone resulted in better clinical outcomes and lower treatment costs (associated with lower therapeutic failures) for two segments of the Spanish population: elderly patients and patients with severe pneumonia (PSI>3)[19].

This study is limited by its retrospective design, including heterogeneous indications and a relatively small sample size. Additionally, it is a single centre study and local epidemiology might have influenced the results. On the other hand, the present study has the strength of evaluating the clinical response to ertapenem under real life conditions, which included using the drug in situations not contemplated in clinical trials.

In conclusion, this study identified several factors associated with time to clinical stability and mortality which may help to identify upon admission patients with CAP, for whom alternative initial treatments, such as ertapenem, may be more appropriate. Further, a prospective controlled study that addressed the optimal regimen for mixed flora aspiration pneumonia would be welcome, as little data currently exists. Future studies are needed to systematically evaluate the efficacy of ertapenem in these situations, and to address the question in a younger population.

ACKNOWLEDGEMENTS

We acknowledge Amparo Otero-Fernández and Noemí López-Varela from the Spanish Clinical Research Network (SCReN), for administrative help in obtaining the Ethical Review Board approval for this project.

DECLARATION OF INTEREST

This study was supported in part by a grant from Merck-Sharp & Dohme de España S.A., Madrid, Spain.

Sponsor's Role: None. Sponsor did not play any role in the design, methods, subjects' recruitment, data collection, analysis and preparation of the manuscript.

All authors state that there is no conflict of interests

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