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Safety profile of cefditoren. A pooled analysis of data from clinical trials in community-acquired respiratory tract infections

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Introduction. A high number of individuals in the population are exposed to antibiotics for the treatment of respiratory tract infections. It is important to review the adverse events profile related to antibiotic exposure during the clinical development of drugs that are or have been recently included in the therapeutic armamentarium.

Material and methods. Safety data from all 13 clinical trials of cefditoren on community acquired respiratory infections were reviewed. Safety population was defined as all randomized patients with at least one dose intake. Adverse events considered by investigators as related during antibiotic exposure were considered.

Results. The overall safety population consisted in 4,592 patients for cefditoren and 2,784 for comparators. Overall reported diarrhoea related to cefditoren administration was significantly higher ($p \leq 0.001$) than comparators (9.9% vs 6.9%) due to the significant difference in the pooled pharyngotonsillitis studies (8.3% vs 3.2%), while no significant differences in others pathologies were found, with 9.4% (with cefditoren) vs 10.3% (with comparators) in the case of community-acquired pneumonia (CAP). Dyspepsia and abdominal pain were reported as adverse events in < 2.7% patients regardless the treated disease. In females population lower related vaginosis rate was found in cefditoren vs comparators, mainly due to differences among patients treated for sinusitis (4.5% vs 8.1%) and CAP (2.3% vs 5.5%) although differences were not significant ($p = 0.017$ and $p = 0.008$, respectively).

Conclusion. This study analysing reported adverse events from clinical trials showed an adverse events profile of cefditoren similar to those of standard antibiotics used in the treatment of respiratory tract infections.

Key words:
Cefditoren. Safety. Clinical trials. Respiratory tract infections. Adverse events.

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Perfil de seguridad de cefditoren. Análisis combinado de los datos de ensayos clínicos en el tratamiento de infecciones respiratorias comunitarias

Introducción. Gran número de sujetos en la población se expone a antibióticos como tratamiento de infecciones respiratorias. Por ello es importante la revisión del perfil de acontecimientos adversos relacionados con la exposición a los antibióticos durante el desarrollo clínico de aquellos que han sido o van a ser incluidos en el arsenal terapéutico.

Material y métodos. Se revisaron los datos de seguridad de 13 ensayos clínicos de cefditoren en el tratamiento de infecciones respiratorias comunitarias. La población para análisis de seguridad se definió con todos los pacientes randomizados que recibieron al menos una dosis de la medicación del estudio. Se analizaron los acontecimientos adversos considerados por los investigadores como relacionados a la exposición al antibiótico.

Resultados. La población para análisis de seguridad consistió en 4.592 pacientes tratados con cefditoren y 2.784 con los comparadores. La tasa global de diarrea comunicada con cefditoren fue significativamente mayor ($p \leq 0{,}001$) que la de los comparadores, debido a la diferencia significativa en el análisis de los estudios de faringoamigdalitis (8,3% frente a 3,2%). No hubo diferencias significativas en las otras patologías estudiadas, con unas tasas de diarrea relacionada de 9,4% para cefditoren y 10,3% para los comparadores en el caso de la neumonía adquirida en la comunidad (NAC). Se comunicó dispesia y dolor abdominal en menos del 2,7% de los pacientes con independencia de la infección tratada o tratamiento. En mujeres, la tasa de vaginosis fue menor con cefditoren frente a comparadores, fundamentalmente debido a las diferencias en sinusitis (4,5% frente a 8,1%) y NAC (2,3% frente a 5,5%), aunque éstas no alcanzaron significación estadística ($p = 0{,}017$ y $p = 0{,}008$, respectivamente).

Conclusión. Cefditoren presenta un perfil de acontecimientos adversos similar al de los antibióticos comúnmente utilizados en el tratamiento de la infección respiratoria comunitaria.

Palabras clave:
Cefditoren. Seguridad. Ensayos clínicos. Infecciones respiratorias comunitarias. Acontecimientos adversos.

INTRODUCTION

Infection, particularly respiratory tract infections, is the major cause of physician visits in the ambulatory care setting.[1,2] Upper respiratory tract infections are annually responsible for 200 visits to physicians/1,000 inhabitants in the United States.[3] Pharyngitis (although more frequent in children) is responsible for an estimated 6.7 million visits to primary care physicians of adults complaining of sore throat,[4] while rhinosinusitis accounts for 1 billion cases of viral etiology per year complicated by 20 million cases of acute bacterial sinusitis in the United States.[5]

With respect to lower respiratory tract infections, Chronic Pulmonary Obstructive Disease is the respiratory disease with the highest prevalence. It presents a prevalence of 9% in population aged > 45 years but increases to > 20% in male smokers aged > 65 years.[6] This type of patients suffers Acute Exacerbations of Chronic Bronchitis (AECB), with around two episodes per year. Half of AECB cases are presumably caused by bacterial infections[7,8] which may respond primarily to antibiotics. Lastly the incidence of Community Acquired Pneumonia (CAP) ranges from 2 to 10 cases / 1.000 inhabitants / year, but with higher rates in elderly patients.[9-11]

Cefditoren (CDN) is an oral 3rd generation cephalosporin that administered as 200 mg or 400 mg bid regimen is approved for the treatment of pharyngotonsillitis, acute sinusitis, mild to moderate CAP and AECB in adults and adolescents (12 years of age or older) by the Spanish Agency (Agencia Española del Medicamento)[12] and the Food and Drug Administration.[13] Cefditoren has shown similar point estimates of success vs comparators (including penicillin, amoxicillin/clavulanic acid, cefuroxime, cefpodoxime and clarithromycin) in the treatment of all above mentioned upper and lower respiratory tract infections.[14,15]

This study presents the results of a pooled safety analysis of all clinical trials of cefditoren in the treatment of community acquired respiratory tract infections.

METHODS

Safety data of cefditoren and comparators in the treatment of upper respiratory tract infections included data from all six prospective, comparative, parallel, randomised, double-blind, multicentre Phase III trials performed: three acute pharyngotonsillitis and three acute sinusitis studies running from 1996 to 1999. Comparators were 400 mg tid penicillin V (one study) and 250 mg qid penicillin VK (two studies) in pharyngotonsillitis trials, and 250 mg bid cefuroxime, 875/125 mg bid or 500/125 mg tid amoxicillin/clavulanic acid in acute sinusitis trials.

With respect to lower respiratory tract infections, safety data were pooled from all six prospective, comparative, parallel, randomised, double blind, multicenter Phase III clinical trials, and one prospective non-comparative trial, conducted from 1996 to 2001. Comparators were 500/125 mg tid or 875/125 mg bid amoxicillin/clavulanic acid and 200 mg bid cefpodoxime in pneumonia studies, and 200 mg bid cefuroxime and 500 mg bid clarithromycin in AECB studies.

Safety population was defined as all randomized patients with at least one dose intake of study medication. Adverse events considered by investigators as related to study medication during antibiotic exposure were considered.

The pooled analysis was performed using absolute data from final study reports of patients included in all clinical trials performed with CDN in respiratory tract infections. Comparison of adverse events rates between different pooled treatment groups (CDN and comparators) was performed using the chi square test or Fisher exact test when necessary. A $p \leq 0.001$ was considered statistically significant in order to reduce the probability of acceptance of false alternative hypotheses due to the multiple comparisons performed between treatment groups including small samples, or due to differences in study designs.

RESULTS

The overall safety population consisted in 4,592 patients for CDN and 2,784 patients for all comparators.

Percentage of patients with related adverse events during the treatment period was similar in CDN vs comparators (table 1) without significant differences ($p > 0.2$) when analysed overall or per-disease.

Table 2 shows per-disease most frequent (> 1%) related adverse events (% patients with a specific adverse event) during the treatment period. While no differences ($p > 0.1$) were found for gastrointestinal symptoms as nausea or dyspepsia between CDN and comparators regardless the infection analysed, diarrhoea was significantly higher ($p < 0.001$) in the CDN vs comparators group in the case of pharyngotonsillitis (8.3% vs 3.2%) or when analysed overall (9.9% vs 6.9%), but not in the case of sinusitis ($p = 0.035$), AECB ($p = 0.002$) or CAP ($p = 0.620$). Percentage of patients with abdominal pain was similar ($p > 0.1$) in the CDN vs comparators group in the case of sinusitis, AECB and CAP, or when analysed overall. Although the percentage of patients with abdominal pain in pharyngotonsillitis studies was higher for CDN (2.6% vs 0.6%), the difference did not reach statistical significance ($p = 0.008$).

Overall, the percentage of female patients with vaginosis was lower with CDN than with comparators, but the differ-

Table 1 Per-disease overall related adverse events during treatment period. Safety population (n) and % of patients with adverse events

Disease		Pharyingotonsillitis	Sinusitis	AECB	CAP	Overall
CDN	n	661	1,177	1,295	1,459	4,592
	%	20.4 %	22.7%	21.9%	25.2%	22.9%
Comparators	n	655	640	798	691	2,784
	%	18.6%	20.3%	23.6%	25.6%	22.2%

ence did not reach statistical significance. The percentage was lower in the case of CAP (2.3% vs 5.5%; p = 0.008) and sinusitis (4.5% vs 8.1%; p = 0.017), and similar in the case of pharyngotonsillitis (1.2% vs 1.9%; p = 0.290) or AECB (5.2% vs 3.1%; p = 0.119) studies.

DISCUSSION

Antibiotics are targeted against prokaryotic bacterial structures not present in human eukaryotic cells, so any action in this latter cells should be considered an adverse event that may have clinical translation or not. The human body also includes the human microbiota (skin, nasopharynx, gut and vaginal microflora) and antibiotic effects on bacterial structures of this microflora may create disbacteriosis that may have clinical translation or not.

Although adverse reactions to antibiotics are usually poorly documented, these drugs have usually a positive risk-benefit ratio, and adverse effects are generally mild and reversible on treatment cessation.[16] However a high number of individuals is exposed to antibiotics since 80% of antibiotic use in the community (where up to 90% of total antibiotic use takes place) is for the treatment of respiratory tract infections,[17] since community acquired respiratory tract infections are the major cause of physician visits in the ambulatory care setting.[1,2] For this reason it is important to review the adverse event profile related to antibiotic exposure during the clinical development of drugs that have shown efficacy in community-acquired respiratory tract infections.[14,15]

A previous overview of adverse reactions to oral antimicrobial agents[18] indicates that nausea and diarrhoea are the most common gastrointestinal adverse events to antibiotics used as comparators in CDN studies. Frequency of nausea is 3-4%, while frequency of diarrhoea is 4% for clarithromycin and cefuroxime, 7% for cefpodoxime and 9% for amoxicillin/clavulanic acid.[18]

In the present pooled analysis the overall reported diarrhoea related to CDN was significantly higher than comparators (9.9% vs 6.9%) due to the significant difference in the pooled pharyngotonsillitis studies (8.3% vs 3.2%), with no significant differences in other treated diseases. In the case of CAP, similar values were obtained for CDN and comparators (9.4% vs 10.3%) and similar to the one re-

Table 2 Per-disease most frequent (>1%) related adverse events (% patients with an specific adverse event) during treatment period

Disease	Drug	n	Diarrhoea	Nausea	Dyspepsia	Abd. Pain	n*	Vaginosis
Pharyngotonsillitis	CDN	661	8.3**	2.7	1.2	2.6	406	1.2
	Comparators	655	3.2	2.9	1.1	0.6	417	1.9
Sinusitis	CDN	1177	10.7	4.3	1.7	1.4	706	4.5
	Comparators	640	7.7	3.0	0.9	0.9	371	8.1
AECB	CDN	1295	10.3	3.3	1.0	1.8	612	5.2
	Comparators	798	6.4	4.8	0.7	1.9	356	3.1
CAP	CDN	1459	9.4	3.3	0.7	1.6	648	2.3
	Comparators	691	10.3	3.5	0.7	1.0	325	5.5
Overall	CDN	4592	9.9**	3.5	1.1	1.8	2372	3.9
	Comparators	2784	6.9	3.6	0.9	1.1	1469	4.6

* only referred to females.

** p <0.001 (CDN vs comparators).

ported as drug-related for amoxicillin/clavulanic acid in a recently published CAP clinical trial (around 10%),[19] regardless the amoxicillin/clavulanic acid formulation and dose (875/125 tid or 200/125 bid). In another CAP clinical trial with these amoxicillin/clavulanic acid formulations, the reported suspected or probably related diarrhoea ranged from 13.0% to 16.5%.[20] This suggests that the reported rate of related diarrhoea under the clinical trials umbrella[20] is higher than that described in overview descriptions of adverse events.[18]

In this pooled analysis, in females, higher rates of related vaginosis were found in comparators vs CDN, mainly due to differences in patients treated for sinusitis and CAP conditions although in both cases differences were not significant ($p = 0.017$ and $p = 0.008$, respectively). An increase in the risk of vaginal candidiasis after oral antibiotic exposure has been previously reported.[21,22]

Cefditoren may offer advantages in the treatment of infections caused by the three most prevalent bacterial isolates from community-acquired respiratory tract infections: *Streptococcus pyogenes* (including the increasing macrolide-resistant phenotype),[23] *Streptococcus pneumoniae* and *Haemophilus influenzae* (including the increasing ß-lactamase negative ampicillin-resistant and ß-lactamase positive amoxicillin/clavulanic acid resistant phenotypes),[24,25] due its intrinsic activity,[25-27] proven its adequate safety profile. This pool analysis analysing reported adverse events in clinical trials showed that the CDN adverse events profile was similar to that of previous antibiotics currently use in the treatment of community-acquired respiratory tract infections.

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