

# Cross-reactivity and Tolerability of Ertapenem in Patients With IgE-Mediated Hypersensitivity to $\beta$ -Lactams

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J Investig Allergol Clin Immunol 2016; Vol. 26(2): 100-105  
doi: 10.18176/jiaci.0019

## ■ Abstract

*Background and Objective:* Administration of carbapenems to  $\beta$ -lactam-allergic patients has always been considered potentially harmful because of a 47.4% rate of cross-reactivity to imipenem reported in a single study. Nevertheless, recent studies have shown that the rate of cross-reactivity of imipenem and meropenem with penicillins is lower than 1%. The aim of this study was to evaluate the possibility of using ertapenem in patients with an established IgE-mediated  $\beta$ -lactam allergy.

*Patients and Methods:* We studied all participants who came to our allergy unit and had a clinical history of immediate hypersensitivity reactions to  $\beta$ -lactams. The inclusion criteria were a positive skin test result to at least 1  $\beta$ -lactam molecule and/or positive specific IgE (when available). All participants underwent immediate-type skin tests with several  $\beta$ -lactam molecules including ertapenem. Challenges with intravenous ertapenem were performed on 2 different days in patients with negative skin test results.

*Results:* We examined 49 patients with a clinical history of immediate reactions to  $\beta$ -lactams. All the patients had positive skin tests and/or positive specific IgE to at least 1  $\beta$ -lactam reagent and negative carbapenem skin tests. Thirty-six patients agreed to undergo the challenges and 35 tolerated the full dose of ertapenem.

*Conclusions:* The practice of avoiding carbapenems in patients with  $\beta$ -lactam allergy should be abandoned considering the very low rate of cross-reactivity.  $\beta$ -Lactam-allergic patients who need ertapenem therapy should undergo skin tests and, if negative, a graded challenge to assess tolerability.

**Key words:**  $\beta$ -lactams. IgE-mediated hypersensitivity. Ertapenem. Cross-reactivity.

## ■ Resumen

*Introducción y Objetivo:* Siempre se ha considerado peligrosa la administración de carbapenems a pacientes alérgicos a betalactámicos por la presencia de reactividad cruzada en el 47,4% de los casos descrita en un estudio previo. Sin embargo, estudios recientes han mostrado que la reactividad cruzada de imipenem y meropenem con penicilinas es inferior al 1%. El objetivo de este estudio es valorar el uso de ertapenem en pacientes diagnosticado de alergia IgE mediada a betalactámicos.

*Pacientes y Métodos:* Se incluyeron todos los pacientes que acudieron a nuestra unidad de Alergia con historia clínica de alergia inmediata a betalactámicos. Los criterios de inclusión fueron prueba cutánea positiva con al menos un betalactámico y/o IgE específica positiva (cuando estuviese disponible). Se realizaron pruebas cutáneas con betalactámicos, incluyendo ertapenem, con lectura inmediata en todos los pacientes. Se realizaron pruebas de provocación endovenosas con ertapenem en los pacientes con pruebas cutáneas negativas frente al mismo en dos días diferentes.

*Resultados:* Se incluyeron 49 pacientes con historia clínica de alergia inmediata a betalactámicos. Todos los pacientes tenían pruebas cutáneas positivas y/o IgE específica positiva al menos a uno de los betalactámicos así como prueba cutánea negativa con carbapenémicos. Treinta y seis pacientes aceptaron la realización de pruebas de provocación con ertapenem que fueron tolerados por treinta y cinco de dichos pacientes.

*Conclusión:* El hecho de recomendar evitar carbapenems en pacientes con alergia a betalactámicos debería ser abandonado, dada la baja reactividad cruzada que presentan. En los pacientes con alergia a betalactámicos que necesiten ertapenem se deberían realizar pruebas cutáneas con el fármaco y en caso de ser negativas, realizar un test de exposición progresiva para confirmar su tolerancia.

**Palabras clave:** Betalactámicos. Hipersensibilidad mediada por IgE. Ertapenem. Reactividad cruzada.

## Introduction

Ertapenem is a 1-beta-methyl-carbapenem that is stable to dehydropeptidase and binds preferentially to penicillin-binding proteins 2 and 3. It has a very broad spectrum of antibacterial activity, including activity against gram-positive and gram-negative aerobic and anaerobic pathogens. However, in contrast to imipenem and meropenem, ertapenem has limited in vitro activity against *Pseudomonas* and *Acinetobacter* species [1].

Administration of carbapenems to  $\beta$ -lactam-allergic patients has always been considered potentially harmful because of a single report of a 47.4% cross-reactivity rate to imipenem [2]. Nevertheless, recent studies have shown that the rate of cross-reactivity of imipenem and meropenem with penicillins is lower than 1% in both adults [3,4] and children [5,6]. Furthermore, a recent study showed a lack of cross-reactivity and tolerability of both aztreonam and carbapenems (imipenem, meropenem, and ertapenem) in a group of penicillin-allergic patients [7]. Finally, tolerability of ertapenem in a group of 42 individuals who reported a clinical history of penicillin allergy was recently demonstrated, although it should be noted that no allergy testing was performed in this case [8].

The aim of this prospective study was to evaluate the possibility of using ertapenem in patients with established IgE-mediated penicillin and/or cephalosporin allergy.

## Methods

Between March 2011 and April 2014, we studied all patients with a clinical history of immediate hypersensitivity reactions to  $\beta$ -lactams seen at the allergy unit of the Università Cattolica del Sacro Cuore in Rome, Italy. The inclusion criteria were a positive skin test result to at least 1  $\beta$ -lactam molecule and/or positive specific IgE when available. The exclusion criteria were pregnancy, treatment with  $\beta$ -blockers, and the presence of cardiovascular, renal, or respiratory disease. A clinical history of anaphylaxis was not an exclusion criterion.

Written informed consent was obtained from all the participants (or from their parents in the case of patients younger than 18 years of age). The study was approved by the local ethics committee (EUDRACT 2009-017828-54) and registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT 01159379).

### Skin Tests

Immediate-type skin tests (prick and intradermal tests) were performed with penicilloyl polylysine (PPL), minor determinant mixture (MDM), and penicillin G at final concentrations of  $1.07 \times 10^{-2}$  mmol/L, 1.5 mmol/L, and 10 000 IU/mL, respectively. Both PPL and MDM were produced by Diater Laboratorios in Madrid, Spain. The maximum drug concentrations were 20 mg/mL for ampicillin, amoxicillin, and piperacillin; 2 mg/mL for aztreonam; 1 mg/mL for imipenem-cilastatin, meropenem, and ertapenem; and 2 mg/mL for ceftazidime, cefuroxime, ceftriaxone, and cefepime.

Skin tests were carried out with the preparation for parenteral use first using the prick method and second, in the

case of negative results, the intradermal method. For the skin prick tests with drugs not available in parenteral form (ie, penicillin V, bacampicillin, cefaclor, and cephalexin) tablets were smashed in a mortar and the powder was dissolved in saline. Histamine (10 mg/mL) and saline were employed as positive and negative controls, respectively. Skin tests and readings were performed as previously described [9,10].

### In Vitro Tests

Assays (UniCAP System, Phadia) were performed for specific IgE to penicilloyl G, penicilloyl V, ampicilloyl, amoxicilloyl, and cefaclor according to the manufacturer's instructions. A value of 0.35 kU/L or less was considered positive. Blood samples were taken at the first evaluation and sera were stored at  $-20^{\circ}\text{C}$  until tested.

### Ertapenem Test Dosing

Challenges with intravenous ertapenem were performed on 2 separate days in patients with negative skin test results. On the first day we administered an initial dose of one-hundredth of the therapeutic dose (10 mg) followed 1 hour later by a dose of one-tenth of the therapeutic dose (100 mg) in patients with a negative result. If the result was again negative, on the second day we administered a full therapeutic dose (1000 mg). During the challenge, all the patients were strictly monitored, with measurement of peak expiratory flow rate, blood pressure, and heart rate at the start of the challenge and 1 hour afterwards. Ready-to-use emergency materials (epinephrine, external defibrillator, oxygen, etc) were available and all the personnel were skilled in treating anaphylaxis.

## Results

We examined 49 patients (11 men and 39 women; median age of 48.1 years [range, 21-76 years]) with a clinical history of immediate reactions to  $\beta$ -lactams. Our work-up was performed at intervals ranging from 1 to 48 months (median, 10.8 months) after the most recent reaction. None of the patients had any exclusion criteria.

The 49 patients experienced 60 immediate reactions, and amoxicillin (plus clavulanic acid) was the most common drug involved. Urticaria and anaphylaxis, as defined by the clinical criteria proposed by Sampson et al [11], were the most commonly reported symptoms (Table).

Seven patients had a family history of IgE-mediated allergic disease and 5 had a personal history of allergic disease: IgE-mediated Hymenoptera venom allergy in 2 cases, respiratory allergy in 2 cases, and shrimp allergy in 1 case.

All the individuals had positive skin tests and/or positive specific IgE to at least 1  $\beta$ -lactam reagent and negative skin test results to carbapenem (imipenem-cilastatin, meropenem, ertapenem) (Table).

Thirty-six patients agreed to undergo the challenges and 35 tolerated the full dose of ertapenem; patient #5 refused to undergo the second part of the challenge and tolerated only 110 mg of ertapenem.

Table. Characteristics of Patients and Skin Test Results

Patient	Sex	Age, y	Drug	Reaction Involved	Specific IgE, kU/L			PPL	MDM	BP	AM	AX	PI	CTX	E <sup>a</sup>	I	Me	CFU	CPM	CLX	CFZ	CCL
					PV	Amy	Axy															
1	M	67	AXC/ CCL	AS/AS	0.07	0.08	0.24	0.20	0.18	-	+	+	-	-	T	-	-	ND	-	-	ND	-
2	F	44	AXC	U	0.01	0.01	0.04	0.12	ND	-	+	-	-	-	T	-	-	ND	-	-	ND	ND
3	F	53	AX	A	0.00	0.03	0.05	0.91	ND	-	+	-	-	-	T	-	-	ND	-	-	ND	-
4	F	42	AXC	UA	0.03	0.01	0.04	0.00	ND	-	+	-	-	-	T	-	-	ND	-	- <sup>b</sup>	ND	-
5	F	55	AX	AS	0.01	0.01	0.09	0.01	ND	-	+	-	-	-	T*	-	-	-	-	-	ND	-
6	F	48	AX	AS	0.01	0.03	0.05	0.03	ND	-	+	-	-	-	T	-	-	-	-	-	ND	-
7	F	32	AXC	AS	0.01	0.01	0.03	0.01	ND	-	+	-	-	-	T	-	-	ND	-	ND	-	-
8	F	58	AXC/ AXC	UA/UA	0.01	0.03	0.05	0.06	ND	-	+	-	-	-	T	-	-	ND	-	ND	-	-
9	F	50	AX	U	4.44	4.63	3.05	2.68	ND	-	-	-	-	-	T	-	-	-	-	-	-	-
10	F	64	AXC	AS	2.69	5.67	4.07	7.89	ND	-	+	+	-	-	T	-	-	ND	-	ND	-	-
11	M	31	AX/ AM	U/AS	0.02	0.05	0.08	0.04	ND	-	+	-	-	-	T	-	-	-	-	ND	-	ND
12	M	54	AM	UA	3.87	2.58	1.16	0.34	ND	-	-	-	-	-	T	-	-	ND	-	-	-	-
13	M	48	AX	UA	0.15	0.37	0.15	0.07	ND	-	+	+	-	-	T	-	-	-	-	-	-	-
14	F	63	AX	A	0.58	2.91	2.20	3.00	ND	+	-	-	-	-	T	-	-	-	-	-	ND	ND
15	F	45	AX	U	0.36	0.33	0.15	0.12	ND	-	-	-	-	-	T	-	-	ND	-	-	ND	-
16	F	48	AXC/ AXC	B/U	0.05	0.07	0.14	0.10	ND	-	+	+	-	-	T	-	-	-	-	-	ND	-
17	F	39	PI	U	0.01	0.04	0.13	0.06	0.11	-	+	+	-	-	T	-	-	ND	-	-	ND	-
18	M	48	AM	AS	11.3	6.88	4.54	0.07	ND	+	+	+	-	-	T	-	-	ND	-	-	ND	-
19	M	70	AXC	UA	0.38	0.72	0.57	2.06	ND	-	+	+	-	-	T	-	-	ND	-	-	ND	-
20	M	21	AX/ AX	U/U	0.03	0.08	0.21	1.24	0.06	-	+	+	-	-	T	-	-	-	-	-	-	-
21	F	53	AXC/ AXC	U/A	N.D.	N.D.	N.D.	N.D.	ND	-	+	+	-	-	T	-	-	-	-	-	ND	-
22	F	65	AXC/ AXC	U/AS	0.09	0.12	0.16	0.10	0.05	-	+	+	-	-	T	-	-	ND	-	-	ND	-
23	F	52	AXC	B	0.19	0.73	0.38	0.65	ND	-	-	-	-	-	T	-	-	-	-	-	ND	-
24	F	67	AXC	AS	8.35	8.69	7.70	4.39	ND	-	+	+	-	-	T	-	-	ND	-	ND	-	-
25	F	50	AXC	AS	0.71	0.14	2.69	1.15	ND	-	+	+	-	-	-	-	-	ND	-	-	ND	-
26	F	42	AXC	U	4.37	7.93	3.75	0.15	ND	-	+	+	-	-	-	-	-	ND	-	-	ND	-



In the absence of in vitro studies to define the antigenic determinants, we divided the patients into 4 groups (Table):

- a) Group 1: patients #1 to #8. These had selective aminopenicillin allergy and some degree of cross-reactivity with aminocephalosporins (patient #1 reacted to cefaclor and patient #4 reacted to a challenge with cephalexin);
- b) Group 2: patients #9 to #35. These reacted to selective penicillin determinants but showed no cross-reactivity with cephalosporins;
- c) Group 3: patients #36 to #41. These reacted only to selective cephalosporin determinants;
- d) Group 4: patients #42 to #49. These reacted to both penicillins and cephalosporins.

## Discussion

Our study confirms the lack of cross-reactivity between penicillins and cephalosporins and ertapenem in a group of patients with demonstrated IgE-mediated hypersensitivity to  $\beta$ -lactams. Previous studies have found a cross-reactivity rate of 7% to 9% among patients who claimed to be allergic to penicillins [11-13]. Cunha et al [8], in turn, found no cross-reactivity between ertapenem and penicillins, either in patients with anaphylactic reactions (urticaria, angioedema) or in those with nonanaphylactic reactions (rash, pruritus, unknown). However, the patients in that study did not undergo allergy testing. The main limitation of the above studies was that patients did not undergo any allergy evaluation, as it has been clearly demonstrated that as many as 80% to 90% of all patients who claim to be allergic to penicillin are not [14]. For these reasons, our study is similar to more recent studies of imipenem and meropenem [3,4,7], although we also included patients with cephalosporin allergy.

Saxon et al [2] observed cross-reactivity to imipenem in 19 of 40 patients with penicillin allergy. The difference between this rate of 47.5% and rates reported by more recent studies may be explained by the fact that all the patients in the study by Saxon et al reacted to benzylpenicillin; this drug is no longer used in southern Europe, explaining why most recently reported allergic reactions are due to aminopenicillins and cephalosporins.

The lack of cross-reactivity between penicillins and ertapenem, imipenem, and meropenem could be explained by the fact that IgE antibodies recognize specific penicillin determinants, such as the thiazolidine ring and side chains, rather than the  $\beta$ -lactam ring which is shared by penicillins, cephalosporins, and carbapenems (patients #1 to #35).

As regards the antigenicity of cephalosporins, both the R1 and the R2 side chains may be involved in the configuration of different epitopes. Once the  $\beta$ -lactam ring has been opened by the amino group of the carrier, the R2 side chain disappears, resulting in heterogeneous fragmentation of the cephalosporin. The resulting epitope is therefore formed by the remaining  $\beta$ -lactam and the R1 side chain [15].

Patients #36 to #41 had a selective response to cephalosporins. In these cases, the main antigenic epitope appears to be the R1 side chain of these molecules; cefazolin, for example, has a single R1 side chain [16], while ceftriaxone has

an aminothiazole side chain. Patients #42 to #49 had positive skin tests to both penicillin and cephalosporin determinants, but did not show cross-reactions with carbapenems.

In conclusion, our data indicate a lack of cross-reactivity between ertapenem and  $\beta$ -lactams, irrespective of the cross-reactivity pattern. Intradermal testing represents a simple yet reliable diagnostic tool with a high negative predictive value. The practice of avoiding carbapenems (and ertapenem) in patients with  $\beta$ -lactam allergy should be abandoned, considering the very low rate of cross-reactivity. A graded challenge, which is a time-consuming procedure, may also be omitted, since several studies have shown the good negative predictive value of skin tests with carbapenems in a large group of penicillin-allergic patients [3-7]. The main limitation of our study is that challenges were not followed by a full therapeutic course. Some authors have proposed prolonged challenges for assessing  $\beta$ -lactam tolerability [17], but this may be helpful for delayed rather than immediate reactions. Our patients all had a confirmed diagnosis of IgE-mediated allergy to a  $\beta$ -lactam moiety and we think a 1-day challenge is sufficient for assessing tolerability. However, since we do not know the sensitizing power of ertapenem in  $\beta$ -lactam-allergic patients after a therapeutic course, ertapenem retesting is recommended to exclude sensitization before any new treatment.

## Funding

The authors received an unrestricted grant from Merck Sharp & Dohme.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Previous Presentation

Part of the data were presented as an oral presentation and abstract at the 2014 XXXIII European Academy of Allergy and Clinical Immunology Congress.

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