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To cite this article: B.A. Cunha, N.S. Hamid, V. Krol & L. Eisenstein (2008) Safety of Meropenem in Patients Reporting Penicillin Allergy: Lack of Allergic Cross Reactions, Journal of Chemotherapy, 20:2, 233-237, DOI: [10.1179/joc.2008.20.2.233](https://doi.org/10.1179/joc.2008.20.2.233)

To link to this article: <https://doi.org/10.1179/joc.2008.20.2.233>



Published online: 18 Jul 2013.



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Safety of Meropenem in Patients Reporting Penicillin Allergy: Lack of Allergic Cross Reactions

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Summary

Over the years, meropenem has become the mainstay of empiric therapy for serious systemic infections in critically ill patients.

Although we have had extensive clinical experience since 1996 using meropenem safely in treating hundreds of patients with reported allergic reactions to penicillin without any adverse events, we have not published our experience. This study was conducted to document our clinical practice experience. Accordingly, over a 12-month period we prospectively monitored 110 patients treated with meropenem reporting penicillin allergic reactions for that 12-month period. Since early empiric therapy in such patients is essential, there is often no time for penicillin skin testing. Penicillin skin testing was not done in this "real world" clinical study. Patients were divided into two groups, depending on the nature of their penicillin allergic reactions. During a 12-month period, 110 patients with non-anaphylactic (59) and anaphylactic (51) penicillin allergic reactions tolerated prolonged meropenem therapy (1-4 weeks) safely without any allergic reactions. Based on these data and our previous clinical experience, there appears to be little/no potential cross reactivity between meropenem and penicillins even in patients with a definite history of anaphylactic reactions to penicillins.

To the best of our knowledge, this is the first prospective clinical study demonstrating that meropenem may be safely given to patients with known/unknown allergic reactions to penicillin, including those with anaphylactic reactions, without penicillin skin testing. We conclude that meropenem may be given safely to patients reporting a history of non-anaphylactic or anaphylactic allergic reactions to penicillins without penicillin skin testing.

Key words: Meropenem, carbapenems, penicillin allergy, penicillin skin testing, carbapenem-penicillin cross reactivity.

INTRODUCTION

For decades, penicillins have been used to treat a variety of infectious diseases. Over time, some individuals have developed allergic reactions to penicillin. The actual incidence of penicillin allergy is difficult to determine in the general population because such estimates have often been based on surveys or, to a lesser extent, on penicillin skin testing studies. There are problems in obtaining an accurate penicillin allergy history, i.e., some patients describe non-allergic side effects, and others cannot remember the exact nature of

the allergic reaction.¹⁻⁶ In clinical practice, few hospitalized patients are evaluated by allergists/immunologists or formally skin tested for penicillin allergy. Furthermore, the major penicillin antigenic determinant for skin testing, benzylpenicilloyl-polylysine, has not been available in the United States since 2004.⁷

Early reports of allergic reactions with cephalosporins suggested high cross reactivity rates with penicillins, i.e., up to 30%.⁸⁻¹⁰ Subsequent careful studies determined the majority of cephalosporin allergic reactions were not, in fact, cross reactions, but were allergic reactions due to other allergens in atopic

individuals. The actual cross reactivity rate between penicillins and cephalosporins is very low, i.e., 1-3%.¹¹⁻¹⁶ In clinical practice, cephalosporins should be avoided in patients reporting anaphylactic penicillin reactions, but may be given with little/no risk to patients reporting non-anaphylactic/non-IgE mediated reactions to penicillins, i.e., drug fever or drug rash.¹⁴⁻¹⁸

To document the lessons learned from our clinical experience since 1996 in treating serious systemic infections in penicillin-allergic patients with meropenem we prospectively monitored hospitalized patients daily for allergy who were receiving prolonged meropenem therapy for 1-4 weeks over the course of a year.

PATIENTS AND METHODS

Patients treated with meropenem consisted of two groups, i.e., those who reported unknown/non-anaphylactic reactions to penicillins, i.e., drug fever or drug rash and those who reported definite anaphylactic/immediate IgE mediated hypersensitivity penicillin reactions. Patients with serious systemic infections with a history of penicillin allergic reaction were treated with meropenem for a duration of 1-4 weeks and assessed daily for allergic reactions by infectious disease physicians. The usual dose of meropenem was 1 g (i.v.) q8h for serious systemic infections in those with normal renal function. In those with renal insufficiency the meropenem dosage was adjusted on the basis of creatinine clearance. In patients with allergic reactions to penicillin, it has not been our clinical practice to do penicillin skin testing. Furthermore, the major penicillin determinant for skin testing, benzylpenicilloypolylysines, remains unavailable in the United States. Exclusion criteria were patients who received meropenem for less than a week since the potential for allergic reaction would be greatest with multiple dosing over days/weeks. Also excluded were patients who received meropenem in combination with another antibiotic except for a few patients with *Clostridium difficile* colitis who were also treated with metronidazole/vancomycin.

The non-anaphylactic group reporting penicillin allergy consisted of 59 patients, and the group reporting anaphylactic reactions consisted of 51 patients. Demographic data for both groups reporting non-anaphylactic and anaphylactic reactions to penicillins were recorded as well as the type of infection and dose/duration of meropenem therapy. (Tables 1, 2)

RESULTS

Fifty-nine (59/110) patients reporting a history of penicillin allergy but were unable to clearly describe the nature of their penicillin allergy. Fifty-one (51/100) patients reported a definite history of penicillin anaphylactic reactions to penicillins, i.e., laryngospasm, bronchospasm, hypotension, shock, angioedema, or

total body, not localized, hives. In both groups, there was a comparable gender/age distribution as well as type/severity of infections. The dose/duration of meropenem in both groups reporting a history of penicillin allergy was also comparable. All patients received prolonged meropenem therapy for 1-4 weeks, depending on the type/severity of infection. The meropenem dosage ranged from 2 g (i.v.) q8h to 500 mg (i.v.) q24h, depending on site of infection and renal function. All patients were monitored daily by infectious disease physicians for potential allergic reactions.

None of the 110 patients in either group developed any allergic reactions to meropenem during the 12-month monitoring period. Most importantly, none of the 51 patients with a history of anaphylaxis to penicillins experienced hypersensitivity reactions, even with prolonged meropenem therapy for 1-4 weeks.

CONCLUSION

Selection of antimicrobial therapy in penicillin-allergic patients is a common clinical problem.^{14,18-21} Surveys reporting the incidence of penicillin allergy vary greatly and are dependent on different criteria to define penicillin allergy. Some physicians have been reluctant to use carbapenems in penicillin-allergic patients.^{22,23} In clinical practice, penicillin skin testing in patients with a history of penicillin allergy is rarely performed.²¹ Since 2004 in the US, the major penicillin skin testing determinant, benzylpenicilloypolylysine, has not been available.⁷ It has recently been shown in a skin testing survey in penicillin allergic patients that meropenem had little/no cross reactivity with penicillins.²⁴

Physicians have been reluctant to use carbapenems in penicillin-allergic patients because of similarities in structure to non-carbapenem β -lactam antibiotics. The reported cross reactivity rates in penicillin-allergic patients receiving carbapenems is very low, but most studies have not separately evaluated imipenem versus meropenem. Carbapenem cross reactivity studies are, in the main, penicillin skin testing surveys in penicillin-allergic patients. Case reports describing carbapenem cross reactivity reactions are rare and have been reported in patients who have received previous therapy with a β -lactam penicillin.

While carbapenems have a β -lactam structure, they are antigenically distinct from β -lactams. Antigenic dissimilarity explains the low cross reactivity rates between β -lactams and carbapenems in the literature and clinical experience.

In studies, there are notable differences between carbapenems in terms of cross reactivity rates in between imipenem-cilastatin and meropenem. It has been shown that there is little/no cross reactivity with meropenem in penicillin-allergic patients by penicillin skin testing.²⁴ Even in combined carbapenem, eg., imipenem-cilastatin and meropenem surveys/studies, cross reactivity is due to the imipenem-cilastatin.²² In contrast, meropenem appears to have minimal or no

TABLE 1 - Meropenem therapy in patients reporting non-anaphylactic allergic reactions to penicillins.

Case Number	Age	Sex	Reaction to Penicillins	Clinical Infection	Meropenem Dose [†]	Meropenem Therapy (weeks)
1.	87	F	Unknown	Ischemic colitis	1 g (IV) q8h	2
2.	48	F	Unknown	Peritonitis	1 g (IV) q8h	2
3.	79	M	Unknown	Urosepsis	500 mg (IV) q24h	1
4.	49	M	Unknown	Sepsis	1 g (IV) q8h	2
5.	82	M	Unknown	Urosepsis	500 mg (IV) q12h	2
6.	80	F	Unknown	<i>C. difficile</i> colitis*	1 g (IV) q8h	2
7.	75	M	Unknown	Pneumonia	500 mg (IV) q24h	2
8.	86	F	Unknown	Urosepsis	1 g (IV) q8h	2
9.	32	M	Unknown	Sepsis	500 mg (IV) q24h	2
10.	92	F	Unknown	Cholecystitis	1 g (IV) q8h	2
11.	81	M	Unknown	<i>C. difficile</i> colitis*	1 g (IV) q8h	2
12.	64	M	Unknown	Severe cellulitis	1 g (IV) q8h	1
13.	80	F	Unknown	Urosepsis	1 g (IV) q8h	1
14.	64	F	Unknown	Sepsis	1 g (IV) q8h	2
15.	71	F	Unknown	Osteomyelitis	1 g (IV) q8h	4
16.	88	F	Unknown	Sepsis, Pneumonia	500 mg (IV) q12h	2
17.	69	F	Unknown	Pneumonia	1 g (IV) q8h	2
18.	73	M	Unknown	Pneumonia	500 mg (IV) q12h	2
19.	70	F	Unknown	Pneumonia	500 mg (IV) q12h	2
20.	87	M	Unknown	Sepsis	500 mg (IV) q12h	2
21.	80	M	Unknown	Fasciitis	500 mg (IV) q12h	2
22.	59	F	Unknown	Osteomyelitis	1 g (IV) q8h	4
23.	88	M	Unknown	Ischemic colitis	1 g (IV) q8h	2
24.	64	M	Unknown	Meningitis	2 g (IV) q8h	2
25.	92	M	Unknown	Pneumonia	500 mg (IV) q8h	2
26.	79	F	Unknown	Urosepsis	1 g (IV) q8h	2
27.	58	F	Unknown	Pneumonia	1 g (IV) q8h	2
28.	76	F	Unknown	Sepsis	1 g (IV) q8h	2
29.	80	M	Unknown	Pneumonia	1 g (IV) q8h	2
30.	47	M	Unknown	Severe cellulitis	1 g (IV) q8h	1
31.	82	F	Unknown	<i>C. difficile</i> pancolitis*, Intra-abdominal abscess	1 g (IV) q8h	2
32.	73	F	Unknown	<i>C. difficile</i> pancolitis*	1 g (IV) q8h	2
33.	84	M	Unknown	Pneumonia	1 g (IV) q8h	2
34.	86	M	Unknown	<i>C. difficile</i> pancolitis*	500 mg (IV) q12h	2
35.	81	M	Unknown	Pneumonia	500 mg (IV) q24h	2
36.	71	M	Unknown	Pneumonia	500 mg (IV) q24h	2
37.	53	F	Unknown	Pneumonia	1 g (IV) q8h	2
38.	87	M	Unknown	Pneumonia	500 mg (IV) q12h	2
39.	56	F	Unknown	Severe cellulitis	1 g (IV) q8h	1
40.	55	F	Unknown	Cholangitis	1 g (IV) q8h	2
41.	59	M	Unknown	Urosepsis	1 g (IV) q8h	1
42.	62	M	Unknown	Pneumonia	1 g (IV) q8h	2
43.	69	F	Unknown	Pneumonia	1 g (IV) q8h	2
44.	80	F	Unknown	Osteomyelitis	1 g (IV) q8h	4
45.	81	F	Unknown	Cholangitis	1 g (IV) q8h	2
46.	81	F	Unknown	Pneumonia	1 g (IV) q8h	2
47.	38	F	Unknown	Pneumonia	1 g (IV) q8h	2
48.	71	F	Unknown	Pneumonia	1 g (IV) q8h	2
49.	69	F	Unknown	Leg abscess	1 g (IV) q8h	1
50.	72	F	Unknown	Urosepsis	1 g (IV) q8h	1
51.	71	M	Unknown	Pneumonia	1 g (IV) q8h	2
52.	34	F	Unknown	Intra-abdominal abscess	1 g (IV) q8h	2
53.	86	F	Unknown	Pneumonia	500 mg (IV) q12h	2
54.	73	F	Unknown	Pneumonia	1 g (IV) q8h	2
55.	73	M	Unknown	Paranasal abscess	500 (IV) q12h	2
56.	80	M	Unknown	Pneumonia	1 g (IV) q8h	2
57.	30	F	Unknown	<i>C. difficile</i> pancolitis*	1 g (IV) q8h	2
58.	71	M	Unknown	Urosepsis	500 mg (IV) q24h	1
59.	82	F	Unknown	Urosepsis	1 g (IV) q8h	1

[†] Meropenem dosing based on creatinine clearance; **C. difficile* colitis: also treated with metronidazole/vancomycin

TABLE 2 - Meropenem therapy in patients reporting anaphylactic allergic reactions to penicillins.

Case Number	Age	Sex	Anaphylactic Reaction to Penicillins	Clinical Infection	Meropenem Dose [†]	Meropenem Therapy (weeks)
60.	35	F	Hives	Hand abscess	1 g (IV) q8h	2
61.	92	M	Hives	Pneumonia	500 mg (IV) q12h	2
62.	80	M	Hives	Parotitis	500 mg (IV) q12h	2
63.	28	F	B/H/S	Pelvic abscess	1 g (IV) q8h	2
64.	66	M	Hives	Pneumonia	1 g (IV) q8h	2
65.	65	M	B/H/S	Urosepsis	1 g (IV) q8h	1
66.	45	M	Hives	Severe cellulitis	1 g (IV) q8h	2
67.	47	M	B/H/S	Pneumonia	1 g (IV) q8h	2
68.	80	M	B/H/S	Urosepsis	500 mg (IV) q12h	1
69.	80	F	Hives	Urosepsis	500 mg (IV) q12h	2
70.	62	M	Hives	Urosepsis	500 mg (IV) q24h	1
71.	33	M	B/H/S	Abdominal wound infection	1 g (IV) q8h	1
72.	58	F	Hives	Osteomyelitis	1 g (IV) q8h	4
73.	73	F	Laryngospasm	Pneumonia	1 g (IV) q8h	2
74.	83	F	B/H/S	Suppurative phlebitis	1 g (IV) q8h	2
75.	40	F	Hives	Intra-abdominal abscess	1 g (IV) q8h	2
76.	53	F	Laryngospasm	Diverticulitis	1 g (IV) q8h	2
77.	76	F	Hives	Meningitis	2 g (IV) q8h	2
78.	76	F	Hives	Severe cellulitis	500 mg (IV) q12h	1
79.	41	F	Hives	<i>C. difficile</i> colitis*	1 g (IV) q8h	2
80.	88	M	B/H/S	Febrile neutropenia	1 g (IV) q8h	2
81.	90	M	Hives	<i>C. difficile</i> colitis*	1 g (IV) q8h	2
82.	92	M	Hives	Endocarditis	500 mg (IV) q12h	4
83.	57	F	Hives	Urosepsis	1 g (IV) q8h	1
84.	45	F	Hives	Sepsis	500 mg (IV) q24h	2
85.	30	F	Hives	Sepsis	1 g (IV) q8h	1
86.	82	F	Hives	Urosepsis	1 g (IV) q8h	2
87.	69	F	B/H/S	Sepsis	1 g (IV) q8h	1
88.	60	M	B/H/S	Sepsis	1 g (IV) q8h	2
89.	75	M	Hives	Severe cellulitis	1 g (IV) q8h	2
90.	90	F	B/H/S	Sepsis	1 g (IV) q8h	2
91.	84	M	Hives	Febrile neutropenia	1 g (IV) q8h	2
92.	64	F	B/H/S	Graft infection	500 mg (IV) q24h	2
93.	78	F	Angioedema	Pneumonia	1 g (IV) q8h	2
94.	80	M	Angioedema	Peritonitis	1 g (IV) q8h	2
95.	94	F	Hives	Ischemic colitis	1 g (IV) q8h	2
96.	75	F	Hives	Pneumonia	1 g (IV) q8h	2
97.	57	M	Hives	Endocarditis	1 g (IV) q8h	4
98.	53	M	Hives	Osteomyelitis	1 g (IV) q8h	4
99.	51	F	Hives	Abdominal wound infection	500 mg (IV) q24h	2
100.	61	F	Laryngospasm	Diverticulitis	1 g (IV) q8h	2
101.	72	M	Hives	Sepsis	1 g (IV) q8h	2
102.	38	M	Hives	Necrotizing pancreatitis	1 g (IV) q8h	2
103.	53	F	Hives	Intra-abdominal abscess	1 g (IV) q8h	2
104.	75	F	Hives	Osteomyelitis	1 g (IV) q8h	4
105.	73	M	Angioedema	Sepsis	1 g (IV) q8h	1
106.	81	F	Hives	Sepsis	1 g (IV) q8h	1
107.	75	F	Hives	Necrotizing pancreatitis	1 g (IV) q8h	2
108.	62	F	Hives	Sepsis	1 g (IV) q8h	1
109.	86	F	Hives	Pneumonia	500 mg (IV) q24h	2
110.	80	M	Hives	Ischemic colitis	500 mg (IV) q24h	2

[†] Meropenem dosing based on creatinine clearance, B/H/S = bronchospasm/hypotension/shock; Hives = total body, not localized, hives; * *C. difficile* colitis: also treated with metronidazole/vancomycin.

potential for allergic cross reactions in penicillin-allergic patients.²⁴

In the largest meropenem safety study published to date, the overall incidence of side effects was less than 0.1%. In this study of 6,000 courses of meropenem therapy, there was not a single anaphylactic reaction.²³ Recently, a case report described a patient who developed a non-anaphylactic hypersensitivity reaction to imipenem-cilastatin and was subsequently treated with meropenem without incident. This suggests that there is no cross reactivity between imipenem-cilastatin and meropenem.²⁶ The authors suggest that meropenem may be safely used in patients with non-anaphylactic hypersensitivity reactions to imipenem-cilastatin. Their report underscores differences in allergic potential between carbapenems, i.e., imipenem-cilastatin versus meropenem and suggests that meropenem may be used safely in imipenem-cilastatin-allergic patients. This has been our clinical experience as well. Since 1996, we have used meropenem safely in hundreds of patients reporting penicillin allergy without prior penicillin skin testing but our experience was never systematically recorded. To document the lessons learned from our extensive clinical experience, we decided to prospectively assess the safety of meropenem in seriously ill hospitalized patients reporting penicillin allergy during a 1-year period. Patients reporting penicillin allergic reactions were divided into two groups, i.e., those who reported unknown or non-anaphylactic allergic reactions to penicillins and those who reported definite anaphylactic reactions, i.e., hypotension, bronchospasm, laryngospasm or total body hives to penicillins. The lack of any allergic reactions in all 110 patients, i.e., reporting anaphylactic (51/110) or non-anaphylactic (59/110) penicillin allergic reactions, supports our years of clinical experience in safely treating hundreds of patients with serious systemic infections with meropenem without penicillin skin testing. Most importantly, no allergic reactions occurred in any of the 51 patients reporting a definite history of anaphylaxis to penicillins—even during prolonged meropenem therapy for 1-4 weeks.

In the "real world" of clinical practice, empiric meropenem is often used to treat serious systemic infections in critically ill patients. Because early empiric therapy is time critical, there is rarely an opportunity for penicillin skin testing. These data and our previous clinical experience indicate that meropenem can be used safely in patients reporting a history of penicillin allergy, particularly those with anaphylactic reactions, and without penicillin skin testing.

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