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THE INTERNATIONAL ARABIC JOURNAL OF ANTIMICROBIAL AGENTS

2012
Vol. 2 No. 2:3
doi: 10.3823/712

Imipenem/cilastatin versus Meropenem on Fever Defervescence in Septic Febrile Patient: A Comparative Prospective Study

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Objective: Meropenem efficacy and tolerability was reported to measure up to imipenem/cilastatin, though some data reported that it may be more efficient in certain clinical and bacteriological settings. Our aim here is to demonstrate any possible difference between the two carbapenems in major septic clinical scenarios. Fever defervescence was selected as a clinical primary "broad" parameter to compare the effectiveness of imipenem/cilastatin and meropenem on fever defervescence in febrile septic patients.

Methods: A prospective multicenter, observational, comparative open label study. The study was conducted in three hospitals between February – September 2009 in Amman-Jordan. Data were collected for patients whom were started on imipenem/cilastatin or meropenem; the study team did not contribute to the antibacterial selection for patients.

Results: Seventy patients were evaluated, thirty-two imipenem/cilastatin and thirty-eight meropenem treated patients. Age mean was 60 and 57.6 years for Imipenem/cilastatin and meropenem respectively. The APACHE II score was similar, mean 14.4 for both study arms. There was no significant difference in rates of clinical diagnoses for both study arms; ventilator-associated pneumonia (VAP), urinary tract infection (UTI), intra-abdominal infections (IAI), blood stream infection (BSI) or for others sources. Additional anti-gram negative agents were administered in 10 and 9 patients, added anti-MRSA agents in 11 and 12 patients, and antifungal agents in 3 and 1 patient in imipenem/cilastatin and meropenem treated patients respectively. There was no significant difference between the mean temperatures (38,6 ^{0}C for both), antimicrobial utilization days (8.33 versus 6.67), mean days for fever defervescence (3.31 versus 2.37, p = 0.36, 95% C.I. (-1.09 - 2.98) for imipenem/cilastatin and meropenem treated patients respectively, mortality was the same.

Conclusion: There is no evidence to support the notion that there is clinical difference in fever defervescence between Imipenem/cilastatin and meropenem in this evaluated group.

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Introduction

Carbapenems are group of useful antibacterial agents that have broad coverage including aerobic (Gram-positive and Gram-negative) and anaerobic pathogens, they are reliable option for the initial empiric treatment of serious infections (1, 2). Imipenem/cilastatin has been in the Middle East for over two decades, a relatively new carbapenem to the area, meropenem was lately introduced. Its efficacy and tolerability

was reported to be similar to imipenem/cilastatin, though some data reported that it may be more efficient in certain clinical and bacteriological studies. (1, 3) Our aim is to demonstrate any possible difference between the two carbapenems in major septic clinical scenarios. Fever defervescence was selected as a clinical primary "broad" outcome measure and mortality as a secondary outcome measure to assess their comparative efficacy. For the treating physician and patients, fever defervescence is a major parameter that demonstrates an adequate response in septic febrile patients to the prescribed antibacterial.

Patients and methods

Study and setup

A prospective multicenter observational comparative open label study evaluating the difference in fever defervescence in adult febrile septic patients, when being treated with imipenem/cilastatin or meropenem, the study was approved by the internal review board of each hospital, study teams has no influence on the treating team for the selection of either antimicrobial. Patients' selection took place by reviewing and following up cases which were treated with the concerned antibacterials. Sampling was done by recruiting all cases that were started on either carbapenem, the treating physicians start their patients on either carbapenem at their discretion. The administered doses were; imipenem/cilastatin 500 mg intravenous every 6 hours, or meropenem 1000 mg intravenous every 8 hours. The study took place in three hospitals in Amman-Jordan with 610 beds, with 69 ICCU beds. The three hospitals host an array of patients including cancer patients, bone marrow transplant, solid organ transplants including kidney in all three hospitals, and one host in addition, liver transplants.

Diagnosis and recruitment of febrile septic patient

All patients with fever were selected defined as; Single rectal temperature of 38.2 C^0 measured within twenty-four hours or two 38C^0 spikes of fever at least two hours apart, and systemic inflammatory response syndrome (SIRS) with suspicion or documentation of microbial cause. (4) SIRS criteria (38°C < Temperature < 36°C, Heart rate > 90 beats/min, Respiratory rate > 20 breaths/min, PaCO2 < 32 mm Hg, 12,000/mm3 < WBC < 4000/mm3, OR > 10% immature (band) forms). Patients' temperature was measured rectally. When (rarely) temperature was measured orally, a 0.5 C^0 was added as a correction factor to account for rectal temperature. Normalized temperature is defined as any twenty-four hours without the above definition for fever. The acute physiologic and chronic health evaluation (APACHE II) score is used as a measure of patient clinical illness severity.

Eligibility

Eligible patients are all febrile septic patients who are ≥ 18 years old. Both genders, meet definition of febrile sepsis, including patients with SSTI, CAP, HCAP, VAP (early and late), UTI, IAI, took carbapenem at least for three days, 500 mg i.v. every 6 hours for imipenem/cilastatin, or 1000 mg i.v. every 8 hours for meropenem. Patients on previous antimicrobials with continuous fever judged to have no response e.g. anti-MRSA agent, and a study antimicrobial was added for non-resolving fever.

Excluded patient are <18 years old, pregnant women or lactating women, took the observed study antimicrobials for less than 3 days, ambiguity and repeated interruption of treatment and CNS infection. Blood culture growing MRSA, VRE or any organism resistant to either carbapenem, unless the patient was not improving on anti-MRSA agent and a study antimicrobial was added for non-resolving fever. Patients whom were on one study drug and switched to the other with fever defervescence in less than 48 hours. Pending mortality defined as death or anticipated death within 24 hours of patients being on either antimicrobial, in addition to violation of the definition of septic patients.

Statistics

The aim of the study is to demonstrate whether there is a difference between imipenem/cilastatin and meropenem in how many days it took either study antimicrobial to defervesce fever in treated patients. The comparison was done by testing the proportion difference between the defervescence days of both antimicrobials. The assumption is that there was no difference, otherwise it would be rejected, and existence of difference is declared. Proportions' difference is assumed normality, its significance is tested by 95% confidence interval (C.I. 95%) and $P \leq 0.05$ was accepted as significance level. The number of patients needed to be studied assuming normal distribution following z statistics is ≥ 30 per study arm.

Outcome measures

The primary measure is the days' difference in that imipenem/cilastatin versus meropenem takes to normalize temperature for ≥ 48 continuous hours. The secondary outcome measure is mortality by discharge, including mortality after starting either study antimicrobial.

Results

Seventy patients were included, thirty-two in imipenem/cilastatin and thirty-eight in meropenem treated patients. Age mean was 60 years for Imipenem/cilastatin and 57.6 years for meropenem. The APACHE II scores were similar (mean = 14.4). The clinical diagnoses were almost similar between the two groups for all diagnoses identified like VAP (early and late), UTI, IAI, BSI, undefined sepsis source or others diagnoses (**Table 1**). Additional gram-negative coverage in combination was utilized in 10 and 9 patients, added anti-MRSA agents in 11 and 12 patients (though no MRSA was isolated later from both arms) and antifungal agents in 3 and 1 respectively in imipenem/cilastatin and meropenem, without significant statistical difference (Data not shown). There was no significant statistical difference in morbidities for both arms including diabetes, hematological malignancies, solid tumors, chronic liver disease and cerebrovascular accidents, but there were four cases of chronic renal failure and one renal transplant in meropenem treated patients. There was no significant difference between the mean temperature (38,6 ^{0}C for both) and antimicrobial utilization days (8.33 versus 6.67, difference = 1.56, 95% P = 0.33, C.I -1.61 – 4.73). The outcome measure; mean days for fever defervescence (3.31 versus 2.37, difference = 0.94 days, p = 0.36, 95% C.I -1.09 - 2.98) for imipenem/cilastatin and meropenem respectively. Mortality in both agents-treated patients was similar (**Table 2**).

Table 1. Patients' characteristics and demographic data for the comparative study of imipenem/cilastatin & meropenem on fever defervescence in febrile adult septic Patient.

Characteristic	Imipenem/ Cilastatin N= 32 (%)	Meropenem N = 38 (%)
Age in years	60.06	57.58
Gender Males	21(65.6)	28 (73.7)
Females	11(34.4)	10 (26.3)
APACHE II Score Range Mean ± S.D	4 – 27 14.43 ± 7.262	2 -40 14.45 ± 10.352
≤ 10	11	18
11 -20	12	9
≥ 21	7	11
Clinical Diagnosis		
Early VAP	2	2
Late VAP	1	1
UTI	5	7
IAI	3	4
BSI	3	4
CAP	4	3
HCAP	1	1
Sepsis (undefined)	7	10
Others*	6	6
Morbidities		
Diabetes mellitus	10	12
Chronic renal failure	0	4
Hematological malignancy	2	1
Solid organ transplant recipient	0	1
Solid tumor	4	2
Chronic liver disease	1	1
Cerebrovascular accidents	3	7
Others	15	24
None	5	7
Not Available	7	3
Other Gram-Negative coverage Agents Added	10	9
Anti-MRSA Agents Added	11	12
Anti-Fungal Agents Added	3	1
Exclusion	4	4

Others*: Hypertension, coronary artery disease, and soft tissue rheumatism, MRSA: methicillin-resistant Staphylococcus aureus
VAP: ventilator-associate pneumonia
IAI: intra-abdominal infection
CAP: community-acquired pneumonia
HCAP: healthcare-associated pneumonia
UTI: urinary tract infection
BSI: blood stream infection

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Table 2. Comparisons in imipenem/cilastatin and meropenem treated patients in temperature, antimicrobial utilization in days, mean days of fever defervescence and mortality in febrile septic patient.

Parameter	Imipenem/cilastatin N = 32	Meropenem N = 38	Difference	P value (95% C.I.) for the difference
Temperature* Mean and ± S.D.	38.6 ± 0.53	38.6 ± 0.63	0.001	0.99 (- 0.28 - 28)
Antimicrobial Utilization Days Mean and ± S.D.	8.33 ± 8.6	6.76 ± 4.2	1.56	0.33 (-1.61 - 4.73)
Mean days to fever defervescence	3.31	2.37	0.94	0.36 (-1.09 - 2.98)
Mortality	6	6	0.0	---

* Temperature maximum reading on the start of therapy
95%CI: Confidence interval at 95% level.
S.D: Standard deviation. N: number

Discussion

Imipenem/cilastatin and meropenem are the only available carbapenems which are indicated in sever sepsis in our part of the world. (1) Ertapenem is also available, but severe sepsis and BSI are not among its labeled uses. However, it is licensed for the treatment of IAI that require or do not require surgery (5, 6, 7), diabetic foot infections, (8) HCAP and inpatient non-ICU HAP. (9, 10)

Earlier studies compared imipenem/cilastatin and meropenem for their in vitro susceptibility in gram-positive and gram-negative isolate, (11, 12) clinical efficacy, tolerability, pharmacodynamic/pharmacokinetic properties, dosing and cost effectiveness analysis. (13, 14, 15, 16) However, there were no studies found comparing fever defervescence as an important clinical indicator of efficacy. This study evaluates both carbapenems in febrile septic patients for fever defervescence, which was our main concern to demonstrate. As this parameter is perceived as an important efficacy parameter for physicians and patients. Both groups had a similar APACHE II score and clinical diagnoses underlying sepsis, including VAP, IAI, UTI, BSI and other unidentified sources.

In conclusion this study demonstrate that the difference in fever defervescence between imipenem/cilastatin and meropenem was not significant, P = 0.36, 95% C.I. (-1.09 - 2.98). Mortality during and at the end of therapy were similar in both groups. Although morbidities appear higher in meropenem, a renal transplant patient, four chronic renal failure patients as well as (others) undefined morbidities. A future study with larger study sample may adjust better for morbidity and microbiological match; it may be needed to amend for some confounders.

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