Comparison of Meropenem with Ceftazidime as Monotherapy of Cancer Patients with Chemotherapy induced Febrile Neutropenia

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Abstract

Background: Ceftazidime is commonly used as monotherapy of cancer patients with fever and neutropenia. Concern, however, has been raised regarding potential for drug resistance due to its widespread use. Meropenem is a new carbapenem with more extended antibacterial spectrum including anaerobes. It provides better coverage against gram positives. Hence, it may offer an advantage over ceftazidime.
Patients and Methods: We prospectively treated 49 patients hospitalized for fever (>38° C) and neutropenia (ANC 500/cmm) with meropenem. We compared their outcome with 50 patients who consecutively received ceftazidime in the immediate past for the same indication.
Results: Comparison of demographic features between the 2 groups revealed no differences in age, gender, type of neoplasm, number of patients with prior antibiotic use, number of days since chemotherapy, absolute neutrophil count and number of patients previously or already hospitalized. Duration of fever, duration of neutropenia and number of patients with pyrexia of undetermined origin were also similar. Therapeutic outcome was same between the two groups. Eighty four percent of patients receiving meropenem and 79% receiving ceftazidime required no modification of the initially assigned therapeutic regimen. Two patients receiving meropenem died. Toxicity was minimal.
Conclusion: We conclude that meropenem offers no significant advantage over ceftazidime in the management of neutropenic febrile patients (JPMA 52:15, 2002).

Introduction

Standard management of neutropenic febrile patients involves immediate hospitalization, prompt institution of empirical antibiotic therapy, provision of skilled nursing care and work-up to elucidate the cause of fever,1'2. Although choice of initial antibiotic varies, monotherapy has become a widely accepted option in most institutions. Monotherapy has been demonstrated as equally effective but more convenient, less toxic and probably cheaper alternative to combination antibiotic therapy3-8. Ceftazidime is the most commonly used agent. Its widespread use, however, has raised concerns regarding potential drug resistance and loss of efficacy over period of time. Meropenem, a new carbapenem, offers a broad spectrum of antibacterial activity against gram-positive and gram-negative organisms as well as anaerobes. Unlike imipenem, side effects are few and drug is extremely well tolerated. Hence, it may have an advantage over cefiazidime as empirical monotherapy of patients with febrile neutropenia. We compared our experience with the 2 drugs.

Patients and Methods

Selection criteria

Patients were eligible for entry into the study if they had fever _ 38°C measured orally atleast twice, 4 hours apart, in a day or a single spike of >_38.5°C, unrelated to the administration of pyrogenic agents and an absolute neutrophil count (ANC) of 500 polymorphonuclear leukocytes (PML) and bands/cmm, or a count of 1,000 PML/cmm that fell to <500 within 24 hrs/ of entry into the study. Reasons for exclusion were: history of hypersensitivity to the study drugs, age 16 years, pregnancy, lactation, hepatic insufficiency (alanine aminotransferase activity _ 4 times normal), significant renal insufficiency (serum creatinine _2.0 mg/dl or need for dialysis), clinical evidence of shock and a history of recurrent pyrexia of undetermined origin.

Study design and treatment regimen

After a detailed history was obtained, each patient underwent evaluation with a thorough physical examination, complete blood count, renal and hepatic function tests, electrolytes and chest radiography. Urine culture and at least two sets of blood cultures were obtained. All possible sources of infection were investigated. Patients received meropenem 1 gm IV stat and every 8 hrs. All patients received their first dose of antibiotic therapy within 2 hrs of presentation. General guidelines for management of neutropenic febrile episodes, such as hygienic diet, proper hand-washing and cleanliness and avoidance of individuals with fever or suspected infections were followed.

For comparative purposes, we selected 50 consecutive patients from our database that had received ceftazidime 2g IV stat and every 8-hr in the immediate past as our standard therapeutic protocol in the same clinical setting. Steroids and growth factors were not routinely used in any of these patients.

Diagnostic criteria and evaluation

Each febrile episode was classified as either due to clinically or microbiologically documented infection or of undetermined origin (PUO). Criteria for microbiologically documented infection were similar to Pizzo et al3. Each patient was physically examined every day. Blood counts were done daily and blood cultures repeated every other day if fever persisted at 38°C or above. Other tests were repeated as needed. Clinical and microbiological outcomes were evaluated at 72 hrs, 7 days after the start of antibiotic treatment and at the resolution of neutropenia. Treatment outcome was classified as success without modification when patient recovered from fever and neutropenia without any modification of the initial regimen. Success with modification involved ultimate recovery from fever and neutropenia but requiring additional treatment with another antibiotic, antifungal, or antiviral agent. Rest was considered failures.

Statistical analysis

Epi Info statistical package (Center for disease control, Atlanta, Georgia) was used for statistical analysis. A •variety of clinical variables at presentation were compared between the two groups and their influence on therapeutic outcome was evaluated.

Results

Clinical characteristics of the 49 study patients who received meropenem are provided in Table 1. Comparative group of 50 patients receiving ceftazidime is also provided.

None had received prophylactic antibiotics, steroids or growth factors. Clinical characteristics are comparable between the two groups. Overall, 38 patients in meropenem and 33 in ceftazidime group had PUO. Eighty-four percent of the patients receiving meropenem and 78% receiving ceftazidime had successful outcome without requiring any modification of the initially assigned antibiotic therapy (Table 1).

Table 1. Clinical characteristics of the study patients.

	Meropenem	Ceftazidime	P-value
Number of patients	49	50	
Mean age in years (SD)	44.0 (18.4)	48.5 (12.4)	0.4
Sex			
Male	16	24	0.1
Types of neoplasm Solid tumor	35	34	0.7
Lymphomas/leukemia	14	16	
Status of cancer			
Progressive diseas Previous hospitalization (4 wks)	12 30	22 34	0.04 0.5
Previous antibiotic use (<4 wks)	20	16	0.4
Day since last chemotherapy (SD)	9.0 (3.7)	9.2 (2.8)	0.8
_7days	14	9	0.2
Number of patients already hospitalized	8	4	0.2
Mean ANC (SD)	203.2 (157.3)	185.3 (152.7)	0.9
_100	23	18	0.3
Duration of fever before admission (SD)	3.6 (3.2)	4.0 (3.5)	0.5
Days with fever post admission (SD)	2.1(2.3)	2.3 (1.8)	0.3
Total days with neutropenia (SD)	5.6 (4.7)	5.2 (4.3)	0.6
Ultimate cause of fever			
PUO	38	33	0.3
Clinical infection	5	10	
Microbiologic infection	6	7	
Therapeutic outcome			
Success without modification	41	39	0.5
Success with modification	6	11	
Failure (Death)	2	0	

Approximately 20% in each group required modification of the initially assigned treatment (in all cases addition of amikacin). There were 2 deaths amongst those treated with meropenem. We also assessed a variety of clinical variables that could have affected the outcome. There were no statistical differences (except for disease status) between the 2 groups (Table 2).

Table 2. Frequency of clinical and laboratory variables assessed at the time of presentation.

Variable	Meropenem	Ceftazidime	p-value
Meansystolic BP(SD)	114.4 (10.3)	116.0 (14.7)	0.7
Meanrespiratory rate (SD)	20.9 (6.3)	18.6 (5.5)	0.1
Dehydration	19	27	0.1
Anaemia	18	16	0.6
Thrombocytopenia	11	14	0.5
Diarrhea	8	15	0.1
Oral candidiasis	11	10	0.7
Severe pain	10	5	0.2
Mucositis	10	10	0.9
Septic appearance	5	11	0.1
Hypotension	2	4	0.4
Bleeding	3	6	0.3
Pneumonia	1	4	0.2
Altered mental status	2	1	0.5
Cardiac dysfunction	1	1	0.9
Bed sores	1	0	0.3
Paraplegia	1	0	0.3
CNS changes	0	1	0.3

Toxicity of therapy was negligible. No renal or hepatotoxicity was observed.

Discussion

Despite theoretical considerations, we observed no advantage of meropenem over ceftazidime as empirical therapy of cancer patients with neutropenic fever. Our results are consistent with two previously published studies[9,10]. Meropenem Study Group reported equivalent efficacy of the two drugs, however, response was lower. This is probably due to differences in the patient characteristics. Majority of the patients enrolled by the Meropenem Study Group had leukemia. In comparison, most of our patients had solid tumors. Several studies have demonstrated that type of underlying neoplasm significantly influences clinical outcome[11-15].

More recently, Feld et al had better success with meropenem than ceftazidime[16]. Meropenem was significantly more effective in severely neutropenic patients, bone marrow transplant patients and those receiving prophylactic antibiotics. We did not observe such a difference. This may be due to small number of subjects as well as absence of transplant patients in our study. Ours is not a randomized study. We prospectively evaluated the patients who received meropenem and compared them with those who received ceftazidime in the immediate past. This may have introduced an unintentional bias. To reduce that possibility, we compared a variety of baseline characteristics between the two groups that may have influenced the clinical outcome. Such characteristics include age, type of cancer, admission status, status of the neoplasm,

burden of illness, dehydration, COPD, hypotension and other co-morbid conditions[11–15]. No significant differences were observed with the exception of more patients with progressive disease in the ceftazidime group. Despite this, ceftazidime was as effective as meropenem. Overall number of patients, however, is small and further studies are needed. In conclusion, we observed no significant differences in efficacy between ceftazidime and meropenem as empirical monotherapy of patients with chemotherapy induced febrile neutropenia. It may be preferable to limit the use of meropenem for selective patients such as those identified by Feld et al[16]. This would minimize the chances of development of drug resistance to an otherwise extremely valuable drug i.e., meropenem.

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