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Research Article

ASSESSMENT OF THE APPROPRIATE UTILIZATION OF IMIPENEM/CILASTATIN IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Background: Imipenem/cilastatin is a broad spectrum antibiotic possessing activity against clinically important aerobic gram positive, gram negative species, and anaerobes. Misuse of this medication has been associated with preventable adverse events, increase in healthcare cost and the emergence of resistant organisms.

Objective: The objective of this study was to evaluate the utilization of imipenem/cilastatin in a tertiary care hospital regarding its indication, dosage, response, and duration of use.

Methods: Charts of all patients receiving imipenem/cilastatin at Rafik Hariri University Hospital (RHUH) during the months of August and September 2008 were reviewed.

Results: One hundred and sixteen patients were included in the analysis. Most studied patients were on the internal medicine floor (44%)(n=55), followed by intensive care unit (ICU) (19%)(n=22) and the oncology floor (15.5%)(n=18). The most common types of infections were urinary tract infections (26.7%)(n=31), respiratory tract infections (17.2%)(n=20), sepsis (14.7%)(n=17), and febrile neutropenia (8.6%)(n=10). The indication of imipenem/cilastatin was appropriate in 96.6% of patients (n=112), questionable in 2.6% (n=3), and inappropriate in 0.9% (n=1). The dose was appropriate in 75.9% of patients (n=88), could not be assessed in 23.3 % (n=27), and inappropriate in 0.9% (n=1). The duration of therapy was appropriate in all patients (100%)(n=116). Therapy was successful in 91 patients (78.4%), could not be assessed in 22 patients (19%), and 3 patients (2.6%) failed to respond to therapy. The most common missing criteria were height and weight in 27 patients. Two patients had seizure episodes while on the medication after which the drug was discontinued.

Conclusion: The use of imipenem/cilastatin was appropriate in the majority of patients. Healthcare professionals should be educated on the importance of obtaining patients' height and weight, since they are required for dose calculation.

Keywords: Imipenem/cilastatin, Antibiotics.

INTRODUCTION

In the late 1970s, a new class of exceptionally broad-spectrum beta-lactams, the carbapenems, was introduced to overcome microbial resistance to older beta-lactams. These carbapenems, including imipenem/cilastatin, have a wide spectrum of antibacterial activity, great beta-lactamase stability, and provide excellent coverage of many Gram-negative and Gram-positive aerobic and anaerobic bacteria (1). For those reasons, imipenem/cilastatin is frequently used empirically as monotherapy in hospitalized patients with serious bacterial infections. In fact, the drug is approved for the treatment of intra-abdominal infections, lower respiratory tract infections, bacterial septicemia, gynecologic infections, urinary tract infections (UTI), bone and joint infections, skin and soft tissue infections, endocarditis and polymicrobic infections (2,3). Its use for empiric coverage should be followed by de-escalation once organisms are isolated by cultures and sensitivity testing in order to treat serious infection immediately and effectively while avoiding antibiotic overuse, potential resistance and excessive cost (4,5,6).

With imipenem/cilastatin being used for over two decades now, the tendency for its misuse is becoming more common (7). Misuse of imipenem/cilastatin such as inappropriate indication or duration can lead to otherwise preventable side effect such as seizure, superinfection, dizziness, pruritus, hypotension and somnolence (8). Also, inappropriate dosing or inaccurate dosage adjustment can lead to underdosing and thus poor response or overdosing and in this case toxicity including neuromuscular hypersensitivity and seizures (8,9).

Another problem that arises with misuse of antibiotics is resistance. Published reports indicate some resistance to imipenem/cilastatin in a variety of gram-negative organisms, including *Pseudomonas aeruginosa*, *Burkholderia cepacia*, *Acinetobacter species*, *Proteus species*, *Serratia marcescens*, *Enterobacter* species, and *Klebsiella pneumoniae* (10, 11). In fact, in a university hospital in Croatia imipenem/cilastatin overconsumption led to changes in resistance to imipenem among *Acinetobacter* strains (12). In addition, a German study showed that periods of extensive imipenem use were associated with significant increases in resistance in *Pseudomonas aeruginosa* (13).

Furthermore, because of the relatively high cost of imipenem/cilastatin, its misuse has been associated with an increase in financial burden on hospitals (14).

Consequently, it is crucial to assess the appropriateness of use of imipenem/cilastatin because of the risks its misuse poses on patient's heath, the excessive but preventable increase in healthcare cost and because of it great impact on resistance.

METHODS

We conducted a retrospective chart review during the month of August and September 2008 at Rafik Hariri Univeristy Hospital (RHUH), a 544 bed medical center that provides acute and tertiary care to patients of all ages in Lebanon and the region. Data collection was done through RHUH's electronic medical record system and all hospitalized patients receiving imipenem/cilastatin during these 2 months were included in the study. The pharmacy department at RHUH maintains a running list of all patients who receive restricted antibiotics, including imipenem/cilastatin. Patients qualifying for the study were identified from these lists. Information gathered include demographic variables, comorbid conditions, physical findings, laboratory and radiographic studies, and patient medical management. Daily follow-up was performed for all patients during their hospital stay to document any changes in their physical findings, clinical status, laboratory and radiological results, and any subsequent alteration in antimicrobial therapy.

Rating of the appropriateness of imipenem/cilastatin use was done through analyzing patient's information one by one and referring to the drug monograph (8), Micromedex™ program, and the IDSA guidelines (15). Therapy success was defined as a resolution of clinical symptoms and normalization of other objective parameters (including white blood cell count, temperature, and radiographs)

while therapy failure was defined as changing imipenem/cilastatin to a different antimicrobial regimen due to inadequate response or evidence of clinical deterioration.

We evaluated the appropriate use of imipenem/cilastatin by examining its indication, dosage, response, and duration of use.

RESULTS

During the study period, 116 eligible patients, 51% of which were females (n=60), were identified. The mean age ± SD was 49.3 ± 26.8 years (range, 1-94 years) and the mean length of hospital stay was 20.2 +/- 11.7 days. Fifty one patients (44%) were managed at the internal medicine (IM) department, and 22 patients (19%) at the intensive care unit (ICU) (Table 1).

The most common types of infection necessitating imipenem/cilastatin use were urinary tract infections (UTI) (26.7%, n=31), respiratory tract infections (RTI) (17.2%, n=20), sepsis (14.7%, n=17) and febrile neutropenia (FN) (8.6%, n=10) (Table 2).

Table 1: Floor distribution

Floor	Number of patients	%
Internal medicine	51	44
Intensive care unit	22	19
Oncology	18	16
Surgery	13	11
Pediatrics	6	5
Cardiac care unit	4	3
Emergency room	2	2

Table 2: Types of infection

Type of infection	Number of patients	%
UTI	31	26.7
RTI	20	17.2
Sepsis	17	14.7
FN	10	8.6
Intra abdominal	10	8.6
Blood	8	6.9
Surgical site	7	6.0
Skin & soft tissue	4	3.4
Questionable	3	2.6
Catheter	2	1.7
Multiple	2	1.7
Endocarditis	1	0.9
Osteomylitis	1	0.9

UTI: urinary tract infection; RTI: respiratory tract infection; FN: febrile neutropenia.

Table 3 summarizes the assessment of the appropriate use of imipenem/cilastatin. Concerning the indication of use, the drug was prescribed appropriately in 96.6% of patients (n=112). One patient (0.9%) was on the drug for an inappropriate indication. In addition, the indication was deemed questionable in 2.6% of patients (n=3) as it was not documented in the medical chart. The dose was appropriate in 88 patients (75.9%). The appropriate dose could not be calculated in 23.3 % of patients (n=27) because of missing information (height and/or weight). One patient (0.9%) was receiving an inappropriate high dose. The duration of therapy was appropriate in all patients (100%). Therapy success was documented in 91 patients (78.4%), while response to therapy could not be assessed in 22 patients (19%) since they died during hospital stay, and 3 patients (2.6%) failed to respond to therapy. Imipenem/cilastatin was given empirically to 104 patients (89.7 %), and was later de-escalated, after results of microbial investigation were available, in all except one patient, who died before culture results were out. Sixty nine (59.5%) of patients were on concomitant antibiotic therapy.

Physicians' orders for imipenem/cilastatin originated from the primary team caring for the patients and was approved by the infectious disease (ID) consultation team or originated from the ID team in 110 (94.8%) of the cases. On the other hand, the ID team was not consulted on 6 (5.2%) patients who received the drug.

Two patients (1.7%) developed seizure while on imipenem/cilastatin.

Table 3: Assessment of Appropriate Use

	Appropriate	Inappropriate	Could not be determined
Indication	112 (96.6%)	1 (0.9%)	3 (2.6%)
Dose	88 (75.9%)	1 (0.9%)	27 (23.3%)
Duration of therapy	116 (100%)	0 (0%)	--
Therapy success	91 (78.4%)	3 (2.6%)	22 (19%)
ID team consulted	110 (94.8%)	6 (5.2%)	--

DISCUSSION

The use of imipenem /cilastatin was appropriate in most of the patients concerning indication, dosing, duration, and response (96.6%, 75.9%, 100%, and 78.4% respectively).

Noticeably, assessment could not be performed in some patients. This was mostly due to missing information, especially when it came to assessing the dose (23.3%). The most common missing criteria were height and weight which prevented us from calculating creatinine clearance, and hence the appropriate dose. Physicians assumed that when creatinine levels were within normal limits, patients had normal kidney function irrespective of the height and weight. In settings where creatinine clearance is not calculated, dose adjustment in renal dysfunction can not be made leading to drug accumulation and toxicity. In our study, the dose was confirmed to be inappropriate in one patient who received a dose higher than required relative to his low creatinine clearance, a case of chronic renal insufficiency. The drug was discontinued after the patient developed seizures. In fact, in the study of Pestotnik et al, 0.2% of patients receiving dosages of imipenem/cilastatin that were excessive with respect to their renal function had seizures (9).

Therapy success was documented in 91 patients (78.4%), while response to therapy could not be assessed in 22 patients (19%) since they passed away during hospital stay. This mortality reflects all causes and may include deaths secondary to non-infectious causes. Thus, the mortality rates do not necessarily reflect therapy failure keeping in mind that the majority of those patients were terminally or critically ill. Three patients (2.6%) failed to respond to therapy and culture results revealed *Acinetobacter* sp sensitive only to colistin.

Only one patient was on the drug for an inappropriate indication. This patient received imipenem/cilastatin prophylactically before surgery, which is not an approved indication.

We could not assess whether the indication for the drug was appropriate in 3 patients. The first patient had fever and throat pain with no clear recorded indication for the antibiotic. The second patient had sudden loss of consciousness and was known to have a history of cerebrovascular accidents (CVA's). The last patient was admitted for CVA.

All patients received the medication for an appropriate duration. In addition, all patients were switched to a narrow spectrum antibiotic once culture results revealed that the microorganism causing the infection was sensitive to that antibiotic.

One patient had an episode of seizure while on the drug and this may be attributed to drug-drug interactions. In addition to imipenem/cilastatin, the patient was on cyclosporine A, which may increase neurotoxicity, and on gancyclovir, which increase the risk of seizures.

A previous study done in Chile tackling the issue of appropriate use of imipenem/cilastatin in a university hospital, found that 58.1% of treatments were considered appropriate and 11.8% inappropriate;

the other 20.6% had been discontinued by physicians in charge prior to evaluation. The main reason for inappropriate use was susceptibility to other antimicrobials compounds (16). Also, the study of Ritchie et al in a retrospective analysis done in a university-affiliated, tertiary-care hospital assessed all courses of imipenem /cilastatin administered to patients over age 60 during a four-month period for appropriateness based on both dosing interval and dosage. Only 37 % of patient days of therapy and 32 % of therapy courses were judged as appropriate based on both dose amount and interval (14). These results were not comparable to our results probably because in our study questionable use of the drug due to missing information were not considered inappropriate. In addition, the overall appropriate use of imipenem/cilastatin at RHUH could be contributed to the antimicrobial restriction policy at the hospital. The antibiotic can be prescribed by any physician, initiated and continued for 48 hours. After 48 hours, the pharmacy department requires a written consult from the ID department to continue dispensing it. ID physicians wrote consults for 94.8% of patients in our study.

Some limitations of our study include being retrospective chart review study and the small sample size. In addition, we could not assess the appropriateness of the drug in some patients due to missing information. The results of this study can not be generalized and are not necessarily representative of the current practice in Lebanon.

In order to maintain satisfactory use of the drug and improve it further, we suggest that the pharmacy department provides healthcare professionals on the floors with inservices and imipenem/cilastatin monograph and templates. Monographs should stress on the appropriate dosage and duration of use in accordance to each indication, and should also include drug-drug interaction and most common and most serious adverse events. The templates on the other hand should include the patient's height and weight, creatinine clearance, indication, regimen (dose and duration) and concomitant medication, and should be filled for each patient receiving imipenem/cilastatin. These preventive measures are expected to decrease medication errors, antibiotic resistance as well as unnecessary healthcare associated cost.

CONCLUSION

In our study, the use of imipenem/cilastatin was appropriate in the majority of patients. However, healthcare professionals should be educated on the importance of complete data entry, especially accurate collection of height and weight, since they are required for dose calculation.

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