Drug Utilization Evaluation of Imipenem in Patients Undergoing Bone Marrow Transplantation

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Abstract

Introduction: Drug Utilization Evaluation (DUE) studies are designed to assess drug usage appropriateness. DUEs have traditionally focused on drugs with high price tags, complicated dosage schedules, narrow therapeutic indices and regular side effects. The primary goal of the present study is to evaluate imipenem usage in Bone Marrow Transplantation (BMT) wards.

Methods: The study was a prospective DUE study, carried out in three BMT wards in Dr. Shariati hospital, Hematology- Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences. The study was performed from April 2008 to October 2008. NCCN Clinical Practice Guidelines in Oncology and AHFS recommended protocols were used for evaluation. For a statistical analysis, SPSS (version 16.0) was used.

Results: A total of 64 patients were evaluated during the study. In all patients, imipenem was started empirically. In thirty five (54.7%) patients, the antibiotic seemed to be effective. Twenty- two (35.9%) patients needed dosage adjustments due to low weight or renal failure, but no action in this regard was taken. In 51.6% of patients, the antibiotic therapy duration was not appropriate. Thirty seven (57.8%) patients experienced nausea.

Conclusion: Imipenem in febrile neutropenic patients is administered empirically. Imipenem induced nausea was observed in 57.8% of patients. This result may be due to rapid infusion of imipenem in the wards. The result of this study indicates the need for further education on dosage adjustment based on renal function and patients' weight.

Improper duration of the treatment could result in resistance and thus should be noted.

Key words: Imipenem, Drug Utilization Evaluation (DUE), BMT

Received: 1, Mar, 2009
Accepted: 20, Mar., 2009

Introduction

Drug Utilization Evaluation (DUE) studies are designed to assess the appropriateness of the usage of various medications.(1, 2) The purpose of a DUE is to describe, verify and finally improve the quality of drug usage. DUE programs will maintain interventions that will improve patient outcomes.(3,4,5) DUEs have traditionally focused on drugs with high price tags, complicated dosage schedules, narrow therapeutic indices and regular side effects. DUEs have addressed broad-spectrum antibiotics, but very few have been devoted to imipenem-cilastatin. The broad-spectrum antibiotics, such as fourth-generation cephalosporins, pipracillin-tazobactam and carbapenems, are prescribed in the empiric therapy of serious nosocomial infections. These antibiotics are also among the most expensive.(6, 7)

The primary goal of the present study is to evaluate antibiotic usage in Bone Marrow Transplantation (BMT) wards. Among all the antibiotics, used in BMT, we chose Imipenem-cilastatin which had not been subjected to any prior DUE or intervention to change physicians’ prescribing behaviors. The investigation was conducted to determine whether prescriptions and the administrations of Imipenem in the hospital complied with the official recommendations. In addition, the data recorded...
about the misuse or inappropriate therapy will be provided to the physicians to evaluate and optimize its administration.

Methods
The study was a prospective DUE study, carried out in three BMT wards in Dr. Shariati hospital, Hematology-Oncology and Stem Cell Research Center, which is affiliated with Tehran University of Medical Sciences (TUMS). The study was performed from April, 2008 to October, 2008. All of the patients, who were included in the study, had gone under bone marrow transplantation procedures.

Observed patterns of drug prescription and administration together with an evaluation of their appropriateness were recorded in a pre-designed form aiming both at improving prescribing habits and preventing inappropriately prescribing in the future.

Appropriateness was determined using a pre-defined guideline, prepared as part of the study. Due to recommendations, Imipenem is one of the choices for febrile neutropenic patients.(8) Fever was defined as a single temperature≥38.3°C orally or single temperature≥38.0°C over one hour. Neutropenia was defined as: <500 neutrophils/mL or <1000 neutrophils/mL and a predicted decline to ≤500/mcL over 48 hours.(9) Criteria for the appropriate usage of imipenem for this indication (Appendix A) were made available to us by using NCCN Clinical Practice guidelines in oncology and the hospital’s protocols.(10, 11) Criteria pertaining to the indication for use, combination therapy, dosage, warnings, monitoring parameters, the administration and drug effectiveness were used.(12,13)

Demographic and clinical data were retrieved from the relevant patients’ charts. Collected data was entered in the computer software SPSS (version 16.0). Independent T-test, logistic regression analysis and a Kaplan-Meyer curve were used for data analysis, with a significance level of p<0.001.

Results
From April, 2008, to October, 2008, a total of 64 inpatients receiving imipenem were identified. The patients were 34 males and 30 females. Mean ± SD age was 32±12 years. Demographic data is shown in table 1.

Imipenem was used for empiric therapy in the febrile neutropenic patients. Patients were distributed among 3 wards (BMT1, BMT2, BMT4). BMT3 was a pediatric ward, which was excluded from our study.

Appendix A: Guidelines for appropriateness of therapy with Imipenem-cilastatin

1. Initiation of empirically selected treatment
   a- infection was acquired in the hospital
   b-patients were febrile or neutropenic or febrile neutropenic
   c-immuno-compromized patients with any sign of infection

2. Continuation of treatment based upon a culture result

3. Continuation of empirically selected treatment
   a-discontinue antibiotic therapy if neutrophils/mL≥500
   b-continue antibiotic therapy if neutrophils/mL<500 till neutropenia disappears, or switch to ciprofloxacin 500mg every 8 hours +co amoxi clav (amoxicillin+clavulonic acid) 500mg every 8 hours, till neutropenia disappears.
   c-continue antibiotic therapy to 7-14 days if neutropenic patients had a stable homodynamic situation.

4. addition of the second antibiotic
   If fever persists after 4 days of starting the first antibiotic, the second antibiotic and an antifungal drug should be added.

5. dosage and administration
   Recommended dose for imipenem in febrile neutropenic patients is 500mg every 6 hours. This dose should be administered through an IV infusion taking at least 20-30 minutes. If higher doses are prescribed (such as: 1g TDS), the infusion time should be 40-60 minutes.

Laboratory tests should be checked daily to monitor patient's homodynamic situation. Blood culture and antibiogram tests should be done after starting antibiotic empirically to evaluate the chosen treatment regimen and make some changes in it, if necessary.

Imipenem was prescribed as 1g every 8 hours for sixty-two of the patients. One patient received 1g every 6 hours and one received 500mg every 8 hours. Dextrose 5% (D5W) was used as a diluting solution for all patients. The mean ± SD infusion time was 26±10minutes. The mean infusion time in BMT1 was 30 minutes, in BMT2 was 22 minutes and in BMT4 was 28 minutes. Thirty-two (46.9%) patients experienced nausea, and five (7.8%) patients experienced nausea, which was resistant to antiemetic drugs. In five (7.8%) patients, creatinine level raised as a result of imipenem infusion. No sensitivity reactions or seizures were reported due to the Imipenem usage. In thirty-five (54.7%) patients, the antibiotic seemed to be effective by lowering patients’ fever during the first five days after starting antibiotic usage. This is shown in figure 1.

Twenty-two (35.9%) patients needed a dosage adjustment due to low weight or renal failure, but no action in this regard was taken. In 51.6% of the patients, the antibiotic therapy duration was not appropriate, as 39.1% of the patients received the antibiotic longer than was needed and in 10.9% the duration was not adequate. In 75% of the cases, the

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Table 1. Characteristics of patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>34</td>
<td>30</td>
<td>64</td>
</tr>
<tr>
<td>Age (mean± SD; years)</td>
<td>32±12</td>
<td>32±12</td>
<td>32±12</td>
</tr>
<tr>
<td>Weight (mean± SD; Kg)</td>
<td>69.34±16.17</td>
<td>64.39±15.57</td>
<td>66.86±15.97</td>
</tr>
<tr>
<td>BMI (mean± SD; Kg/m²)</td>
<td>25.32±5.33</td>
<td>25.91±5.14</td>
<td>25.62±5.24</td>
</tr>
<tr>
<td>BSA (mean± SD; m²)</td>
<td>1.74±0.21</td>
<td>1.75±0.21</td>
<td>1.74±0.21</td>
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<tr>
<td>Transplant type (allogeneic/autologous)</td>
<td>40/24</td>
<td>30/24</td>
<td>30/24</td>
</tr>
</tbody>
</table>

Diagnosis

- AML: 21 (32.8%)
- ALL: 11 (17.2%)
- HD: 7 (10.9%)
- NHL: 7 (10.9%)
- MM: 6 (9.4%)
- Others: 12 (18.8%)

<table>
<thead>
<tr>
<th>Wards</th>
<th>Inappropriate (%)</th>
<th>Appropriate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMT1</td>
<td>11</td>
<td>89</td>
</tr>
<tr>
<td>BMT2</td>
<td>33</td>
<td>67</td>
</tr>
<tr>
<td>BMT4</td>
<td>20</td>
<td>80</td>
</tr>
</tbody>
</table>


Second antibiotic was added to the first one at the appropriate time. In all patients, imipenem was started empirically and the antibiogram test results were not performed for the evaluation of the appropriateness of the therapy or for modifying the empiric therapy, except regarding the patients with persistent fever.

Discussion

According to the result of this study, the inappropriate dosing, administration and prescribing of imipenem is relatively common in our hospital. Imipenem is ordered in febrile neutropenic patients empirically. This performance may be due to the routine protocol of the ward or inaccessibility of antibiogram results, when they are needed. Imipenem induced nausea was observed more than in the reference predictions (59.4 % versus 4%). This result (59.4%) may be due to the rapid infusion of the drug(14) only in 15.6% of administrations, was the duration of infusion long enough (40-60 min).

Imipenem dosage was adjusted for none of the patients with low weight or renal failure during the study. This performance may show that physicians are not obeying the guidelines or that the patients’ data, which is registered, is not being used whenever it is needed.

The Duration of antibiotic therapy with imipenem should be emphasized in BMT wards in order not to use the drug insufficiently (10.9%) or longer than needed (39.1%).(15)

Empiric antibiotic therapy modification should be based on the result of microbial cultures and antibiogram tests when needed.(16) This type of study can alert the physicians, of the need for changes in medications, prescribing patterns and monitoring or the need for dosage adjustment in different indications, special populations, etc. This is mainly useful when a specific prescription is compared with some form of the best practice or guideline. The key physician(s) must then be alerted so that educational programs and protocols can be implemented.(17)

Our study had several limitations. The first concern was the lack of local guidelines for which should be considered the resistance pattern of our center for appropriate imipenem usage. So, physicians, pharmacists or clinical microbiologists may define the appropriate use of imipenem in similar, but not necessarily identical, ways. Also, appropriateness should be evaluated as an adherence with the pre-defined guideline, rather than as an objective fact.(18)

In conclusion, the education and implementation of protocol especially for highly used and expensive medications may be needed in the teaching hospitals to control prescribing patterns and make some necessary changes in them.(19,20) In addition, the data recorded about misuse or inappropriate therapy should be provided to the physicians to evaluate and optimize the drug administration.

Table 2. Summary of the Imipenem usage appropriateness

<table>
<thead>
<tr>
<th>Variable</th>
<th>Inappropriate (%)</th>
<th>Appropriate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Duration of therapy</td>
<td>51.6</td>
<td>48.4</td>
</tr>
<tr>
<td>Infusion time</td>
<td>84.4</td>
<td>15.6</td>
</tr>
<tr>
<td>Antibiotic effectiveness</td>
<td>45.3</td>
<td>54.7</td>
</tr>
<tr>
<td>Dosage adjustment if needed</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Time of adding the second antibiotic</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>Infusion solution</td>
<td>0</td>
<td>100</td>
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</tbody>
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References