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Research article

Drug Utilization Evaluation of Meropenem and Vancomycin In Febrile Neutropenic Patients

Sudhakar. R*[1], Ahamada Safna Mariyam.M[2], Ashok Kumar T. R.[3]

[1]Pharm. D, Nandha College of Pharmacy, Erode.
[2]Assistant Professor, Dept of Pharmacy Practice, Acharya and B.M Reddy College of Pharmacy, Bangalore.
[3]Head of Department, Dept of Pharmacy Practice, Nandha College of Pharmacy, Erode.

Abstract

Background: Cancer patients treated with Cytotoxic chemotherapy drugs are prone to develop febrile neutropenia which is a major cause of infection, requires a prompt and effective use of broad-spectrum antibiotics to prevent infection related mortality and morbidity. The purpose of present study is to evaluate the use Meropenem and Vancomycin in Febrile Neutropenia (FN) patients. **Materials and Methods:** A prospective observational study conducted in hematological oncology ward between February 2014 - July 2014. **Results and discussion:** A total of 113 patients' fulfilled the inclusion criteria, were recruited for the study. The percentage of males and females was found to be 62.83% and 37.16% respectively. The median age of patients was 50 years (ranges from 20 - 80 years). In our study Meropenem and Vancomycin were started empirically in 84.2%, Specific in 15.5% patients. The result shows that Empiric therapy was justified in most of the cases (72%), but continuation of treatment according to the culture reports in several cases was unjustified (45%). Regarding drug utilization monitoring, we observed that out of 34 patients, 21(33.87%) patients were dose adjusted with Meropenem and 2(9.09%) patients with Vancomycin therapy, based on baseline blood urea nitrogen and serum creatinine assessment and 11(17.74%) patients were not adjusted with Meropenem. The gram-negative bacteria (59.4%) are most commonly isolated in our study followed by gram-positive bacteria (40.5%). **Conclusion:** Drug use evaluation studies should be performed as a routine program in hospitals by the clinical pharmacist to evaluate and improve the quality of patient care, especially in treatment with antimicrobial agents.

Key words: Cytotoxic chemotherapy, Febrile Neutropenia, Meropenem, Vancomycin and Drug Use Evaluation.

***Corresponding Author: Sudhakar .R,** Pharm. D Nandha College of Pharmacy, Perundurai main road, Erode- 638052 Tamil Nadu.

1. Introduction

Despite recent advancement in medical science, Cytotoxic chemotherapy remains as a cornerstone for the treatment of hematological malignancies. Cytotoxic chemotherapy drugs have their own plethora of adverse complications. Febrile Neutropenia (FN) is one such severe complication of cancer chemotherapy, and is a major cause of mortality and morbidity [1, 2]. Febrile neutropenia is considered as a serious adverse event and oncologic medical emergency [3-5]. It has been reported that the mortality rates due to FN is 5-10%, and more than 80% of AML patients treated with chemotherapy have at least one episode of fever during neutropenia period [5-7]. Several studies reported that gram-positive bacteria causes 60 to 70% FN in cancer patients' which includes coagulase-negative *Styphylococci* followed by *Styphylococcus Aureus* and *Enterococci Faecium* and gram-negative bacteria includes *Escherichia Coli*, *Pseudomonas Aeuroginosa, Enterobacter Species and Acinetobacter* [8-10]. A rapid assessment and prompt initiation of effective empirical broad spectrum antimicrobial therapy is absolutely essential for managing the patients with FN in order to avoid progression to sepsis. Empiric antibiotics are selected according to the foci and type of infection, patients' characteristics, local pathogens, central venous catheter presence and clinical flora [10, 11-14]. Vancomycin is a glycopeptides antibiotics it is active against gram-positive bacteria including (Methicillin Resistant *Staphylococcus Aureus*) MRSA and *Enterococcal Species* [15]. It has been manifested that treatment with Vancomycin may increase the risk factor of colonisation and infection with *Vancomycin Resistant Enterococci (VRE)*, especially among immune-compromised patients; therefore appropriate use of this antibiotic is very important in preventing of VRE genes to other bacteria [16-18]. Meropenem belonging to carbapenem class of antibiotics was approved by the US Food and Drug Administration (US-FDA), against gram-positive and gram-negative aerobic and anaerobic bacteria, and is used empirically in FN patients [19-20]. Only 10-40% of FN episodes are microbiologically documented, which hampers appropriate antibiotic spectrum adjusted in most of the cases [21].

Drug Utilization Evaluation (DUE) is an effective tool for monitoring the appropriateness of the usage of various medications. It is an essential component of the pharmacy service provision, and clinical pharmacy practice [22]**.** DUEs traditionally focus on drugs with high price tags, complicated dosage schedules, Narrow Therapeutic Indices and regular side effects [23]. Drug use evaluation is an ongoing systematic process designed to maintain the appropriate and medication data before, during and after dispensing in order to assure appropriate therapeutic decision making and positive patient outcome [24].

The purpose of the present study was to evaluate utilization pattern of Meropenam and Vancomycin among Febrile Neutropenia patients.

2. Materials and Methods

This is a Prospective Observational study conducted in hematology-oncology wards at Coimbatore between February, 2014 to July, 2014. An oral informed consent was obtained from each patient prior to the study. Patients' are included in this study if they met all of the following criteria: 1) oral temperature of and above 38.8^0C (101^0F) lasting one hour; 2) Neutrophil

count of <500 cells/mm^3 or a count of <1000 cells/mm3 with predicted decrease to <500 cells/mm^3 within next 48-72 hours; [2, 25-27]. 3) Received chemotherapy prior to the episodes of Febrile Neutropenia. Patients were excluded from the study if they had had fever and fever with neutropenia as a result of their underlying disease, without having received chemotherapy, and who are hypersensitive to these drugs. Each separate hospital admissions for febrile neutropenia are defined as one episode. Bacteremia was defined as blood culture yielding a pathogenic organism.

The patient's relevant information which includes patient's demographics, clinical data, antibiotic regimens and dosing, indications for antibiotic use, culture reports, laboratory values, co-administration of other antibiotics, possible drug interactions, adverse drug reaction and outcomes of therapy, were collected in a pre designed data collection form. Microbiological data and adverse events were collected from patient's record. The data were followed until the discontinuation of Vancomycin and Meropenem or when patient was discharged from the hospital or patient death.

Evaluation Of Antibiotic Use In Accordance With Antibiotic Order Form (AOF)

The patient's charts and all relevant clinical data were received within 72 hours of drug dispensing. They included underlying diseases, site of infection, place where the infection was acquired, reasons for using drug, suspected or known causative bacteria and microbiological investigation of each patient. The patients were followed from the first day to the third or fifth day of treatment when the microbiological results were available. The clinical progress notes of the attending physicians were used to evaluate the clinical outcome on the follow-up day.

Appropriateness of these Restricted Antibiotics was assessed according to the following criteria:

- Evaluation of antibiotic prescribing as stated in the AOF (Antibiotic Order Form).
- Appropriateness of dosage regimen which included route of administration, dosage, dosing interval as well as dosage adjustment in Geriatrics, in patients with hepatic or Renal Function Impairment.
- Re-evaluation of the Empirical treatment when the microbiological and susceptibility data were obtained. Discontinuation, continuation, changing of antimicrobial or dosage regimens was recorded.

Data Analysis

Parameters to be measured

1. Prescribing pattern (empirical or directed therapy).
2. Appropriateness of antibiotic use.
3. Duration of treatment.
4. Culture and antimicrobial susceptibility report.
5. Other antibiotics which were used concurrently with restricted antibiotics.
6. Treatment outcome.

Statistical Method

The information collected regarding all the selected cases were recorded in a Master Chart. Chi-square test was performed and a p-value of ≤ 0.05 was considered to be significant.

3. Results

A total of 113 patients who fulfilled the inclusion criteria, were recruited for the study. The percentage of males and females was found to be 62.83% and

37.16% respectively. The median age of patients was 50 years (ranges from 20 - 80 years). In FN patients treated with Meropenem and Vancomycin, the major underlying disease was found to be Acute lymphocytic leukemia (ALL) with 45.1% followed by Acute myeloid leukemia (AML) 23%, Hodgkin's lymphoma 13.2% and Non-Hodgkin's lymphoma 9.7%. Most (76.9%) of the patients had active disease, i.e., either newly diagnosed or on treatment without having achieved remission, or relapsed. A total of 68 patients (60.1%) were receiving primary chemotherapy, 35 patients (30.9%) received salvage chemotherapy. Another 10 patients (8.8%) underwent bone marrow transplantation. Diabetes and Hypertension is a co-morbid condition identified in our study group followed by Asthma, Rheumatoid Arthritis and Tuberculosis. Detailed patient characteristics are shown in Table 1.

Infection FOCI

Table no.2 represents patients treatment patterns with Meropenem & Vancomycin for FN, the major infection foci was related to central line 37.9% & 28.5%, respiratory tract infection 17.2% & 33.3%, peripheral 31.0% & 9.5% GI 6.9% & 23.8% and others 6.8% & 4.7% respectively which is represented in Table 2.

Microbiology Results

A total of 113 culture reports were received, of these 65 shown positive for culture test. Among these 44 grew gram negative bacteria, 30 grew gram positive bacteria. *Klebsiella Species* and *Streptococcus species* was the most commonly isolated gram negative bacteria and gram positive bacteria respectively which were depicted in table 3. A total of 71 patients treated with Meropenem in which 7 gram-negative isolates were shows resistant to Meropenem and 2 patients show resistance to Vancomycin treated group which is shown in Table 3.

Outcomes of Therapy

The clinical outcomes of the patients' treated with Meropenam and Vancomycin is shown in Table 4. Patients treated with Meropenem shows success in 71(91.0%), failure in 7(8.9%) and success rates with Vancomycin is 33(94.2%), and failure in 2(5.7%).

Appropriateness of Treatment

The appropriateness of antibiotic use is shown in Table 5. Amongst 113 patients 85 patients received appropriate dose of antibiotics based on their weight and renal function. Baseline blood urea nitrogen and serum creatinine was ordered for both the drugs. . Dose adjustment done during the therapy with Meropenem in 21(33.8%), Vancomycin 4(9.09%) in patients and dose was not adjusted in 11 patients treated with Meropenem and 3 patients with Vancomycin. Dosing interval and dilution for Meropenem and Vancomycin was found to be 100%.

4. Discussion

Owing to the rapid progression of infection in FN patients' initial administration of broad spectrum empirical antibiotic therapy and knowledge of the likely pathogen and the local antibiotic sensitivity patterns in individual centers is crucial.

The Inappropriate and Irrational use of Antibiotics is a common practice in healthcare settings, which leads to an increase in the morbidity and mortality rate in community, healthcare settings and resistance development against

antibiotics [28-29]. Appropriate use of antibiotics could be promoted by use of an Antibiotic Stewardship Programme (ASP's) like drug utilization evaluation with a name of maximizing the therapeutic response by limiting the unintended side effects [31]. Drug utilization studies are helpful in understanding the current practice in clinical settings. The results of this study may be helpful for clinicians to improve the patient care. It is also very helpful for health systems decision makers to reduce the costs of treatment by utilizing the Therapeutic drug monitoring (TDM) and culture and sensitivity testing in hospitals [32].

Our results shows that most antibiotic therapy was empirically selected based on clinical judgments and the continuation of the treatment followed by culture results. Our results are comparable with several other previous Drug Use Evaluation studies [1, 21-24]. Bacterial infections are life-threatening complications in febrile neutropenic patients, to prevent this broad-spectrum antibiotics are started empirically in these patients. Beta-lactam antibiotics along with amino glycosides or glycopeptides were considered as gold standard of empirical therapy in febrile neutropenic patients [33].

In our study Meropenem and Vancomycin were started empirically (based on clinical evidence) in 84.2%, Specific (based on culture result) 16(15.5%) patients. The result shows that Empiric therapy was justified in most of the cases (72%), but continuation of treatment according to the culture reports in several cases was unjustified (45%). This result with vast number of Empirical cases indicates that Meropenem is used mainly on the basis of clinical Judgment and experience without considering the Standard Treatment Guidelines [34].

Empirical treatment of Meropenem was more than 95% in a study conducted at Sukhothai Hospital in Thailand [35]. Vancomycin, another cell wall inhibitor, was used empirically in 98% of cases in a study conducted in hematological patients, supports our results [36]. Several investigators evaluated the use of Meropenem as an empirical monotherapy in febrile neutropenic episodes and it was well tolerated. The success rates ranges from 48 to 82% for Meropenem [37]. The study conducted in hematology-oncology wards of teaching hospital by vazin et al., shows that the emperical use of vancomycin shows the effective treatment outcomes in febrile neutropenic patients. The study conducted by Commete et al., shows that the combination therapy with β-lactum antibiotics plus aminiglycosides considered as a standard treatment therapy with febrile granulocytopenic cancer patients [33].

Regarding drug utilization monitoring, we observed that out of 34 patients, 21(33.87%) patients were dose adjusted during the therapy with Meropenem and 2(9.09%) patients with Vancomycin therapy, based on baseline Blood Urea Nitrogen and serum Cr assessment and 11(17.74%) patients were not adjusted the dose with Meropenem. The other study conducted shows 84% adherence to guidelines in relation to the routine drug monitoring of Meropenem [35]. It reflects neglecting monitoring parameters in our practice settings too, since our study shows 67.64% adherence to guidelines for the routine drug monitoring. The other study conducted in Iran shows that appropriate dose adjustment was done in all the study participants [38].

Notifying physicians about long-term cost-saving quality of TDM and use of a consultant

clinical pharmacist for dosing adjustments can improve the treatment standardization. Dose adjustments were necessary for about 11 patients due to diminished renal function that were not performed accordingly in study population. Vazin et al., also reported that in the setting of diminished renal function, appropriate Vancomycin dose adjustments were not performed. This again demonstrates the strong need for more widespread implementation of Clinical Pharmacist's role in Hospital wards [32].

Meropenem is one of the most commonly used broad spectrums with relatively fewer side effects. However studies have shown that two major adverse effects do occur during Meropenem therapy i.e., diarrhea and rashes which should always be considered while using this drug [19]. Another study showed that abdominal discomfort was the most common adverse effect occurred with the use of Meropenem [39].

During our study 3 patients were developed seizures, 4 patients with diarrhea and 3 patients with skin rashes as an adverse drug event of Meropenem and it is over-come by dose adjustment and no adverse event was observed during the treatment with Vancomycin. However none of these side effects observed was of life threatening intensity. This indicates that these drugs were well tolerated by patients and has an acceptable safety profile. In spite of that, Meropenem dosing strategies must be optimized to further decrease in the incidence of side effects.

Lack of documented microbial growth and anti-bigram results may be associated with prolonged courses of unnecessary combined antibiotic regimens. Such methods of antibiotic usage are associated with development of microbial resistance. Optimization of sampling methods and laboratory techniques can improve the culture yield. The gram-negative bacteria (59.4%) are most commonly isolated in our study followed by gram-positive bacteria (40.5%). Microbial resistance to the Antimicrobial treatment is a global issue. In our study, Meropenem shows Resistant to *Klebseilla pneumonia* in three patients and 4 patients with *E.coli* and only 2 patients' shows resistance with Vancomycin treatment. Those patients were treated with the combination of Meropenem and Colistin to overcome this Resistance problem. One of the key contributors to Resistance is prolonged use of Antibiotics. In order to overcome this issue, every institution should bear the responsibility to address the Microbial Resistance Problem [40].

In our study, dosing interval and dilution of the patients treated with Meropenem and Vancomycin was found to be hundred percent. Duration of treatment was calculated and 15.3%, 17.1% patients 1-3 days treatment with Meropenem and Vancomycin, 46.1%, 34.2% patients have 4-7 days, 7-14 days, and in 8.8% of cases observed over use of Meropenem and Vancomycin. In our study, 91.15% of patients treated with Meropenem and Vancomycin showed positive clinical outcome, 8.83% patients showed therapeutic failure, thus they discharged from the hospital against medical advice and death.

Conclusion

Meropenem and Vancomycin is most widely used restricted antibiotics empirically in febrile neutropenic patients. This study can be an alert for physicians and clinical pharmacist to restrict the Antibiotic administrations in unnecessary situations and to emphasize in dose adjustment for drugs like Meropenem and Vancomycin

when needed, in order to reduce adverse drug reactions such as seizures. In addition, the DUE programs should be performed as a routine program in hospitals to evaluate and improve the quality of patient care, especially in treatment with antimicrobial agents. The data documented through DUE program should also be distributed to the physicians to optimize their medication orders.

Table No.1. Patient's demographic details

Patient's demographic information:		
Sex	**NO. OF PATIENTS**	**PERCENTAGE**
Male	71	62.83%
Female	42	37.16%
Age		
20-40 years	38	
40-60 years	44	Median: 50 years
60-80years	31	
Underlying disease		
Acute lymphocytic leukemia	51	(45.1%)
Acute myeloid leukemia	26	(23%)
Hodgkin's lymphoma	15	(13.2%)
Non- Hodgkin's lymphoma	11	(9.7%)
Others	10	(8.8%)
Disease status		
Remission	26	(23.2%)
No remission	87	(76.9%)
Treatment settings		
Primary chemotherapy	68	(60.1%)
Bone marrow transplantation	10	(8.8%)
Presence of co-morbidities		
Yes	80	(70.7%)
No	33	(29.2%)

Table No. 2. Source of infection and treatment patterns.

Infection foci	**MEROPENEM**	**VANCOMYCIN**
Central line	11(37.9%)	6(28.5%)
Respiratory	5(17.2%)	7(33.3%)
Peripheral	9(31.0%)	2(9.5%)
GI	2(6.9%)	5(23.8%)
Others	2(6.8%)	1(4.7%)
Treatment patterns		
Empirical	69(88.4%)	28(80.0%)
Microbiological evidence	9(11.5%)	7(20.0%)

Table No. 3. Organisms isolated from the bacterial cultures (n=65)

Gram-negative bacteria	
Acinetobacter species.	6(14.2%)
Escherichia coli	11(26.1%)
Enterobacter	4(8.79%)
Klebsiella species.	15(35.7%)
Pseudomonas aeuroginosa	8(19.0%)
Subtotal	44(59.4%)
Gram-positive bacteria	
Coagulase negative staphylococcus	6(20.6%)
Bacillus species	4(13.7%)
Staphylococcus aureus	9(31.0%)
Streptococcus species	6(20.6%)
Enterococci species	5(16.7%)
Subtotal	30(40.5%)
Total	74

SUSCEPTIBLE PATTERNS OF ISOLATED ORGANISMS IN FEBRILE NEUTROPENIA PATIENTS

ANTIBIOTICS	SENSITIVITY	RESISTANCE
MEROPENEM	71	7
VANCOMYCIN	33	2

Table No.4. Clinical outcomes of patients treated with Meropenem and Vancomycin

GROUPS	SUCCESS		FAILURE		X^2 VALUE
	No. of Patients	Percentage	No. of Patients	Percentage	
Patients treated with Meropenem (78)	71	91.0%	7	8.9%	0.343
Patients treated with Vancomycin (35)	33	94.2%	2	5.7%	

'p' value *<0.05 is consider as significant (X^2 standard value is 3.84)

Table No. 5. Appropriateness of Meropenem and Vancomycin therapy (*n=113*)

APPROPRIATE UTILIZATION	MEROPENEM	VANCOMYCIN
Maintenance dose		
Dose adjusted during therapy	21(32)	4(7)
Dose not adjusted during therapy	11(32)	3(5)
Dosing interval	78(100%)	35(100%)
Dilution	78(100%)	12(100%)
Duration of treatment		
1-3 days	12(15.3%)	6(17.1%)
4-7 days	36(46.1)	12(34.2%)
7-14 days	23(29.4%)	15(42.8%)
More than 14 days	7(9.0%)	2(5.7%)

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