Drug utilization evaluation of meropenem and correlation of side effects with renal status of patients in a teaching based hospital

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Abstract: Meropenem is a restricted, broad spectrum and expensive antibiotic. The major consequences of irrational use of restricted antibiotics are increase drug resistance and drug expenditure. The use of antibiotics, specifically restricted antibiotics, must be monitored continuously to increase its adherence to the standard guidelines to avoid such problems. The objective of this study was to evaluate the appropriateness of meropenem use with respect to renal status of patients in a teaching based hospital. A retrospective study was carried out from 1st January 2013 to 30th June 2013 to determine the evaluation of meropenem use in accordance to the criteria developed through national (Infectious disease society of Pakistan) and international guidelines (Health care infection control practices advisory committee). The data was recorded on data collection form by thorough reviewing of patients' medical records. Main outcomes measured were indication, dose, interval, duration, creatinine clearance, complete blood count and culture sensitivity test. Correlation of different variable (side effects and generalized health) was also observed with reference to renal status of patients. Statistical analyses were performed using descriptive statistics. A total of 201 cases of meropenem prescription were identified during the study period. The variable, which was most consistent with the criteria was 'indication', in which 97.52% of meropenem prescription was indicated in diseases encouraged by guidelines. However, the use of meropenem as an empirical therapy was the major problem reported in this study as it adhered to in only 43% of the cases. It was also noted that prevalence of side effects increased when meropenem was prescribed in renal compromised patients, and also observed that generalized health of patients decreased with meronem use in renal unstable patients. Thrombocytopenia was the major problem associated with the meropenem use (37.81%). The study detected various areas where use of meropenem was not according to the standards. Strict policies and procedures need to be implemented to use meropenem in line with the standard guidelines.

Keywords: Drug utilization evaluation, meropenem, clinical pharmacy.

INTRODUCTION

The inappropriate and unnecessary use of antibiotics is a common practice in health care setting (Hersh *et al*., 2011, Istúriz and Carbon, 2000). It has been observed that irrational utilization of antibiotics lead to an escalation in the morbidity and mortality rate in community, healthcare cost and development of resistance against antibiotics (French, 2005, Monroe and Polk, 2000). Appropriate use of antibiotics could be promoted by use of an antibiotic stewardship program like drug utilization evaluation (DUE) with an aim of maximizing the therapeutic response while limiting the unintended side effects (Dellit *et al*., 2007). DUE is an ongoing, systematic criteria-based evaluation of drug use that helps to ensure that medicines are used appropriately at an individual patient level (World Health Organization, 2002). The overall objective of DUE is to promote rational medication use. Rational use of medicines is essential to practice in health care setting as drugs are expensive and they constitute a large percentage of health care cost (Kleinke, 2001). WHO has defined rational use as 'patients receive medicines appropriate to their clinical needs, in doses that meet their own requirements for an adequate period of time, and at the lowest cost to them and their community (WHO, 2002) .

Antibiotics are one of the most common drugs prescribed in hospitals today. The use of antibiotic in hospitals has been a major concern in the last few decades for several reasons. It has been estimated that up to two third of all patients receive at least one antibiotic during hospitalization and the cost involved is therefore correspondingly high and up to 40% of a total hospital's drug expenditure may be devoted to the purchase of antibiotics (Mauldin *et al*., 2010). From Administration point of view, it has contributed to the significant rise in hospital budget. Furthermore, from community perspective, inappropriate usage of antibiotic is considered to be a major reason for development of drug resistance against various pathogens. Similarly, patients have also suffered in the past due to increased side effects of antibiotics (Kleinke, 2001).

In view of the above-mentioned problems, various societies and organizations have developed strict policies and procedures for antibiotic usage; especially for restricted antibiotics. This is because restricted antibiotics

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are more susceptible of producing unintended outcomes with major problem of adverse effects and resistance. Hence, there is a need to monitor continuously the effect of, and adherence to, the hospital antibiotic policies.

DUE is an appropriate tool to monitor the use of restricted antibiotics in hospital settings and compare it with the standard guidelines (Gupta *et al*., 1997). Meropenem is a broad spectrum restricted antibiotic effective against Gram positive and Gram-negative organism and also against anaerobes. Various researchers have proved that meropenem is equally or more effective than conventional choices in conditions like febrile neutropenia and urinary tract infections, thereby increasing the frequency of prescriptions (Klastersky *et al*., 2000, Talcott *et al*., 1992). However, at the same time, the drug is comparatively of high cost and can produce unintended side effects if not used appropriately, as they are mainly eliminated by kidneys and dose adjustment in patients with renal impairment is necessary. There is a need to ensure that meropenem must fully comply with the standard guidelines so that the maximum benefits can be extracted from its use without any troublesome effects.

The objective of this study was to evaluate the utilization pattern of meropenem in a teaching based hospital and to correlate its variables with the renal status of patients.

METHODS

This study was a retrospective drug utilization study carried out in different wards of multispecialty, 600 beds teaching based hospital well equipped with latest diagnostic techniques. The hospital also provides services in cardiology, gastroenterology, infection control, critical care, paediatrics, neonatology and surgery.

The study was conducted for the period of 6 months from 1st January 2013 to 30th June 2013 in study hospital. All those patients who were prescribed with meropenem were included in this study. Subjects were identified by meropenem orders submitted to pharmacy department of the hospital and also from the daily review of patients profile and their medication chart in each of the participating wards.

The data was collected on a pre designed data collecting tool by a clinical pharmacist. All the relevant information were extracted by thorough reviewing of patient profile and were recorded on the data collection form. In case of any query or difficulty in interpretation of any information, resident doctors were consulted to build a consensus on any existing issue. The confidentiality of patients was highly maintained.

Demographic information, clinical data, indication, dose, frequency, duration of therapy, culture reports, creatinine clearance, co administration of other antibiotics, possible drug interactions, adverse drug reactions and the outcomes of therapy were observed and noted in the data collection form. Response of meropenem was mainly evaluated on the basis of fever, total leukocyte count and overall stability of patients. The reported data was then analyzed in accordance with criteria developed in view of national (Infectious disease society of Pakistan) and international (Health care infection control practices advisory committee) guidelines and on the basis of criteria used in previous published studies (Brink *et al*., 2004, IDSOP, 2012, Lledo *et al*., 2009, Ouwuttipong, 2010). The important points considered while developing the criteria were; it should be supported by national drug compendia, unbiased drug information and peer reviewed literature. The relationship between renal status of study participants and side effects with general health of patients (fever, total leukocyte count and over all stability of the patient), were also observed. The relationship was observed by categorizing the renal status of patients in 4 groups according to the value of creatinine clearance (Kotapati *et al*., 2004, Kuti *et al*., 2004, Kuti *et al*., 2003) and relationship was observed between the frequency of side effects and patients having different creatinine clearance value. Descriptive analyses of data were performed using SPSS software (SPSS Statistics for Windows, Version 17.0, Chicago) and the results are expressed in frequency and percentage.

The study protocol was approved by the ethical committee of the study hospital.

Criteria for the appropriate use of meropenem

Meropenem should be considered for severe life threatening infections like sepsis.

It should be used for documented Gram-negative infections involving multiple resistant organism.

It could be used as an empirical therapy for severe life threatening infections.

Antimicrobial therapy for all serious infections should be administered without delay and reassessed within 2-3 days to determine if step down to narrower regimen is possible.

Creatinine test report must be obtained within 48 hrs prior to drug initiation and at least once a week for normal patients and twice a week for renal compromised patients.

Doses must be corrected based on creatinine clearance

Culture and Susceptibility reports must be obtained within 72 hrs of drug initiation and decision to continue or withdraw drug should be made accordingly.

In case of documented therapy, culture and Susceptibility test should be repeated at least once a week.

Complete blood count must be obtained within 48 hrs prior to drug initiation and at least once a week during therapy.

The appropriate use of meropenem in different disease conditions are as mentioned in table 1

The renal adjusted doses of meropenem should be as it is mentioned in table 2

RESULTS

During a study period of 6 months, 201 cases of meropenem were identified. The major use of meropenem was observed in pneumonia (27.36%, n=55) while in otitis infection only a single course of therapy was noted (0.4%, n=1). The results showed that meropenem was also prescribed in renally compromised patients; however the prescription of meropenem in such patients was less in numbers as compared to renally stable patients. The meropenem was used more frequently as an empirical therapy, followed by documented therapy and prophylactic therapy respectively. Further evaluation of meropenem use acknowledged that amikacin and vancomycin was the two most co-prescribed antibiotics with meropenem. Demographic information is summarized in table 3.

Table 1: Appropriate use of meropenem in different disease conditions

Diseases Condition	Dosage
Malignant otitis externa	1 g IV
Peritonitis mild to moderate (intra abdominal)	1 g IV
Acute uncomplicated pylonephritis	500 mg
Osteomyelitis polymicrobial	1 g IV
Cellulitis	1 g IV
Nacrotizing Fasiitis	1 g IV
Sepsis	1 g IV
Meningitis	2 g IV
VAP* in penicillin allergy	1g IV

*Ventilator associated pneumonia Frequency of administration and duration of use in all disease condition is eight hourly and 7-14 days respectively.

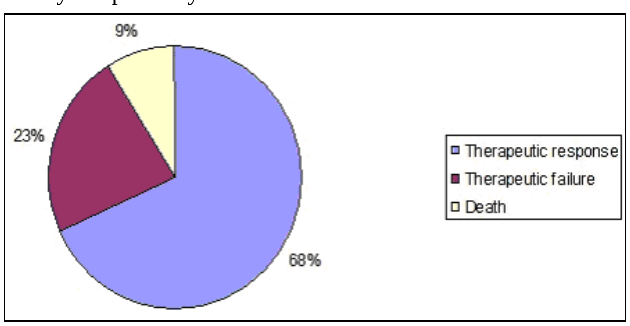

Fig. 1: Clinicaloutcomes after meropenem use.

Interestingly, the results showed that in majority of the patients culture and Susceptibility test was not done (61.2%, n=123). However in remaining cases, major microorganisms reported were *Streptococcus pneumoniae* and *klebsiella pneumoniae* (13.93%, n=28), contrary, only a single case of *proteus mirabilis* was reported (0.5%, n=1). The results are expressed in table 4**.**

Surprisingly, 97.52% of the observed cases were consistent with indication, while only 70.64%, 75.62%, 64.67% of the cases were meeting the criteria of dose, interval and duration of therapy respectively. It was also prominent that the practice of calculating creatinine clearance was being exercised at the hospital (99%). At the same time the custom of repeating the creatinine test was moderately in line to the standardized criteria (76.11%). Furthermore, in empirical therapy, the hospital was following the guidelines related to culture and Susceptibility test in only 43% of the cases, though the fig. was comparatively better in documented therapy (61.5%). The results of appropriateness of meropenem are summarized in table 5.

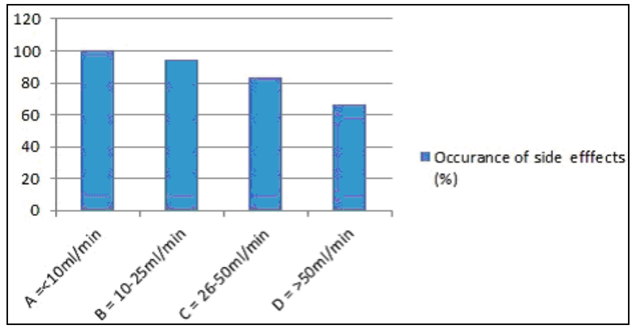

Fig. 2: Relationship between renal status and side effects of meropenam

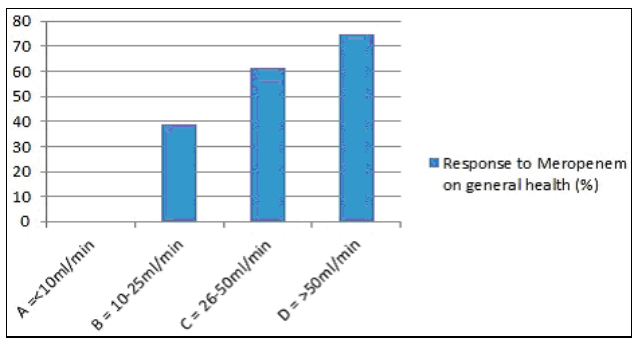

Fig. 3: response to meropenem on general health (%)

Adverse effect of meropenem was prominent in majority of the patients and thrombocytopenia appeared to be the most prevalent one as is mentioned in table 6 (37.81%, n=76). Upon investigating the outcome of therapy, it was revealed that therapeutic response was observed in 68% of the patients, while 23% patients showed no response and death occur in 9% of the patients as depicted in fig. 1. The study also highlighted that the occurrence of side effects were greater in patients with low renal status as shown in fig. 2. Similarly it was also observed that the response of meropenem on generalized health of patients was declining with the loss of renal function as depicted in fig. 3.

DISCUSSION

Infectious diseases are one of the most important causes of morbidity and mortality throughout the world (Murray and Lopez, 1997). However, the high level of availability

Table 2: Renal dose adjustment of meropenem

Indication	Normal doses	Mild renal failure (26-50ml/min)	Moderate renal failure (10-25ml/min)	Severe renal failure (< 10ml/min)
Pneumonia/UTI/ Gynae/Soft skin tissue	500 mg q 8hrly	500mg q 12hrly	250mg q 8hrly	250mg q 24hrly
Nosocomial pneumonia/ peritonitis/ neutropenia	1g 8 hrly	1g q 12 hrly	500mg q 12hrly	500mg q 24 hrly
Meningitis	2g q 8hrly	2 g 12 hrly	1 g 12 hrly	1g 24 hrly

and consumption of antibiotics, for the management of infectious diseases, have led to higher incidence of irrational use and greater incidence of resistance to antibiotics (Al-Niemat *et al*., 2008). The goal of this study was to evaluate the appropriateness of meropenem in a teaching based hospital of Pakistan.

Table 3: Demographic information of patients prescribed with meropenem during 6 months study at teaching based hospital

Demography	
Age (Mean ± S.D)	42±26
Gender (Male / Female)	84/117
Weight in kg (Mean ± S.D)	57.47±25.21
Types of Infection	N (%)
Intra abdominal	18 (8.95)
Urinary tract	14 (6.7)
Sepsis	38 (18.9)
Skin and soft tissues	50 (24.87)
Meningitis	20 (10)
Otitis Infection	1 (0.4)
Febrile Neutropenia	5 (2.4)
Pneumonia	55 (27.36)
Meropenem used in renal stages (creatinine clearance in ml/min)	N (%)
>50	139 (69.15)
26-50	42 (20.89)
10-26	18 (8.95)
<10	2 (1)
Used of Meropenem	
Prophylactic	23 (11.44)
Empirical	100 (49.75)
Culture documented	78 (38.80)

The result of this study showed that in majority of the cases meropenem was prescribed empirically. At the same time, it was also noted that empirical therapy remained appropriate in just 43% of the cases in view of the predefined criteria. The vast number of empirical cases also indicated that meropenem is used mainly on the basis of clinical judgment and experience without considering the standard guideline. Similar results were obtained in study conducted to evaluate the use of other broad spectrum antibiotics where empirical treatment outnumbered the culture documented use of antibiotics (Murray and Lopez, 1997). Surprisingly, vancomycin, another cell wall inhibitor, was used empirically in 98% of the cases in a study conducted by Vazin *et al* (Vazin *et al*., 2012). However, the appropriateness of its use in empirical treatment was greater (68%) as compared to this study (43%). Conversely, empirical treatment of meropenem was more than 95% consistent in accordance to the guideline in a study conducted at Sukhothai Hospital in Thailand (Brink *et al*., 2004).

Microbial resistance to antibiotic treatment is a global issue. In order to combat this issue on a micro level as not only each and every country, but every institution should bear the responsibility to address this problem (Hammerman *et al*., 1997). One of key contributors to resistance is prolonged use of antibiotics. In this study duration of therapy of meropenem was inappropriate in one third of the studied patients. This practice is certainly not an acceptable one as it could has serious implication on public health. This also means that the resistant microorganism would be more prevalent in community and continue to be transmitted from person to person which in return would facilitate the development of resistant strains. In comparison to other available literature, imipenem, a drug of similar class, was also inappropriately used with respect to duration of therapy in more than half of the patients (Sakhaiyan *et al*., 2009). These figs. show that health care providers are not obeying the standard guidelines nor they are emphasizing on restricting the use of antibiotics in healthcare facility.

Table 4: Bacterial culture results from patients

Microorganism	Number of cases	Percentage of all cases
Escherichia coli	16	7.96
Pseudomonas aeruginosa	16	7.96
Proteus mirabilis	1	0.5
Streptococcus & Klebsiella pneumoniae	28	13.93
Enterobacter spp	2	1
Moraxella catarrhalis	4	2
Bacteroides fragilis	2	1
Neisseria meningitides	6	3
Pneumocystis carinii	3	1.5
Culture not done	123	61.2

Regarding drug monitoring, it was noted that serum creatinine test was performed initially on 99% of patients; however, the same assessment was done on only 76% of the patients during the therapy. The result was comparatively better when the same variable was assessed in another study which showed 84% adherence to guidelines in relation to the routine monitoring of meropenem (Brink *et al*., 2004). It reflects neglecting monitoring parameters in our practice setting. Similarly in 75% of the patients, dose adjustment was done as indicated in guidelines. The appropriateness of this variable was found better as compared to other variables; still there is a room for improvement as shown in an Iranian study that appropriate dose adjustment was done in all the study participants (Erden *et al*., 2013).

Meropenem is one of the most commonly used antibiotics with relatively fewer side effects. However studies have shown that adverse effects do appear during meropenem therapy. Diarrhea and rashes are the two major adverse effects that should be borne in mind while using this drug (Mohr, 2008). Another study showed that abdominal discomfort was the most common adverse effect occurred with the use of meropenem (Norrby *et al*., 1995). In this study, frequently occurred adverse effect was thrombocytopenia followed by dermatological problems and abdominal discomfort. However none of the side effects observed was of life threatening intensity. This indicates that meropenem was well tolerated by patients and has an acceptable safety profile. In spite of that, meropenem dosing strategies must be optimized to further decrease the incidence of side effects.

Table 5: Appropriateness of Meropenem Use

Variable	Consistent with criteria (%)
Indication	97.52
Dose	70.64
Dosing Interval	75.62
Duration of therapy	64.67
Creatinine clearance Within 48 hrs. of drug initiation Repetition of creatinine clearance tests	 99 76.11
Correcting dose based on serum creatinine	74.62
Culture and Sensitivity testing Empirical therapy Documented therapy	 43 61.5
Complete blood examination	71.14

Another principal finding of this study was the linear relationship between side effects and the renal status of patients. It was noted that side effects were becoming prevalent with the decrease of renal function. In contrast, another study showed that presence of renal impairment did not alter the safety profile of meropenem (Linden, 2007). This discrepancy could be due to the reason that appropriate dose adjustment was not done in large number of patients in current study, which could have increased the incidence of side effects in renal compromised patients. The same reason could also be valid on another correlation, which showed that generalized health of the patients deteriorated with the decline of renal function in patients who are on meropenem. Proper educational, financial and regulatory programs directed towards health care professionals must be organized to promote rational use of meropenem. In addition provision of standard treatment guidelines, accompanied with onsite training and supervision may be helpful in guiding physicians in the appropriate use of meropenem in particular and anti-microbial in general.

CONCLUSION

Meropenem use evaluation in this study appears to be inconsistent with evidence based assessment criteria. The most evident inappropriateness was observed when meropenem was used as an empirical therapy. The study also detected other potential problematic areas where concordance with standard guidelines is yet to be achieved. The direct correlation between occurrence of side effects and declining renal function suggests the use of therapeutic drug monitoring in routine practice especially in renal compromised patients. Continuous medical education, functional drug and therapeutic committees and regular drug utilization evaluation programs could help in accomplishing the milestone of rational medication use. Lastly, efforts of individuals may not change the practice altogether, but it could influence on the numerous negative aspects of antibiotic usage in healthcare practice.

Table 6: Complications of meropenem use

Complications	N (%)
Abdominal discomfort	25 (12.43)
Thrombocytopenia	76 (37.81)
Abnormal liver function tests	5 (2.48)
Dermatological problem	28 (13.93)
Vestibular disturbances	7 (3.48)
Phlebitis	5 (2.48)
No Complications	55 (27.36)

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