

Drug utilization evaluation of Piperacillin/Tazobactam: A prospective and cross sectional investigation in tertiary care setup

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Abstract: Drug utilization evaluation (DUE) is an arrangement of continuous, orderly, criteria-based assessment of medication utilizes to guarantee that medicines are utilized suitably. In the event that treatment is regarded to be improper, provider and patient intervention may be important to optimize therapeutic efficacy. In the present study drug utilization evaluation of Piperacillin/Tazobactam was carried out in prospective manner. A well structured data collection form was constructed to collect the related information regarding demographic, clinical use, indication, culture sensitivity criteria, outcomes of therapy, renal impairment cases of dose adjustments and appropriate use. Results of chi square indicated insignificant relationship between gender and as p value was found to be $p=0.446$ and 0.111 for use of drug alone and in combination. Similarly insignificant relationship between gender and use of drug in combination with other antibiotics as p value was found to be $p=0.111$. It was found that from 61-70 years (Therapeutic Effectiveness; $n=12$, 9.37%), (Therapeutic Failure; $n=10$, 45.45%) and mortality ($n=1$, 50%) were quite higher. The prescription pattern was in accordance with standard guidelines. Study indicated need to elevate prescribers to pursue generic prescribing and rationally utilize antibiotics to avert advancement of resistance at the level of hospital and community. These sorts of studies are valuable for acquiring data about medication utilize designs and for recognizing inconceivable expense of medicines.

Keywords: Drug utilization evaluation (DUE), therapeutic effectiveness, Piperacillin/Tazobactam, renal impairment.

INTRODUCTION

Drug use evaluation (DUE), medication use evaluation (MUE), drug utilization review (DUR) are used in literature extensively to demonstrated that a examination should be carried out before and after the therapy given to individuals and an assessment should be conducted to achieve best outcomes. This method is attributed as efficient regular monitoring and dispensing of drug. In this method a strategy is developed to establish the specific therapy and it can be modified depending on the requirement (Raveh *et al.*, 2006; Fatima *et al.*, 2012). Ways to establish drug utilization review may encompass from a range of prospective, concurrent and retrospective based on time of commencement of study (Ali *et al.*, 2018a). DUE increases the role of pharmacists so that pharmacists can execute these rules to better analyze drug related issues. Pharmacist can also modify and / or improve the therapy design, manage and evaluate the pharmaceutical preparation and it helps in controlling the irrational utilization of medications (Bouchand *et al.*, 2012). Such studies are performed in several stages including identification for optimal use, determine actual use, intervene, evaluate the program and report the DUE findings (Pathak *et al.*, 2016; Patel *et al.*, 2016). The main objectives of such studies are to control the inappropriate

use of medication, to improve the quality related issues and to reduce the cost of treatment by avoiding inappropriate use of drug (Fatima *et al.*, 2012; Mah *et al.*, 2012). Piperacillin/Tazobactam is a combination of two types of pharmacological drugs that is Piperacillin (extended-spectrum penicillin class) while as Tazobactam (inhibitors of β -lactamase enzymes) (Kim *et al.*, 2007). Piperacillin attacks on the biosynthesis of cell wall muco-peptides of bacteria and completely destroys the gram positive and negative bacteria. The combination has the poly-bacterial effect (Ismail *et al.*, 2010). The current study was designed to evaluate the appropriateness of Piperacillin/Tazobactam indications, dosing, and duration of therapy in tertiary care settings. Furthermore the use of Piperacillin/Tazobactam in renal compromised patients was also studied. Clinical outcomes of the therapy including the studied drug were also investigated. Drug Utilization Studies (DUE) are receiving substantial attention in current era and they can be successfully implemented in the management of diseases. As Pakistan is a developing country where affordability and accessibility is a critical health concern, an irrational prescribing patterns leading to adverse drug reactions, complications and an ultimate increase in health care and pharmaceutical cost can also worsen the conditions. Also it serves the prescribers and clinician to understand, interpret and improve the prescribing, administration and use of drug.

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MATERIALS AND METHODS

Study design and protocols

This study proposed the use of therapeutic drug monitoring in regular practice particularly in renal compromised subjects. Drug utilization evaluation studies could help in accomplishing the goal of appropriate medication use, which intern benefited the patient by improving therapeutic outcome at reasonable cost. A concurrent (prospective) study was conducted for the drug utilization pattern of Piperacillin/Tazobactam. In this study we used national guidelines (Infectious disease society of Pakistan) and international recommendations for the assessment of the rationale use of the antibiotic. Study was conducted in different wards of different tertiary care hospitals. The duration for the collection of sample was six (6) months and during this period we recorded the findings obtained from medical prescriptions (pharmacy departments of different hospitals). Inpatients of ICU, MICU, surgical ICU and general wards receiving Piperacillin/Tazobactam therapy for different indications were included in the study. Adult, pediatric oncology patients and pregnant and lactating mothers were excluded from investigation.

Data collection procedure

All the related information was extracted by thorough reviewing and recording prescription orders submitted to pharmacy department of each hospital setting, also data was collected from patients' medical records and also by documenting the medication chart in each of the participating wards. In case of any query during the analysis of any information, doctors were consulted to develop a consensus on that issue. Main parameters were measured as demographic information, indications for therapy, empirical indication for piperacillin/tazobactam use, culture sensitivity test, initiation of therapy, duration of therapy, creatinine clearance, Co-administration of other antibiotics and adverse events in different age groups.

Ethical approval

Study was approved for ethical and scientific considerations from Board of Advanced Studies and Research, Federal Urdu University of Arts, Science and Technology. Informed consent was obtained from patients and caregivers. The confidentiality of subjects was highly maintained.

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS software for Windows, Version 20.0. Results were expressed in frequency and (%) percentage and Chi-square test was also applied on selected parameters.

RESULTS

The broad-spectrum antibiotics, particularly Piperacillin/Tazobactam are used in managing serious infections. table 1 encompasses the therapy guidelines for Piperacillin/Tazobactam. table 2 demonstrated the demographic and clinical presentation of drug utilization. In this study the patients of different ages were assessed who were receiving the piperacillin / Tazobactam therapy. We divide 152 patients in different age groups, for age range 21-30 years (n= 17, 11.18%), 31-40 years (n= 35, 23.02 %), 41-50 years (n= 28, 18.42%), 51-60 years (n= 25, 16.44%), 61-70 years (n= 23, 15.13%) and 71-80 (n=24 people, 15.78%) as shown in table 2. Gender distribution of patients were estimated, it was found that male were (n=74, 48.68%) where as the female were (n=78, 51.31%) as mentioned in table 2. Also BMI (Body Mass Index) distribution was determined as greater and less than 21. It was found that BMI range > 21 were (n=149, 98.02%) whereas BMI range < 21 (n=3, 1.97%) as shown in table 2. In this study culture sensitivity assessments based on gender, it was found that male patients (n=35) and female patients (n= 23) were having culture sensitivity.

In this study results of culture sensitivity tests indicated that different microorganisms were observed in male and female patient's i.e. E. Coli (male; n= 7, 43.75% and female; n= 9, 64.28%), Haemophilus (male; n=3, 42.85% and female; n= 4, 57.14%), Enterobacter (male; n= 4, 44.44% and female; n= 5, 55.55%), Staphylococcus Aureus (male; n= 8, 72.72% and female; n= 3, 27.27%), Streptococcus (male; n=4 , 33.33% and female; n= 8, 66.66%) and Pseudomonas Auriginosa (male; n= 1, 33.33% and female; n= 2, 66.66%) as shown in table 3. In this study we assessed the utilization of Piperacillin / Tazobactam in various infections based on gender i.e. sinusitis were observed in (male; n= 5, 35.71% and female; n= 9, 64.28%), pneumoniae (male; n= 5, 62.5% and female; n= 3, 37.5%) and pelvic cellulitis (male; n= 4, 44.44% and female; n= 5, 55.55%) were prevalent. gastroenteritis, colitis, appendicitis and peritonitis, abscess and cellulitis, bacterial septicemia, presumptive vascular surgery, trauma/RTA (road traffic accidents), hospital borne complicated cases were shown in table 3. The use of Piperacillin/Tazobactam in different renal stages based on age was also estimated i.e. for 21-30 years (mild; n=3, 8.57%), (moderate; n=9, 13.84%) and severe (n=5, 9.61%), 31-40 years (mild; n=7, 20%), (moderate; n=15, 23.07%) and severe (n=13, 25%), 41-50 years (mild; n=13, 37.14%), (moderate; n=12, 18.46%) and severe (n=3, 5.76%), 51-60 years (mild; n=4, 11.42%), (moderate; n=11, 16.92%) and severe (n=10, 19.23%), 61-70 years (mild; n=5, 14.28%), (moderate; n=10, 15.38%) and severe (n=8, 15.38%) and 71-80 years (mild; n=3, 8.57%), (moderate; n=8, 12.30%) and severe (n=13, 25%) as shown in table 4.

Table 1: Therapy Guidelines for Piperacillin / Tazobactam

Disease Condition	Dosage Recommended	Route of Administration	Duration	Dose (Mild Renal Failure)	Duration (Mild Renal Failure)	Dose (Moderate Renal Failure)	Duration (Moderate Renal Failure)	Dose (Severe Renal Failure)	Duration (Severe Renal Failure)
Appendicitis	4.5 gm Q8H	Intravenous	10 days	3.375 gm	10 days	2.25 gm	10 days	1.125 gm	10 days
Peritonitis									
Cellulitis									
Abscess									
Endometritis									
Presumptive therapy									
Wound/trauma									
vascular wound									
Gastro enteritis									
Pneumonia									
DOSES ACCORDING TO CREATININE CLEARANCE									
Creatinine Clearance (ml/min)	20								
Max. Dosage Frequency/Day	4 gm/0.5 gm BID 24H	30	40	50	60	70	80	90	100
		12 gm/1.5gm (TID / 24H) *** 12 gm/1.5 gm=4.5 gm in 3 equally divided doses in 24 hours							

In the present study appropriateness and inappropriateness were also assessed in different parameters (table 5). Appropriateness in therapy in current investigation following reported guidelines was 93.24%. Clinical outcome results are summarized in table 6 (A). Therapeutic effectiveness, therapeutic failure and mortality are considered as outcome parameters. A partial

correlation was run to determine the relationship between therapeutic effectiveness, therapeutic failure and mortality rate whilst controlling for age. There was a moderate, negative partial correlation between therapeutic effectiveness (21.26±7.82), therapeutic failure (3.67±3.95) and mortality (0.33±0.47) whilst controlling for age (55±17.135 years) (table 6(B)).

DISCUSSION

In the present study drug utilization evaluation of Piperacillin/Tazobactam was carried out. Selected drug is a combination of Penicillin and beta-lactamase inhibitor. In this prospective study irrational use of Piperacillin/Tazobactam in the tertiary care setting was estimated. The previous studies revealed that about 15 % to 65% drugs were used irrationally. Although the use of several antibiotics in the tertiary care settings is most demanding, and must be considered very crucial. Misuse of these antibiotics is very common. Several authors reported that the use of antibiotics has been evaluated widely in different hospitals by assessing the number of daily doses / occupied bed-days, but this estimation does not completely indicate appropriateness of therapy (Patel et al, 2018; Kala et al, 2018). In this study we assessed the appropriate use of piperacillin / Tazobactam due to its extensive prescription volume and escalated expenditure. In the present study we calculated the empirical use of piperacillin / Tazobactam based on gender, results indicated that patients male (n=35) and female (n=46) were treated empirically. Results of chi square indicated insignificant relationship between gender and empirical use of drug as p value was found to be p=0.149 as indicated in table 2.

Drug utilization study completely assessed the prescribing trends and justifies the appropriate use of drugs (Chaudhary et al, 2015). In this study we assessed the utilization of piperacillin/tazobactam alone or in combination. Results indicated that patients treated alone with piperacillin/tazobactam were (n=56, 36.84%) while (n=96, 63.15%) were treated in combination with other antibiotics as shown in table 2. Results of chi square indicated insignificant relationship between gender and alone use of drug as p value was found to be p=0.446 as indicated in table 2. Also it was assessed that other antibiotics which were administered along with Piperacillin / Tazobactam were Gentamicin (n=13, 8.55%), Amikacin (n=15, 9.86%), Ceftriaxone (n=11,

Table 2: Demographic and Clinical Presentation of Drug utilization

AGE RANGE	Frequency/Parameters		[n (%)]		Pearson Chi-Square	
	21-30		17	(11.18)		0.710
31-40		35	(23.02)			
41-50		28	(18.42)			
51-60		25	(16.44)			
61-70		23	(15.13)			
71-80		24	(15.78)			
GENDER	Males		74	(48.68)	0.690	
	Females		78	(51.31)		
BMI RANGE	>21		149	(98.02)	0.02	
	<21		3	(1.97)		
Culture Sensitivity Test	Count	Yes	No	Total	0.241	
		58	94	152		
	Expected Count	58.0	94.0	152.0		
	% within Gender	38.2%	61.8%	100.0%		
Empirical use of piperacillin/Tazobactam	Count	81	71	152	0.149	
		Expected Count	81.0	71.0		152.0
	% within Gender	53.3%	46.7%	100.0%		
Piperacillin/Tazobactam utilization	Alone		56 (36.84)	96 (63.15)	152	0.446
	Combination With Other Antibiotic		96 (63.15)	56 (36.84)	152	0.111

Table 3: Utilization of Piperacillin/Tazobactam in Different Infections Based on Gender

Infections	Frequency [n (%)]		
	Male	Female	Total
Sinusitis	5 (35.71)	9 (64.28)	14
Pneumoniae	5 (62.5)	3 (37.5)	8
Pelvic Cellulitis	4 (44.44)	5 (55.55)	9
Gastroenteritis, Colitis, Appendicitis, Peritonitis	8 (42.10)	11 (57.89)	19
Abscess, Cellulitis	10 (55.55)	8 (44.44)	18
Bacterial Septicaemia	3 (24)	9 (75)	12
Presumptive	17 (51.51)	16 (48.48)	33
Vascular Surgery	4 (66.66)	2 (33.33)	6
Rta/Trauma (Road Traffic Accidents)	14 (51.85)	13 (48.14)	27
Hospital Borne Complicated Cases	4 (66.66)	2 (33.33)	6
Results of Bacterial Cultures Based on Gender			
<i>E. coli</i>	7 (43.75)	9 (64.28)	16
<i>Haemophilus influenzae</i>	3 (42.85)	4 (57.14)	7
<i>Enterobacter</i>	4 (44.44)	5 (55.55)	9
<i>Staphylococcus aureus</i>	8 (72.72)	3 (27.27)	11
<i>Streptococcus pneumoniae</i>	4 (33.33)	8 (66.66)	12
<i>Pseudomonas aeruginosa</i>	1 (33.33)	2 (66.66)	3

7.23%), Clindamycin (n=21, 13.81%), Vancomycin (n=19, 12.5%), Metronidazole (n=11, 7.23%) and Moxifloxacin (n=6, 3.94%).

Regarding drug monitoring in renal compromised individuals, it was found that assessment of creatinine was done on only 76% individuals during the therapy. Prescribing patterns of medicines in chronic kidney disease patients on maintenance hemodialysis was also estimated by other investigators (Ahlawat *et al.*, 2015;

Chakraborty *et al.*, 2016). In this study we assessed the utilization of drugs in patients of different renal stages i.e. Mild renal stage (n=35, 23.02%), moderate renal stage (n=65, 42.76%) and severe (n=52, 34.21%) as shown in table 4. Results of chi square indicated insignificant relationship between gender and use of piperacillin/tazobactam in mild, moderate and severe renal stages as p value were found to be p=0.127, p=0.232 and p=0.052.

Table 4: Use of Piperacillin/Tazobactam in different renal stages based on age

Age Range	Different Renal Stages	No Of Patients [N (%)]
21-30	Mild (26-50 mL/min)	3 (8.57)
	Moderate (10-25 mL/min)	9 (13.84)
	Severe (< 10 mL/min)	5 (9.61)
31-40	Mild (26-50 mL/min)	7 (20)
	Moderate (10-25 mL/min)	15 (23.07)
	Severe (< 10 mL/min)	13 (25)
41-50	Mild (26-50 mL/min)	13 (37.14)
	Moderate (10-25 mL/min)	12 (18.46)
	Severe (< 10 mL/min)	3 (5.76)
51-60	Mild (26-50 mL/min)	4 (11.42)
	Moderate (10-25 mL/min)	11 (16.92)
	Severe (< 10 mL/min)	10 (19.23)
61-70	Mild (26-50 mL/min)	5 (14.28)
	Moderate (10-25 mL/min)	10 (15.38)
	Severe (< 10 mL/min)	8 (15.38)
71-80	Mild (26-50 mL/min)	3 (8.57)
	Moderate (10-25 mL/min)	8 (12.30)
	Severe (< 10 mL/min)	13 (25)
Different renal stages	Mild (26-50 mL/min)	35 (23.02)
	Moderate (10-25 mL/min)	65 (42.76)
	Severe (< 10 mL/min)	52 (34.21)

Table 5: Appropriateness of Piperacillin/Tazobactam

Parameters	Variable	Prevalence
“Used as empirical therapy following reported guidelines	Appropriate (%)	93.24
	Inappropriate (%)	6.76
Dose	Appropriate (%)	87.25
	Inappropriate (%)	12.75
Duration of Therapy	Appropriate (%)	78.12
	Inappropriate (%)	21.88
Frequency of Administration	Appropriate (%)	83.33
	Inappropriate (%)	16.67
Indications	Appropriate (%)	97.56
	Inappropriate (%)	2.44
Dosing Interval	Appropriate (%)	87.25
	Inappropriate (%)	12.75
Dose adjusted based on Creatinine Clearance	Appropriate (%)	85.46
	Inappropriate (%)	14.54
Complete Blood Examination	Appropriate (%)	99.13
	Inappropriate (%)	0.87

Appropriateness in empirical therapy in current investigation following reported guidelines were (93.24 %), dose (87.25%), duration of therapy (78.12%), frequency of administration (83.33%), indication (97.56%), dosing interval (87.25%), dose adjusted based on Creatinine Clearance (85.46%) and complete blood examination (99.13%) as shown in table 5. Author from other investigation revealed unseemly remedies of antibiotics that were 27.18% against the sign, wrong term /period of utilization 24.16 and 18.12% insufficient range were the continuous errors (Ali *et al.*, 2018b).

In the present study we also estimated various complications during the use of piperacillin/tazobactam. In the present study we also evaluated the clinical outcomes of therapy based on age of the patients. Highest therapeutic effectiveness was found in 31-40 years i.e., n=35, 27.34% followed by, 41-50 years n=27, 21.09%. While therapeutic failure was found more in cohort of 61-70 years (n=10, 45.45%) and mortality (n=1, 50%) as shown in table 6(A). Among 152 individuals, different complications were observed i.e. nausea / vomiting (n= 8, 5.26%), diarrhoea (n = 15, 9.86%) and Abdominal pain

Table 6(A): Different Clinical Outcomes of Piperacillin/Tazobactam Based on Age

Age Range	Different Renal Stages	No Of Patients [N (%)]
21-30	Therapeutic Effectiveness	17 (13.28)
	Therapeutics Failure	-
	Mortality	-
31-40	Therapeutic Effectiveness	35 (27.34)
	Therapeutics Failure	-
	Mortality	-
41-50	Therapeutic Effectiveness	27 (21.09)
	Therapeutics Failure	1 (4.54)
	Mortality	-
51-60	Therapeutic Effectiveness	22 (17.18)
	Therapeutics Failure	3 (13.63)
	Mortality	-
61-70	Therapeutic Effectiveness	12 (9.37)
	Therapeutics Failure	10 (45.45)
	Mortality	1 (50)
71-80	Therapeutic Effectiveness	15 (11.71)
	Therapeutics Failure	8 (36.36)
	Mortality	1 (50)
Different Complications	Nausea/Vomiting	8 (5.26)
	Diarrhoea	15 (9.86)
	Abdominal Pain	10 (6.57)

Table 6(B): Zero-Order (Pearson) Correlations Based on Age

Age	Therapeutic effectiveness	Partial Correlation	1.000	-0.697	-0.578
		Significance (2-tailed)		0.000	0.000
		df	0	147	147
	Therapeutic failure	Correlation	-0.697	1.000	0.858
		Significance (2-tailed)	0.000	.	0.000
		df	147	0	147
	Mortality	Correlation	-0.578	0.858	1.000
		Significance (2-tailed)	0.000	0.000	.
		df	147	147	0

(n=10, 6.57%) table 6(A). Non-randomized examinations recommended that blend antibiotic treatment may introduce a relative favorable position over mono-therapy in perspective of mortality of severely sick population (Falagas *et al.*, 2014). A partial correlation was applied to find out the association between therapeutic effectiveness, failure and rate of mortality whilst controlling for age which was statistically significant, $r(147) = -.697$, $N=150$, $p=.000$. However, zero-order correlations showed that there was a statistically significant, moderate, negative correlation between therapeutic effectiveness, therapeutic failure and mortality ($r(148) = 0000$, $n = 150$, $p < 1.000$); $r(148) = -.734$, $n = 150$, $p<.000$); $(r(148) = -.707$, $n = 150$, $p< .000$) respectively indicating that age had very little influence on therapeutic effectiveness of piperacillin/tazobactam but mortality and therapeutic failure has significant partial correlation with age. Scientists reported that several reasons for inappropriate therapy due to uncertain differential diagnoses,

complicated comorbidities and particularly lack of training of the physicians (Randad *et al*, 2017; Kala *et al.*, 2018).

CONCLUSION

This study proposed the use of therapeutic drug monitoring in regular practice particularly in renal compromised subjects. However, study findings also suggest that age had very little influence on therapeutic effectiveness of piperacillin/tazobactam but mortality and therapeutic failure has significant partial correlation with age. Drug utilization evaluation studies could help in accomplishing the goal of appropriate medication use. These types of studies are useful for obtaining information about drug use patterns and for identifying high cost drugs and treatments. Thus it will play a key role in serving the prescribers and clinician to understand, interpret and improve the prescribing, administration and use of drug.

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