PRESCRIPTION AUDIT OF DOSES OF NEWER ANTIMICROBIALS IN RENAL IMPAIRMENT IN A MULTISPECIALITY HOSPITAL

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Several parenteral antimicrobials have been introduced into clinical practice over the course of the last decade. Information about antibiotic use patterns in a hospital is therefore necessary for a constructive approach to problems that arise from the multiple antibiotics available. [1]. Safe usage of these antimicrobials in accordance with the guidelines provided by the manufacturing companies is an important issue in the context of patient safety. The safety of a drug in an individual depends upon the processes by which a drug is absorbed into systemic circulation, distributed through tissues, metabolized and excreted. Kidney and liver diseases can modify the kinetics of drug excretion and biotransformation. Therefore, a normal functioning kidney and liver can maintain a normal response of the drug. The extent of loss of renal function is judged by calculating creatinine clearance which is a useful measure of glomerular filtration rate. It is calculated by the following methods- inulin clearance (standard method, not used clinically), 30-min creatinine clearance, 24-hr creatinine clearance, Modification of Diet in Renal Disease (MDRD) equation and creatinine clearance estimates by the Cockcroft-Gault equation, using ideal body weight and the corrected serum creatinine concentration. Cockcroft-Gault equation was found to be the best predictor of inulin clearance in a study by Robert S et al. [2] But this method is not useful for patients with unstable renal function, defined as an increase in creatinine of > or = 1.0 mg/dl/day. [3] Renal impairment in a patient could be divided into categories of mild, moderate and severe according to the creatinine clearance values. [4] Individualization of drug dosage in patients with renal failure may prevent excessive drug accumulation and thus potentially

reduce adverse drug reaction and costs. Unlike in renal disease, where creatinine clearance estimates provide a reasonable guide to alterations in drug dosage requirements, indicators of hepatic disease, such as elevated liver enzymes, low serum albumin concentrations and clotting abnormalities, cannot be directly related to drug clearance.

The Newer Antimicrobial Agents (approved by the FDA after 1Jan 1999) are frequently prescribed now a day in resistant microorganism infections. So, a proper antimicrobial consumption pattern study needs to be conducted. To study the antimicrobial drugs consumption, the Anatomic Therapeutic Chemical (ATC) code and Defined Daily Dose (DDD) concept of World Health Organization (WHO) has been used in the hospital set up. The ATC classification assigns code letters and numbers to drugs. [5], [6] The DDD concept was developed to overcome objections against traditional units of drug consumption. The DDD for a given drug is established on the basis of an assumed average use per day of the drug for its main indication in adults. [5] DDD will be assigned only for drugs that already have an ATC code. DDD is a unit of measurement and may not reflect the prescribed daily dose; however they provide a fixed unit of measurement independent of price and formulation and enable the researcher to perform comparisons between population groups. DDD/100 bed-days provide a rough estimate of consumption of drugs among hospital in-patients. The appropriate dosing of these newer antimicrobial agents needs proper attention especially in patients with organ failures like renal impairment. In the present study the doctors' prescription were checked for appropriate doses of NAMAs in renal impairment patients.

Materials and Methods

The present study was conducted from 1 January 2005 to 30 June 2005 in a 695 bedded multi-speciality hospital in Delhi. The consumption of newer antimicrobials agents approved by FDA after 1 Jan 1999 was studied for first three months (January–March) of the study using

computerized drug order entry software data. The DDD/100 bed days was calculated to provide a rough estimate of consumption of these drugs among hospital inpatients. From 1 April 2005 to 30 June 2005 the prescription of patients with renal impairment were checked for doses adjustments of the newer antimicrobial agents. The definition of "Renal impairment" for the purpose of drug dose adjustment and cautions was obtained from the British National Formulary, which categorizes renal impairment into mild, moderate or severe and the following ranges of Glomerular filtration rate (GFR) have been used to define these terms: [4]

- Mild 20 to 50ml/min
- Moderate 10 to 20ml/min
- Severe<10ml/min

In patients with stable renal function (unstable renal function, defined as an increase in creatinine of > or = 1.0 mg/dL/day [3]), a population-based estimate of creatinine clearance was derived from a single measurement of serum creatinine, using Cockcroft's and Gault equation. [7]The equation most commonly used is:

$$\text{Creatinine clearance (ml/min)} = \frac{[140 - \text{Age}]\,[\text{Weight \{Kg\}}]}{72 \times \text{Serum creatinine (mg/dl)}}$$

In case of females multiply the equation by 0.85.

The appropriate doses of newer antimicrobial agents in normal and in renal impairment were obtained from British National Formulary and also from pharmaceutical product catalogue

For calculating Defined Daily Dose/100 bed days, the following formula was used

$$\text{DDD/100 bed days} = \frac{\text{No. of units administered (mg)} \times 100}{\text{DDD (mg)} \times \text{no. of days} \times \text{no. of beds} \times \text{OI}}$$

OI is the Occupancy Index in the hospital (0.65 in our hospital).

Results

During first three months period of the study a total of 54680 drug order entry were monitored in the pharmacy. All these drug entries were screened for the newer antimicrobial agents. The Defined Daily Dose (DDD) per 100 bed-days was calculated for the NAMAs administered parenterally, using number of units administered in milligrams over three months, the Defined Daily Dose as per WHO, total number of beds (695) and occupancy index (0.65).[Table 1]

Table 1: ATC codes and DDD/100 bed days of the five most commonly used newer antimicrobial agents (NAMAs)

NAMAs	ATC code	DDD/100 bed-days
Piperacillin-Tazobactum	J01CR05	1.69
Meropenem	J01DH02	1.08
Linezolid	J01XX08	0.54
Cefepime	J01DE01	0.48
Impenem-Cilastin	J01DH51	0.28
Aztreonam	J01DF01	0.08

During the next three months of study period 44 inpatients of renal impairment were monitored for parenterally administered newer antimicrobial drug doses. Out of these 44 patients of renal impairment, 31 (70.5%) were males and 13 (29.5%) were females. The maximum number of patients 32 (72.7%) were between 40-60 years age. [Table 2]

Table 2: Age and sex distribution of the patients

Age Group in years	Sex		Total (%)
	Male (%)	Female (%)	
20-40	3 (9%)	1(7.6%)	4 (9%)
40-60	22 (68%)	10(76.9%)	32(72.7%)
60-80	2 (6%)	2(15.4)	4(9%)
> 80	4 (12.5%)	0(0%)	4(9%)
Total	31	13	44

Out of 44 renal impairment patients, 8 patients had mild renal impairment, 16 had moderate, and 20 patients had severe renal impairment. 36 patients of renal impairment received Piperacillin-Tazobactum; Meropenem was prescribed in 26; Cefepime in 12; Impenem-Cilastin in 10 and Aztreonam in 5 patients. Linezolid was not monitored in these patients since it do not require dose adjustment in renal impairment. [Table 3]

Table 3: The total number of patients with renal impairment categorized according to the creatinine clearance values and the prescribed NAMA.

Newer antimicrobial agents (NAMA)	No. of renal impairment patients treated withNAMAs	Patient categorized according to renal impairment		
		Mild (20-50ml/min)	Moderate (10-20ml/min)	Severe (<10ml/min)
	Total-44	**8**	**16**	**20**
Piperacillin-Tazobactum	36	8	12	16
Meropenem	26	2	16	8
Cefepime	12	4	1	7
Impenem-Cilastin	10	6	2	1
Aztreonam	5	2	1	2

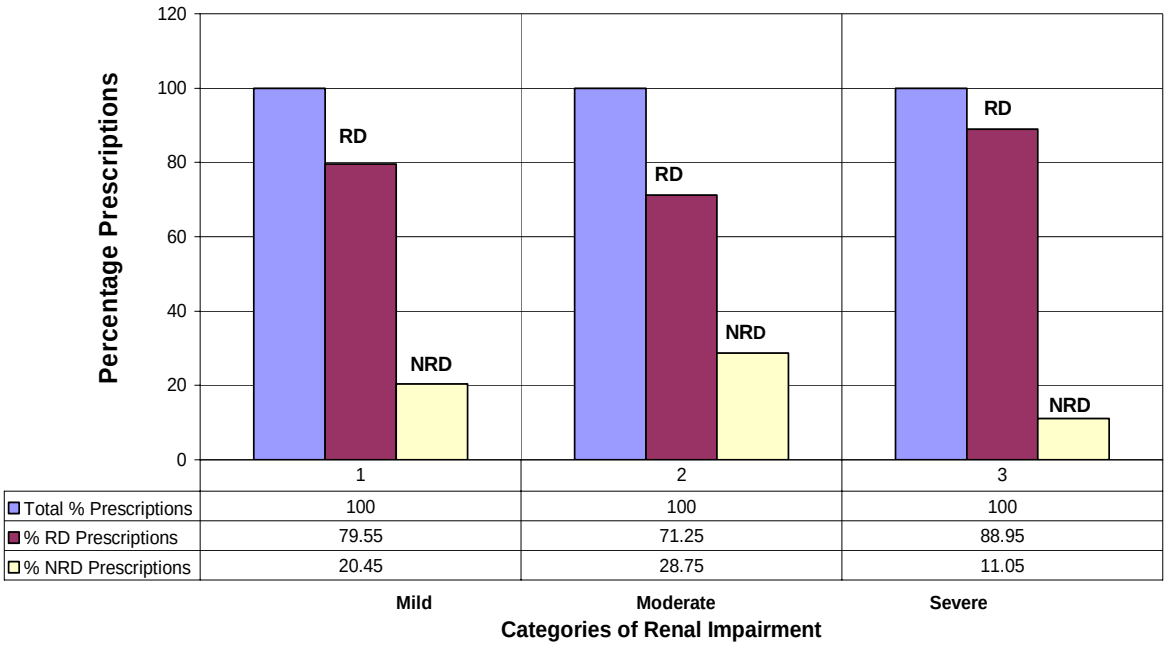
Total 296 prescriptions written for these 44 patients were checked for appropriate doses of newer antimicrobial agents depending upon the creatinine clearance value. Piperacillin-Tazobactum was prescribed in 227 prescriptions; Meropenem in 181; Cefepime in 73; Impenem-Cilastin in 64 and Aztreonam in 45 prescriptions. [Table 4]

Out of 296 prescriptions checked for the doses of newer antimicrobial agents in renal impairment patients, about 51 (17.23%) prescriptions were written with an inappropriate dose. Out of these 51 prescriptions 9 (20.1%) belonged to Mild renal impairment patients; 23 (28.8%) to Moderate and 19 (10.9%) to Severe renal impairment patients. In all 51 prescriptions appropriate doses were suggested to the doctor in charge. About 68.6 % (35) of the recommendations were accepted and 31.4 % (16) recommendations were not accepted by the physicians.

Table 4: The total number of prescriptions in renal impairment patients categorized according to the creatinine clearance values and the prescribed NAMA.

Newer antimicrobial agent (NAMA)	No. of prescriptions containing NAMA	No. of prescription in renal impairment		
		Mild (20-50ml/min)	Moderate (10-20ml/min)	Severe (<10ml/min)
	Total-296	**44**	**80**	**172**
Piperacillin-Tazobactum	227	40	63	124
Meropenem	181	36	80	65
Cefepime	73	26	8	39
Impenem-Cilastin	64	38	14	12
Aztreonam	45	14	7	24

Fig 1. Percentage of Recommended Doses (RD) and Non-Recommended Doses (NRD) prescribed in Renal impairment patients



Discussion

The estimation of antimicrobials consumption is a complex task and the results of each study may vary depending on the manner in which it is quantified. [8], [9] In our study the defined daily doses (DDD) concept of assessing antimicrobial usage, has been considered the preferred technical measurement for assessing consumption patterns of newer antimicrobial agents or NAMAs in hospital set up. In spite of certain limitations, the DDD method is still preferred to statistically compare the antimicrobial consumption pattern in different hospitals. [6] The DDD/100 bed days was calculated in the present study, which was found to be highest for piperacillin-tazobactum (1.10) and lowest for aztrenam (0.05).

Medication error as defined by the National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP), is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Prescribing inappropriate doses to patient with organ failure like-kidney failure and liver failure could lead to a dose dependent adverse drug reactions due to excessive accumulation of the drug in the body, which is dangerous to the patient safety but could be prevented by certain precautionary measures or counter checking processes. [10]

Adverse drug events (ADEs) rank fifth, after congestive heart failure, breast cancer, hypertension, and pneumonia, among the leading causes of preventable threats to the health of older Americans.[11] Renal failure patients have more chances of adverse drug events because of altered pharmacokinetics of excretion. Recommendations on dosage adjustments for renal impairment in sources that are considered reliable and are in common use were often worded in qualitative and undefined terms, ill suited for practical use. The variation between sources was remarkable, including drugs for which no adjustment was recommended in one source while another marked them as contraindicated in renal failure. [12] Here, we classified renal impairment

patients on the basis of British National Formulary (BNF) explicit defining criteria of mild (GFR-50-20 ml/min), moderate (20-10 ml/min) and severe (<10ml/min) category. [4] Total 296 prescriptions written for 44 inpatients with renal impairment were checked for appropriate doses of newer antimicrobial agents depending upon the creatinine clearance value. Piperacillin-Tazobactum was prescribed most commonly among the NAMAs in 76.7% (227) prescriptions; Meropenem in 61.1% (181); Cefepime in 24.7% (73); Impenem-Cilastin in 21.6% (64) and Aztreonam in 15.2 % (45) prescriptions. The highest percentage of inappropriate doses of NAMAs was prescribed in moderate renal impairment (28.8%); the second highest in mild renal impairment (20.1%) and lastly in severe renal impairment (10.9%). Inappropriate doses in any category of renal impairment was discussed with the concerned doctor and suggestions were made regarding the recommended dosing guidelines as per British National Formulary (BNF) or the pharmaceutical catalogues for that particular brand names. In case of difference between the above two sources, the guidelines from BNF were accepted. Out of 296 prescriptions, 51 (17.2%) prescriptions were found to contain inappropriate doses. For these 51 prescriptions, a telephonic discussion was done to correct the doses according to the creatinine clearance. Suggestions made by the clinical pharmacologist of the hospital were accepted by the concerned doctors in 35 (68.6%) prescriptions and not accepted in 16 (31.4%).

This study does have certain limitations because of less number of patients and prescriptions. This might be one reason for lower numbers of errors (17.2%) in our study as compared to previous retrospective studies (error percentage- 34%). [3] The other reason for lower error might be the functioning drug information center in the hospital.

In this prospective study, few important points were raised-

- Different reference standard for classification of renal impairment, have different opinions regarding doses adjustments.

- Doses adjustments by the doctors in renal impairment patients are not perfect.

Despite numerous secondary sources of drug dosing information, drug prescribing in renal impairment remains imprecise and relies on interpolation, extrapolation and estimation. [13] Even with the best evidence base, dosing recommendations for patients with renal impairment are extrapolated to the general population from the study of a very few patients. True individualization of dosing cannot come from a table of dosing recommendations, but awaits new technologies for predicting drug behavior in individual patients. [14] Doses adjustments in renal impairment should be based on the plasma concentration of drug in therapeutic range especially in elderly patients where adverse drug reaction are much more common because of age related changes in the drug pharmacokinetics due to deteriorating renal functions. Where ever, therapeutic drug monitoring is not available doses adjustments should be based on clearance values taking into account the lean body weight. In case dose recommendations are suggested to the prescribing doctors, the sources utilized for making this effort should be informed and after each dose recommendation the following comments illustrating the basis for the recommendations should be mentioned: Level A: good and consistent scientific evidence; Level B: limited or inconsistent scientific evidence ; Level C: consensus and expert opinion. The emphasis should be made on suggestions rather than corrections, keeping in view the dignity of a doctor. The process of individualization of appropriate doses in long term could be helpful in reducing the adverse drug reaction and cost of treatment and in improving the patient safety.

Conclusion

Ideally in planning ‘dose regimen’ drug dosage adjustment is of paramount importance in all patients with organ failures. In treating such critically ill patients, drug treatment should be so

instituted looking forward to their organ display using a battery of selected tests as indicated in order to achieve steady state plasma concentration required with in a known and safe effective therapeutic range.

Medication errors due to inappropriate doses are common in hospitalized patients especially in those patients where a dose adjustment is needed because of altered pharmacokinetics and pharmacodynamics. Newer antimicrobial agents being frequently prescribed now a days needs proper attention in administering appropriate doses. The prescribing of appropriate doses is an important step towards reducing the associated adverse drug events and the drug cost.

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