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THERAPEUTIC DRUG MONITORING OF GENTAMICIN: A PROSPECTIVE STUDY

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ABSTRACT

Gentamicin sulphate is an important drug in the class of aminoglycosides, most commonly used to treat resistant gram-negative organisms. Although highly effective, reservations concerning potential otovestibular toxicity and nephrotoxicity have often limited the use of these agents. Therapeutic drug monitoring has been extensively used to guide dosage adjustments to maximize efficacy and minimize toxicity in aminoglycosides. This was a prospective op en study which enrolled patients who were on Gentamicin during the study period of 6 months after taking the informed consent. A base line serum creatinine level was taken before initiating gentamicin. The dose of gentamicin given was based upon the actual body weight of the patient at 3-4mg/kg body wt. After the patient had been "stabilized" with drug, second day after drug administration two blood samples constituting peak and trough were withdrawn. The serum concentrations were checked to see if they were in the therapeutic range (1 microgram/ml to 10 microgram /ml) or not. The patients were also monitored for their creatinine clearance, if the levels were not within the therapeutic range or if there was an undesirable change in creatinine clearance, dosage adjustments were carried out and the process repeated. It was also found that the dosing interval should be lengthened (e.g,. 36, 48 hrs etc) in patients with decreased renal function (creatinine clearance less than 60ml/min). Single daily dosing was comparatively safer and effective than multiple dosing. In conclusion, therapeutic drug monitoring is a useful tool for dosage adjustments in patients with a CLcr < 60ml/min leading to better safety and reduced toxicity.

Key words: Gentamicin sulphate, Aminoglycosides, Resistant gram-negative organisms.

INTRODUCTION

The aminoglycoside gentamicin is commonly used to treat gram-negative infections and continues to be widely applied in hospitalized patients [1,2]. However, the occurrence of nephrotoxicity and ototoxicity in a significant number of patients has been the main drawback [3,4]. Hence, it is important to devise dosing regimens for gentamicin that both optimize its clinical efficacy and minimize its toxicity. Nephrotoxicity has generally been associated with trough gentamicin concentration that exceeds 2.0 mg [5]. Traditionally, gentamicin is administered in multiple daily doses (once every 8 or 12 h), with the peak concentration measured 30–60 min after the end of intravenous infusion and the trough concentration measured immediately before the next dose. Based on this dosing method, clinicians aim to achieve traditional target peak and trough concentrations of 5–10 and 1–2 mg respectively [6]. Recently, once-daily dosing strategies have been recommended in many clinical settings. The rationale for these strategies is that high peak serum concentrations enhance the concentration dependent bactericidal activity of gentamicin against gram-negative infections [7, 8] and that this drug has a post antibiotic effect that is longer when the peak drug level is higher [9]. Once-daily gentamicin has an equivalent efficacy and a trend towards reduced toxicity compared with traditional dosing methods. low serum gentamicin concentrations will be effective. In contrast, adverse effects of gentamicin (particularly in relation to kidney function and hearing) are

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more closely related to the total amount of the drug in the circulation (as measured by the area under the concentration:time curve). Thus, adjusting the dosage interval provides a means of ensuring sufficiently low trough serum gentamicin concentrations and, therefore, the safety of the dosage regimen [10]. Clinically important variability in gentamicin pharmacokinetics occurs even in babies of the same gestational age and postnatal age, and further variability occurs between babies with and without infection; these sources of variability necessitate individualisation of dosage regimens during gentamicin treatment to ensure effectiveness and safety. Individualising gentamicin dosage regimns involves therapeutic drug monitoring (that is, measuring serum gentamicin concentrations or other parameters linked to the distribution of gentamicin in the body), comparing observed concentrations with target concentrations, and (where necessary) adjusting gentamicin doses or dosing intervals to ensure differences between observed and target concentrations are sufficiently small [11].
TDM involves measurement of Minimum (Cmin) and Maximum (Cmax) plasma levels.

Objectives

The process of taking plasma drug concentrations, basic pharmacokinetic principles and the patient's clinical response and combining them to optimize drug therapy for the patient is termed as therapeutic drug monitoring. Therapeutic drug monitoring is useful for those drugs that have narrow therapeutic index and those that cause toxicity.

Genatmicin is an antibiotic belonging to the class aminoglycosides, it has a narrow therapeutic range (4-10mcg/ml), wide interpersonal pharmacokinetic variation characterized by ototoxicity and nephrotoxicity. Monitoring of gentamicin levels has been recommended routinely in all patients who are receiving the same for more than 2 days, mainly to minimize toxicity and increase the efficacy [14].

The objectives of the present study were

- To monitor the serum peak and trough levels of gentamicin with OD and BD dose and carry out dosage adjustment if the levels are out of therapeutic range in patients admitted to medicine ward of selected hospitals.
- To assess the nephrotoxicity of the drug in terms of creatinine clearance by measuring the serum creatinine levels in all the patients.
- To identify the risk factors that can lead to nephrotoxicity in patients receiving gentamicin**.**

MATERIALS AND METHOD

Source of data

Data was obtained from prospective series of patients who were admitted to medicine unit selected hospital with a diagnosis of infection and who were on gentamicin. Informed consent was taken from the patients or their relatives.

Study Design and Criteria

Prospective open study where all patients are treated with the same drug throughout the study where criteria may be established to allow for dosage reduction or dosage increase.

Inclusion criteria: All inpatients who are diagnosed with bacterial infection during the study period, and who were on Gentamicin, and Patients who have creatinine clearance of greater than 60ml/mt.

Exclusion criteria: Patients with the history of allergy to aminoglyoside**,** Patients with severe renal disease (creatinine clearance <30ml/min)**,** Patients with severe liver disease e.g. Ascites**,** Patients with history or signs of hearing loss or vestibular dysfunction**,** Pregnant women and lactating mothers.

Method of collection of data

Ethical committee clearance was obtained from Institutional Ethical Review Board, informed consent was obtained from the patients who were on gentamicin, detailed history was taken for all the patients enrolled in the study. A base line Serum creatinine level was taken before initiating gentamicin therapy and patients with CLcr of 60-100ml/mint were given single dose administration of gentamicin whereas patients with CLcr > 100ml/mint were given multiple dosing. The dose of gentamicin given was based upon the actual body weight of the patient at 3-4mg/kg body wt. The route of administration was either IV bolus or IV Infusion. After the patient has been "stabilized" with drug, two blood samples constituting peak and trough were withdrawn. Peak concentration was determined from the serum separated from blood sample collected after 5 minutes after the IV administration of a drug and trough concentration from the sample before the next dose is administered and in case of IV infusion the peak sample was collected 30 minutes after the infusion stopped and trough concentration from the sample before the next dose is administered. The serum concentrations are checked to see if they are in the therapeutic range (1 microgram/ml to 10 microgram /ml) or not.

The patients were also monitored for their creatinine clearance, if the levels are not within the therapeutic range or if there was an undesirable change in creatinine clearance, dosage adjustments were carried out and the process is repeated [15].

Estimation of Gentamicin

Principle: Randox Gentamicin assay is a latex enhanced inmmunoturbidimetric assay. It is based on the principle of measuring changes in the scattered light. The latex

particles are coated with gentamicin, which in the presence of gentamicin antibody solution, rapidly agglutinate.

Instrument: Rx Daytona Analyzer.

Calibrators: Gentamicin calibrators vial A B C D E and F, containing 0, 3.0, 10.0, 20.0, 35.0 and 50.0 mcg/ml of gentamicin, respectively.

Reagents:

Contents	Initial Concentration of Solutions
Antibody Buffer (anti-gentamicin antibody sodium azide)	Lot specific 0.09% w/v
Latex reagent (latex sodium azide)	Lot specific 0.09% w/v

Specimen collection and preparation for analysis

2 ml of blood was collected using normal aseptic venipuncture technique. Each assay requires at least 75 mcl of serum. Large particles in patients' serum samples were removed by centrifugation prior to pipetting. Serum samples were placed in sample cartridges prior to performing assay procedure. Finally, Rx Daytona Analyzer was run for determining the drug concentration in the sample [16].

RESULT AND DISCUSSION

A base line serum creatinine level was taken before initiating gentamicin therapy. Patients with CLcr of 60-100ml/mint were given single dose administration of gentamicin of 5-7mg/kg whereas patients with CLcr > 100ml/mint were given BD or TID multiple dosing. The dose of gentamicin given was based upon the actual body weight of the patient at 3-4mg/kg body wt in multiple dosing. The route of administration was either IV bolus or IV Infusion.

After the patient has been "stabilized" with drug, second day after drug administration two blood samples constituting peak and trough were withdrawn.

Peak concentration was determined from the serum separated from blood sample collected 5 minutes after the IV administration of a drug and trough concentration from the sample before the next dose is administered. In case of IV infusion, the peak sample was collected 30 minutes after the infusion stopped and trough concentration from the sample before the next dose is administered. The serum concentrations are checked to see if they are in the therapeutic range (4-10 microgram /ml) or not [17].

The patients were monitored for their therapeutic range drug level, if the levels are not within the therapeutic range and if there was an undesirable change in creatinine clearance, dosage adjustments were carried out and the process is repeated.

During the 6 month study, 52 consecutive patients, receiving gentamicin were enrolled, out of whom 25 (47.16%) were males and 28 (51.92%) were females. The mean age ± SD was 53.12 ± 32.55 and majority of the patients 22(42.3%) belong to the age group of 51-70 years with an average weight of 40 to 60 kilograms. The majority of patients 35(67.3%) were admitted to medical ward and the remaining17 (32.6%) to Medical Intensive Care Unit.

Out of 52 patients, 12 had serum levels out of therapeutic range and hence dosage adjustment was carried out for them upon discussion with the clinician. In the present study, 31(59.6%) patients were administered with multiple dosing and the remaining 21(40.38%) patients received once daily dosing. Of the patients receiving multiple dosing; 2(6.45%) patients had elevated peak levels, 2(6.45%) of them had elevated trough levels and 5 (16.12%) had increased both peak and trough levels. It was seen that in patients receiving once daily dosing only 2(9.52%) patients had high peak levels and 1(4.76%) patient had both high peak and trough levels. Rest was in the therapeutic range. Our findings suggest that single daily dosing is safe and effective compared to multiple dosing.

An estimated GFR of less than 60ml/mint/1.73m^2 is associated with a graded increase in the risk of each of the major adverse outcomes of chronic kidney disease, which are impaired kidney function, progression to kidney failure. Creatinine clearance is a close approximation of GFR. So creatinine clearance of 60ml/min is taken as a standard value.

It is seen that creatinine clearance is lower in certain renal conditions like polycystic kidney disease, tubulointesterstitial diseases or urinary tract diseases. It is also seen to be low in hypertensives patients and increased on diuretics and creatinine clearance is decreased in patients having low protein diet. [18]

With regard to peak and trough levels 17(34.61%) patients were out of therapeutic range.

There were 9 patients with creatinine clearance <60ml/min out of which 3 had increased peak level, 1 had increased trough level , 4 had both increased both peak and trough level 1 patient with both decreased peak and trough level and one had decreased trough level .

There were 6 patients with creatinine clearance 60-90ml/min out of which 4 had decreased trough level i.e. subtherapeutic range, 1 had increased peak level and 1 had both increased peak and trough level indicating toxicity.

There were 2 patients with >90ml/min of which 1 patient had decreased trough level and the other had increased trough level.

Increase in both peak and trough levels indicate toxicity which is probably due to decreased creatinine clearance of < 60ml/min.

Out of 52 patients, 20 patients above 60 years were found to have mean creatinine clearance values of 52.01ml/min which is below the normal and 32 patients

below 60 years were found to have the mean creatinine clearance value of 80.27ml/min.

Out of 52 patients, 24 patient were found to have creatinine clearance <60ml/min of which 15 patients were above 60 years and 9 patients below 60 years. This result indicates that there is a decrease in creatinine clearance values with the increase in age.

Out of 52 patients, 24 patients with creatinine clearance of <60ml/min`, 11 patients had renal infection and 13 patients had non renal condition with sepsis seen most common,

Among the 52 patients, 29 of them received cephalosporins, 4 received extended spectrum penicillins and 9 received diuretics. Of the 14 patients who had elevated peak and trough levels, 7 patients were receiving cephalosporins , 2 patients were receiving diuretics and 3 patients were receiving NSAIDS . Our findings suggest that concomitant administration of nephrotoxic drugs are additional risk factors leading to nephrotoxicity.

Probably those patients with nonrenal conditions also exhibited low CLcr due to the concomitant administration of nephrotoxic drugs.

We were unable to determine the ototoxicity due to drug which is also a problem of concern.

Thus, therapeutic monitoring of gentamicin was a useful tool to identify the patients who had blood levels out of therapeutic range, so that dosage adjustments could be made. It also helped to identify risk factors that caused nephrotoxicity as represented by the creatinine clearance.

Table 1. Details of peak levels in patients

Peak readings (mcg/ml)	No of patients	Percentage
1-5.	5	9.61
5.1-10	38	73.1
10.1-15	8	15.37
15.1-20	0	0
20.1-25	1	1.92
Total	**52**	**100**

Table 2. Details of trough levels in patients

Trough Reading (mcg/ml)	No of Patients	Percentage
0-0.5	9	17.3
0.6-1	15	28.84
1.1-1.5	8	15.38
1.6-2	13	25
2.1-2.5	2	3.85
2.6-3	3	5.77
3.1-3.5	0	0
3.6-4.0	1	1.93
7.6-8	1	1.93
Total	**52**	**100**

Table 3. Peak levels out of therapeutic range

Age (yrs)	Peak (mcg/ml)	Frequency of administration
72	10.03	BD
32	9.9	BD
25	11.35	BD
45	12.29	BD
52	10.83	BD
61	10.45	BD
50	21	BD
77	10.43	OD
58	10.29	OD
72	12.6	OD

Table 4. Trough levels out of therapeutic range

Age (yrs)	Trough (mcg/ml)	Frequency of administration
29	2.3	BD
25	2.1	BD
70	2.01	BD
45	3.94	BD
61	2.1	BD
50	7.8	BD
72	2.8	OD

Table 5. Creatinine clearance of patients with non renal condition

Age (yrs)	CLcr (ml/min)	Non Renal	Concomitant drugs
44	43.44	fever with unknown sepsis	None
56	50.2	LRTI	None
38	57.64	fever with unknown sepsis	None
70	39.9	Respiratory failure with septic shock	Cefixime,Furosemide
57	35.43	Sepsis	Furosemide
45	58.04	Cellulitis	Penicillin,Baxin
61	50.24	Pneumonia	None
77	49.48	fever with unknown sepsis	Furosemide
58	44.58	Fever	None
85	28.21	Sepsis	Cefixime
70	23.48	COPD with chest infection	Furosemide
70	29.88	BA	None
50	17.24	Metabolic encephaolopathy	Cefixime

Table 6. Creatinine clearance of patients with renal condition.

Age (yrs)	Clcr (ml/min)	Renal	Concomitant drugs
58	48.12	UTI,Sepsis	None
70	58.57	UTI,Sepsis	None
76	50.26	Pyleonephritis	Ceftriaxone
65	46.45	UTI,Sepsis	None
65	53.01	UTI	Cefixime
70	37.24	UTI	Cefotaxime,Penicillin
72	42.29	UTI	Penicillin
72	49.9	UTI,Sepsis	Cefotaxime,Furosemide
48	28.21	UTI	Cefotaxim
72	23.48	UTI	None
65	27.89	UTI	Furosemide

CONCLUSION

Pharmacokinetic monitoring helped to determine whether serum levels were within the range or not. Dose was adjusted in 27% of the patients in whom the levels were out of therapeutic range. Nephrotoxicity was also determined by way of measuring serum creatinine levels and creatinine clearance.

Dosing interval was lengthened (24-48hours) in patients with decrease renal function (CL cr < 60ml/min).Single daily dosing was comparatively safer and effective than multiple dosing. Additional risk factors like age and concomitant administration of nephrotoxic drugs caused decrease in creatinine clearance.

Thus it can be concluded that therapeutic drug monitoring is a useful tool for dosage adjustments in patients with a CLcr < 60ml/min leading to better safety and reduced toxicity.

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