COMPARING THE EFFECT OF MULTIPLE-DOSE AND ONCE DAILY REGIMENS OF GENTAMICIN THERAPY ON FRACTION EXCRETION OF MAGNESIUM

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ABSTRACT

This study was designed to compare the influence of ordinary (multiple-dose) and once-daily administration of gentamicin on tubular nephrotoxicity based on the urinary excretion of magnesium (Mg) as an indicator for this type of side effect.

Thirty-two hospitalized patients, who were assigned to receive at least 5-days treatment with gentamicin at the infectious disease ward of Imam Hospital in Tehran, were prospectively studied. Seventeen patients received multiple-doses of gentamicin per day and 15 patients received once-daily regimen.

At the beginning and at the end of of gentamicin therapy, blood urea, serum creatinine (Cr) and Mg levels were measured. Additionally 24-hour urine samples were collected for measurement of urinary volume, creatinine and Mg excretions.

In both treatment groups serum Mg concentration was significantly lower and fraction excretion of (FEMg) were considerably higher at the end of gentamicin therapy compared with the beginning of the treatment. However, the serum and urinary creatinine levels did not change significantly in the two groups

Keywords: Aminoglycoside nephrotoxicity, once-daily regimen, Fraction excretion of magnesium (FEMg)

INTRODUCTION

Aminoglycosides, as a group of bactericidal antibiotics, continue to serve an important role in the treatment of serious enteroccocal, mycobacterial, and gram negative bacillary infections. Because of its low cost, gentamicin remains the aminoglycoside of choice in hospitals that have minimal background resistance (1). The uses of aminoglycosides are associated with nephrotoxic effects, including glomerular impairment and renal tubular dysfunction. Therapeutic dosages of aminoglycosides may cause hypomagnesemia in more than one-third of patients. Approximately 20-30% of tubular reabsorption of magnesium takes place in the proximal tubule after kidney glumerular filtration. The nephrotoxic effects of aminoglycosides on the proximal renal tubule may lead to excess urinary magnesium losses and result in hypomagnesemia. Magnesium depletion may results in abnormal function of the neurologic, neuromuscular, and cardiovascular systems (2).

Gentamicin at standard clinical doses may causes immediate and transient renal Mg and calcium depletion before other evidences of toxicity are observed (3,4).

Once daily regimen has been reported to be a convenient, cost- effective strategy that is safe and effective as traditional, multiple dose regimen (1,5,6). It has been found that for the same daily dose, multiple dose regimens of aminoglycosides in comparison to once daily schedule induced nephrotoxicity, which appeared more rapidly, was more prolonged and resultsed in greater decrease in renal functions (7).

The objective of this study was to compare the effect of once-daily and multiple-dose regimens of gentamicin on the excretion of magnesium.

MATERIALS AND METHODS

Forty-three adult patients who were admitted in the infectious disease ward of Imam Referral hospital, of Tehran University of Medical Sciences who received gentamicin therapy for at least 5 days, were subjects of this prospective study. Patients did not receive any other nephrotoxic medication(s) that could affect urinary Mg excretion, serum Mg or creatinine levels.

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Patients with previous history of electrolytes abnormality, renal, hepatic or cardiovascular disorders, diabetes mellitus and pregnant women were excluded from the study. All patients signed informed consent forms.

Thirty-two patients with mean age 36.4±13.6 complied with the criteria of the study and completed the study. Patients were randomly divided into two groups according to the gentamicin therapy regimen. Seventeen patients received infusion of 80mg gentamicin over 30 minutes three times per day and 15 subjects were treated with infusion of 240 mg of gentamicin within 1 hour once daily(6).

At the initiation and the end of gentamicine administration (day 7), blood urea, serum creatinine and Mg concentrations were determined. In addition 24 hour urine samples were collected for measurement of urine volume, urinary level of creatinine and Mg. Fraction excretion of Mg was calculated by using the following formula:

$$\% FEMg = (U_{Mg} \times S_{Cr} / S_{Mg} \times U_{Cr}) 100$$

Data were analyzed using SPSS software version 11. The changes in blood urea, serum creatinine and Mg concentrations, urine volume and urinary levels of creatinine and Mg before and after gentamicin therapy in each group of patients were compared by paired t-test.

Independent sample t-test was used to compare changes in the previously mentioned laboratory parameters between two regimens of therapy.

RESULTS

Fifteen patients (12 male and 3 female) received 240 mg of gentamicin once daily by infusion over 1 hour. Mean of measured renal indices (urine volume, urinary creatinine and Mg levels, FEMg, blood urea and serum creatinine and Mg concentrations) of these subjects on the days of initiation and termination of gentamicin therapy are shown in table 1.

Seventeen patients (11 male and 6 female) received 80mg of gentamicin every 8 hours by infusion within 30 minutes. Table 2 shows renal indices of these patients.

In tables 3 and 4 laboratory parameters of the two regimen groups at the initiation and the end of gentamicin therapy are compared.

DISCUSSION

Nephrotoxicity of aminoglycosides is a concentration dependent side effect that is observed in 5-10% of patients receiving these drugs (8).

Renal toxicity of aminoglycosides is non-oliguric at the beginning of therapy and is accompanied by an increase in BUN over 3-7 days in susceptible patients. By continuation of treatment, serum creatinine increases gradually and urine volume decreases (9). While serum creatinine increment is usually reversible; long-term aminoglycoside therapy, especially in critical conditions (such as dehydration and septicemia), might result in permanent renal damage (10). Aminoglycosides might induce tubular and to a lesser extend glomerular damages. Primarily increasin urinary excretion of enzymes and tubular proteins represent tubular defects. Impaired proximal tubular function has harmful impact on reabsorption of electrolytes (K, Mg and Ca) (6).

Magnesium plays an important role in different metabolic processes, and Magnesium depletion may results in abnormal functions of the neurologic, neuromascular, and cardiovascular systems. Hypokalaemia, hypocalcaemia, or hypophosphataemia sometimes occur in patients with sever hypomagnesemia (11).

Several studies in patients treated by aminoglycosides have shown increase in urinary excretion of these electrolytes and changes in their serum concentrations (5,12).

Animal study has shown that glomerular damage is secondary to aminoglycoside- induced tubular necrosis and obstruction (13). Therefore one may expects that urinary excretion of electrolytes manifests faster than changes in serum creatinine concentration.

Several studies have shown priority of once- daily dosing of aminoglycosides because of the higher peak serum concentration, lower nephrotoxicity, and cost of treatment (14,15). Decreased in aminoglycosides nephrotoxicity in these studies are due to changes in serum creatinine. In the present study, no increase in serum creatinine concentration of the patients at the end of gentamicin therapy were observed which may be due to adequate hydration and feeding by patients.

Magnesium is mainly an intracellular cation, therefore, serum Mg level is not a good indicator of the total body stores of this ion (11). Although serum Mg concentration decreased significantly during gentamicin therapy in this study, it was not found to be a suitable indicator of gentamicin nephrotoxicity

In this study, no significant differences in FEMg were observed between once-daily and multiple-dose regimens. It is suggested that gentamicin-induced tubular damages which may causes FEMg increment, is mostly related mostly with daily amount of drug which is eliminated renally than its trough concentration. Since, the amounts of daily administered gentamicin were equal in both groups, tubular damage was not significantly different between these two groups.

Table 1. Comparisons of renal indices of patients on once-daily regimen at the initiation and termination of gentamicin therapy

Parameters	At the initiation of treatment	At the end of treatment	P value
Urine Volume(ml)	3276.00±776.48*	2958.00±611.46	0.064
Urine Creatinine(mg)	1158.40±422.62	1128.26±601.23	0.847
Urine Magnesium(mg)	102.08±56.88	98.82±43.80	0.818
Serum Creatinine(mg/dl)	0.82±0.23	0.77±0.19	0.218
Serum Magnesium(mg/dl)	1.57±0.33	1.50±0.37	<0.001
FEMg%[1]	4.84±2.96	5.72±3.51	0.002
BUN[2](mg/dl)	27.20±9.57	23.00±6.39	0.103

* Values are presented as mean ± SD, 1- Fraction Excretion of Magnesium, 2- Blood Urea Nitrogen

Table 2. Comparisons of renal indices of patients on multiple-dose regimen at the initiation and termination of gentamicin therapy

Parameters	At the initiation of treatment	At the end of treatment	P value
Urine Volume(ml)	2702.94±972.18*	2176.47±711.97	0.013
Urine Creatinine(mg)	1247.64±382.23	896.47±415.19	0.001
Urine Magnesium(mg)	103.09±72.41	101.08±62.23	0.875
Serum Creatinine(mg/dl)	0.76±0.02	0.73±0.12	0.477
Serum Magnesium(mg/dl)	1.44±0.33	1.38±0.29	0.035
FEMg[1]%	5.02±3.77	6.35±3.50	0.012
BUN[2](mg/dl)	26.47±8.86	23.76±7.79	0.271

* Values are presented as mean ± SD, [1] Fraction Excretion of Magnesium, [2] Blood Urea Nitrogen

Table 3. Comparisons of renal indices between once-daily and multiple-dose regimens at the initiation of gentamicin therapy

Parameters	At the initiation of OD[1] treatment	At the initiation of MD[2] treatment	P value
Urine Volume(ml)	3276.00±776.48*	2702.94±972.18	0.078
Urine Creatinine(mg)	1158.40±422.62	1247.64±382.23	0.535
Urine Magnesium(mg)	102.08±56.88	103.09±72.41	0.965
Serum Creatinine(mg/dl)	0.82±0.23	0.76±0.02	0.455
Serum Magnesium(mg/dl)	1.57±0.33	1.44±0.33	0.265
FEMg[3]%	4.84±2.96	5.02±3.77	0.880
BUN[4](mg/dl)	27.20±9.57	26.47±8.86	0.824

*Values are presented as mean ± SD, [1] Once Daily, [2] Multiple Doses, [3] Fraction Excretion of Magnesium
[4] Blood Urea Nitrogen

Table 4. Comparisons of renal indices between once-daily and multiple-dose regimens at the end of gentamicin therapy

Parameters	At the end of OD[1] treatment	At the end of MD[2] treatment	P value
Urine Volume(ml)	2958.00±611.46*	2176.47±711.97	0.002
Urine Creatinine(mg)	1128.26±601.23	896.47±415.19	0.210
Urine Magnesium(mg)	98.82±43.80	101.08±62.23	0.908
Serum Creatinine(mg/dl)	0.77±0.19	0.73±0.12	0.524
Serum Magnesium(mg/dl)	1.50±0.37	1.38±0.29	0.320
FEMg%	5.72±3.51	6.35±3.50	0.614
BUN(mg/dl)	23.00±6.39	23.76±7.79	0.765

*Values are presented as mean ± SD, [1] Once Daily, [2] Multiple Doses, [3] Fraction Excretion of Magnesium
[4] Blood Urea Nitrogen

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