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ORIGINAL ARTICLE

A prospective comparative study of gentamicin- and amikacin-induced nephrotoxicity in patients with normal baseline renal function

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ABSTRACT

The aim of this study was to compare the nephrotoxic potential of amikacin (AK) and gentamicin (GM) in patients with normal baseline renal function. This study was a 1-year, non-interventional prospective study of patients administered either GM or AK. The study was carried out at the internal medicine department of Al-Watani governmental study. Nephrotoxicity was defined as a serum creatinine (SCr) increase of ≥0.5 mg/dL from the basal (normal) SCr level. The two groups (GM, $n = 45$ and AK, $n = 49$) were similar in population composition, and underlying pathological and infectious processes requiring antimicrobials. No significant difference in age was found between patients in the GM and AK groups, $P = 0.83$. Patients in the GM group received comparatively lower doses than those in the AK group (mean = 2.5 mg/kg/day and 14.4 mg/kg/day, respectively) but the duration of treatment was similar. Sixteen of 45 patients receiving GM (35.6%) and eight of 49 patients receiving AK (16.3%) developed nephrotoxicity, $P = 0.033$. Single daily dosing with GM, regardless of the total daily dose, produced less nephrotoxicity than multiple dosing. In contrast, AK given at a total dose of 1 g daily, showed no benefit of single dosing compared with multiple dosing. In patients with initial normal renal function, GM was significantly more nephrotoxic than AK. Multiple dosing of GM was more nephrotoxic than single dosing. AK-induced nephrotoxicity was not significantly dependent on dosing frequency.

INTRODUCTION

Aminoglycosides are commonly used in everyday clinical practice for the treatment of gram-negative infections [1]. However, aminoglycosides are known to have nephrotoxic activity characterized by tubular necrosis without gross morphological changes in glomerular structures [2]. The most frequently used drugs of the aminoglycoside group include gentamicin (GM) and amikacin (AK). Animal studies suggest that AK induces signs of nephrotoxicity less frequently than GM [3–5]. However, the comparative nephrotoxicity of GM and AK in treated human patients is not fully unequivocal. For example, a study comparing AK and GM nephrotoxicity found that there were no significant differences between AK and GM nephrotoxic potential in matched critically ill patients [6]. A controlled comparison study between GM and AK indicated that AK is effective against severe gram-negative infections and is not more or less nephrotoxic than GM [7]. A comparative study of nephrotoxicity in patients randomly assigned to treatment with AK or GM indicated that AK may be less nephrotoxic than GM in humans [8]. A 4-day study of the effects of GM, tobramycin, and AK on the human kidney revealed that AK induces significantly lower lysosomal overloading and no loss of phospholipase A1 activity compared

with GM [9]. The conclusions of published comparative nephrotoxic studies in hospitalized patients are also complicated by the status of the renal function at the initiation of therapy. Therefore, the following study was carried out to compare the nephrotoxic potential of AK and GM in patients with normal baseline renal function.

PATIENTS AND METHODS

The study was conducted at Al-Watani hospital, a 100-bed facility located in Nablus city, north Palestine. The hospital is a governmental referral hospital that serves the general population in northern Palestine. The hospital contains all major medical services. There is no specific infectious unit in the hospital and patients with suspected infections are treated in the internal medicine department unit. Aminoglycosides are commonly used in the hospital as empiric therapy and in infections caused by gram-negative bacilli, e.g intra-abdominal, urinary tract and most nosocomial infections.

In this non-interventional prospective study we screened all in-patients receiving aminoglycoside treatment, GM or AK, in the ward of internal medicine during a 12-month period. The patients were hospitalized because of infections – mainly infections of the respiratory tract, abdomen and urinary tract – who had to be administered antibiotics of the aminoglycoside group, GM or AK, by the intravascular route. Inclusion criteria for this study were: patients with initial serum creatinine (SCr) level ≤1.2 mg/dL, administration of either GM or AK for not less than 5 days, availability of SCr levels obtained before initiation of the treatment and during therapy up until the sixth day of the study and finally, no GM or AK in the previous month. SCr levels were measured daily by laboratory medical technologists by the following method: a sample of 2 mL of venous blood is drawn in a plain test tube and spun for 5 min. Then, 5 μL of serum was taken from the supernatant and treated with picric acid according to the Jaffe method [10]. The intensity of the color was measured at 510 nm which is directly proportional to the SCr concentration. Demographic, clinical and laboratory data and those on medications administered were obtained from the patients' medical charts. Information obtained included age, gender, previous hospitalization or aminoglycoside use, presence of other factors predisposing to renal disease (such as diabetes mellitus, hypertension, peripheral vascular disease, and congestive heart failure). SCr was measured at the commencement of the aminoglycoside course in all patients. The outcome of interest was aminoglycoside-induced nephrotoxicity. In this study, nephrotoxicity was defined as an increase in SCr of ≥0.5 mg/dL from the baseline value. Dose and frequency of aminoglycoside administration were obtained from each patient's medical chart. Administration of aminoglycosides every 24 h was considered as single daily dosing while administration every 8–12 h was considered as multiple daily dosing. Use of potentially nephrotoxic drugs that were given to >10% of the study patients was included in the analysis.

Statistical analysis

Continuous variables were described using mean ± standard deviation (SD). The proportion of patients developing nephrotoxicity in the study population was expressed as frequency and percentage. The association between nephrotoxicity and the variables of interest was evaluated using the Pearson chi-square or Fishers' exact test for categorical variables and the independent Student's *t*-test for continuous variables. Differences in SCr level between consecutive days were tested using paired-sample *t*-test. Data analysis and graphics were carried out using SPSS 16 (SPSS Inc., Chicago, IL, USA).

RESULTS

During the 12-month study period, 94 patients met the inclusion criteria. In the study group, 52 (55.3%) were male and 42 (44.7%) were female. Mean (±SD) age was 63.84 ± 14.59 (range 17–100); 46 patients (48.93%) were ≥65 years old. Forty-five patients (47.9%) received GM, 49 AK (52.1%). Baseline demographic, clinical and laboratory data of the patients are presented in *Table I*. Nephrotoxicity, defined as an increase of ≥0.5 mg/dL in SCr from the baseline value was detected in 24 of the 94 patients (25.5%). Univariate analysis of clinical and laboratory risk factors for nephrotoxicity showed that the type of aminoglycoside ($P = 0.033$), frequency of dosing ($P = 0.021$), and concomitant diuretic administration ($P = 0.004$) were statistically linked to nephrotoxicity.

Patients on GM and AK were compared. Patients in both groups had comparable characteristics. No significant differences in gender ($P = 0.23$), age ($P = 0.06$), initial SCr ($P = 0.97$), number of co-existing chronic diseases ($P = 0.81$), and concomitant furosemide administration ($P = 0.26$) were found between the two groups. The GM group received an average of 2.5 ± 0.94 mg/kg/day while the AK group received an average of

Table I Baseline demographic, clinical and laboratory data of 94 patients receiving aminoglycosides.

Variable	Statistics*
Gender (male)	52 (55.3)
CHF	6 (6.4)
HTN	33 (35.1)
DM	42 (44.7)
Concomitant furosemide	39 (41.5)
Gentamicin	45 (47.9)
Amikacin	49 (52.1)
Gentamicin (total dose)	
160 mg/daily	22 (48.9)
240 mg/daily	23 (51.1)
Amikacin (total dose)	
500 mg/daily	12 (24.5)
1000 mg/daily	27 (55.1)
1500 mg/daily	10 (20.4)
Frequency of dosing	
Single (once daily)	32 (34%)
Divided multiple dosing	62 (66%)
Age	63.84 ± 14.59
SCr level before treatment	0.96 ± 0.23
Duration of hospitalization	8.52 ± 1.52
Nephrotoxicity	24 (25.5)

CHF, congestive heart failure; DM, diabetes mellitus; HTN, hypertension.
*Statistics are expressed as mean ± SD for continuous variables, and as frequency for categorical variables.

14.40 ± 6.0 mg/kg/day. The difference in dosage was significant ($P = 0.001$), but the duration of treatment was similar. Sixteen patients of the GM group (35.6%) and eight patients (16.3%) of the AK group experienced nephrotoxicity; the difference was significant ($P = 0.033$). *Table II* shows the baseline clinical and demographic characteristics of the GM and AK groups.

Gentamicin- and amikacin-induced nephrotoxicity was compared based on SCr levels (*Figures 1* and *2*).

Table II Baseline demographic, clinical and laboratory data of patients receiving either gentamicin or amikacin.

Variable	GM group	AK group	*P*-value
Age	66.53 ± 12.56	61.37 ± 15.97	0.083
Dose (per kg/day)	2.5 ± 0.94	14.39 ± 6.0	**<0.0001**
Initial SCr	0.95 ± 0.22	0.96 ± 0.23	0.97
SCr at day 6	1.33 ± 0.2	1.15 ± 0.34	**0.002**
Number of chronic diseases	2.2 ± 1.2	1.76 ± 1.4	0.081
Gender (male)	22 (48.9%)	30 (61.2%)	0.23
Concomitant furosemide	16 (35.6%)	23 (46.9%)	0.26
Single dosing (once daily)	14 (31.1%)	18 (36.7%)	0.57
Nephrotoxicity	16 (35.6%)	8 (16.3%)	**0.033**

Bold values are significant at $P < 0.05$.

The comparison included both the total dose given, frequency, and single vs. multiple dosing. *Figure 1* shows that administration of 0.5 or 1.0 g AK once daily or 1.0 g AK in divided multiple dosing did not significantly increase the SCr level for a period of six consecutive days. However, administration of 1.5 g of AK in divided multiple daily dosing significantly induced an increase in SCr level ($P = 0.0001$) at the sixth day of monitoring compared with the baseline SCr level. In the case of GM, single daily dosing with 180 mg/day did not significantly induce a rise in SCr during the 6-day study period. However, single dosing with 240 mg/day induced a significant rise in SCr level at the sixth day compared with the baseline SCr level. Similar effects were obtained with multiple dosing of GM with 160 mg/kg/day. At a dose of 240 mg/day GM in divided multiple dosing, a significant rise in SCr started to appear at the fifth and sixth days. In general, there was a positive correlation between SCr change and dose/kg/day of AK with $r = 0.32$, $P = 0.021$. Stronger correlation was found between dose/kg/day of GM and change in serum creatinine with $r = 0.36$, $P = 0.017$.

Finally, within the GM group, there was no significant difference ($P = 0.99$) in nephrotoxicity between dosing with 160 and 240 mg/day when administered once daily. However, 240 mg/day GM administered in divided multiple dosing produced significantly ($P = 0.001$) more nephrotoxicity than 160 mg/day administered in divided multiple dosing. Within the AK group, no significant differences in nephrotoxicity were observed between 0.5 gr/day and 1.0 g/day AK regardless of the dosing frequency.

DISCUSSION

In this study, GM was significantly more nephrotoxic than AK in hospitalized patients with normal baseline renal function despite the fact that AK patients received significantly higher dose per kilogram body weight than those in GM group. This finding cannot be attributed to demographic or baseline clinical characteristics as they were comparable in both groups. Furthermore, the study showed that signs of GM-induced nephrotoxicity became apparent earlier than that of AK-induced nephrotoxicity. Our findings regarding GM- and AK-induced nephrotoxicity are similar to those found by a Spanish study carried out on 65 patients with initial normal renal function. The authors of the Spanish study concluded that in patients with normal renal function, GM was significantly more nephrotoxic than AK [11]. However,

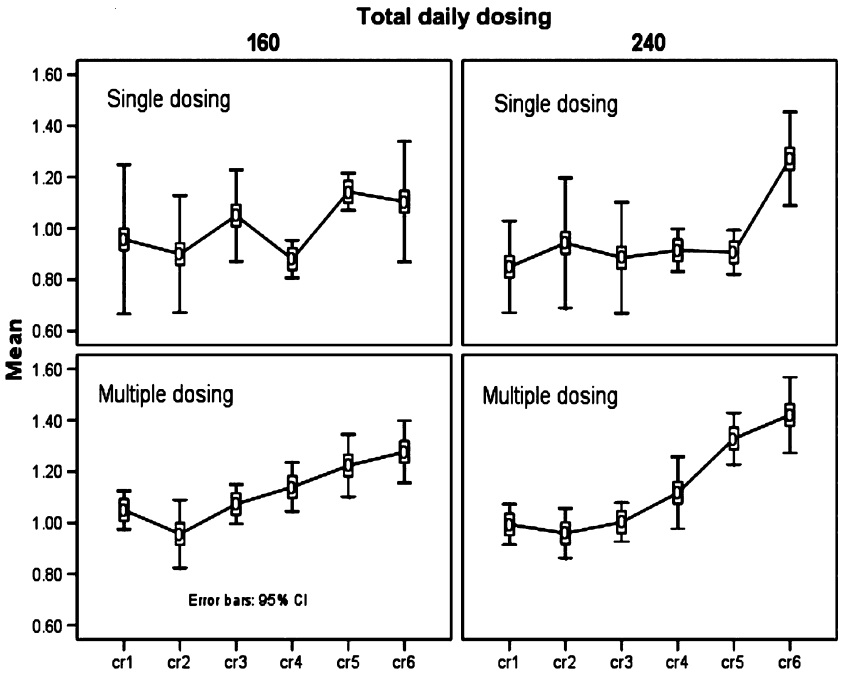

Figure 1 Changes in serum creatinine level during the 6 days of treatment with gentamicin given in 160 or 240 mg/day as single or in divided multiple dosing.

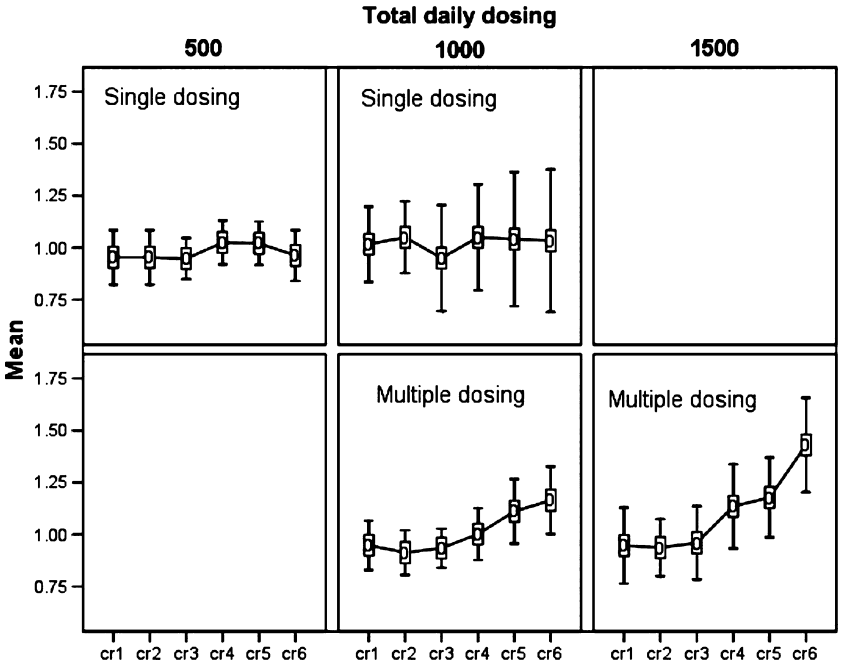

Figure 2 Changes in serum creatinine level during the 6 days of treatment with amikacin given in 500 or 1000 mg/day as single or in divided multiple dosing.

in a study carried out to compare nephrotoxicity and ototoxicity between GM and AK among 106 hospitalized patients, the authors used different definitions of nephrotoxicity and found no significant differences in the incidence of nephrotoxicity between the GM and AK treatment arms [8]. The authors also concluded that nephrotoxicity in general is associated with impaired baseline renal function and presence of bacteremia. In a human study comparing lysosomal morphology and function in proximal tubule cells 4 days after AK, GM, and tobramicin administration, GM and tobramicin were found to be significantly more nephrotoxic than AK and netilmicin, and that the nephrotoxicity of AK and netilmicin was comparable [9]. The differences in our

results with those obtained by others could be attributed to the differences in the baseline clinical characteristics between the groups, or to differences in the methodology applied, particularly, the definition of nephrotoxicity.

Aminoglycosides are often administered twice or thrice daily. Recently, increasing numbers of experimental and clinical studies have demonstrated that a once-daily dosing regimen may be at least as effective as, and possibly less toxic than, multiple dosing [12–20]. In the meta-analyses published by Blaser and Konig [12], a total of 24 randomized prospective clinical trials comparing multiple and single daily dosing of AK, GM, netilmicin, or tobramycin were pooled. In most trials, no significant difference between the regimens was detected. The overall analysis of the 3181 patients enrolled in this meta-analysis revealed no significant difference between single and multiple daily dosing. However, there was a trend towards less nephrotoxicity in the once-daily treatment groups. Overall, the Blaser and Konig meta-analysis study indicated that: (i) GM delivered in multiple daily doses was significantly more nephrotoxic than AK; (ii) AK did not show a significant benefit of single daily dosing regarding renal toxicity; and finally (iii) only GM exhibits a benefit from being used once daily. In the experience of the Hartford Hospital, the incidence of nephrotoxicity was reduced from about 4% with conventional dosing to 1.2% with once-daily aminoglycoside regimens [21]. In a study investigating the costs associated with aminoglycoside administration, the authors concluded that once-daily dosing of aminoglycosides saved approximately $40 000 in drugs, supplies and labor for 2200 patients enrolled in the study compared with conventional dosing [22]. The authors further concluded that once-daily dosing with aminoglycosides is cost-effective leading to a reduction of >$10 000 in therapeutic drug-monitoring requests per month for GM [22]. The results of this study indicate that multiple dosing of GM produced more nephrotoxicity than single daily dosing. In case of AK, no differences were observed between single and multiple dosing. These results are in agreement with the overall conclusion of the meta-analysis study mentioned earlier.

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