Gender Differences in Aminoglycoside Induced Nephrotoxicity. A Prospective, Hospital - Based Study.

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Running Title. Impact of Gender on Aminoglycosides Nephrotoxicity

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Abstract

Aim: Impact of gender on aminoglycoside induced nephrotoxicity is still controversial and inconclusive. The objective of this study was to investigate the nephrotoxic potential of amikacin (AK) and gentamicin (GM) in male and female hospitalized patients. **Methodology**: A one-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 hospital. Nephrotoxicity was defined as a blood creatinine (Cr) increase of ≥ 0.5 mg/ dL from the basal (normal) Cr level. Data were entered and analyzed using SPSS 16. **Results:** A total of 94 patients were identified (GM, n = 45 and AK, n = 49). Male and female patients on GM had comparable characteristics except that males had significantly higher number of co-existing chronic diseases. No gender differences were observed in gentamicin induced nephrotoxicity (37% in males versus 33.3% in females, $P = 0.8$). Male and female patients on AK were also comparable in demographic and clinical characteristics. However, significant differences in gender susceptibility were observed with AK induced nephrotoxicity (31.6% in females versus 6.7% in males, $P = 0.043$). Pattern of serum creatinine changes in patients on GM were comparable between males and females. However, in females on AK, s.cr levels were rising sharply after the fourth day compared with that in male patients on AK. **Conclusion:** Gender differences in aminoglycoside induced nephrotoxicty were seen with AK where females were more vulnerable to nephrotoxicity. Such gender differences did not exist with GM.

Key Words: Gentamicin, Amikacin, Nephrotoxicity, Gender.

Introduction

Aminoglycosides are antibiotics which are commonly used in everyday clinical practice especially in 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 applied drugs of aminoglycoside group include gentamicin (GM) and amikacin (AK). Numerous factors are known to be associated with aminoglycoside nephrotoxicity, such as age, renal function, and frequency of dosing [3-5]. The impact of gender as a risk factor for aminoglycoside – induced nephrotoxicity among patients is not conclusive yet and information in this regard are contradictory and mainly came from animal studies [6]. The purpose of this prospective study was to investigate the impact of gender on gentamicin (GM) and amikacin (AK) induced nephrotoxicty among hospitalized patients. The findings of such a study might shed more light on the clinical toxicology of aminoglycosides and might influence the clinical practice.

Patients and Methods

The study was conducted in Al-Watani hospital, a ~ 200-bed located in Nablus city, 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. The aminoglycosides are commonly used in the hospital as an 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. Given that there is as high as 56% reported aminoglycoside induced nephrotoxicity, the goal sample size was not to be less than 90 patients in order to get a sizable number of patients with aminoglycoside induced nephrotoxicity [7]. The patients were hospitalized due to infections, mainly infections of respiratory tract, abdomen and urinary tract that had to be administered antibiotics of aminoglycoside group, GM or AK, by intravascular route. Inclusion criteria for this study were: patients with initial serum creatinine level ≤ 1.2 mg/dL, administration of either GM or AK for not less than five days, availability of serum creatinine levels obtained before initiation of the treatment and during therapy up until the sixth day of the study and finally, had no GM or AK in the previous month. Exclusion of patients with high serum creatinine was made to avoid misinterpretation of the data since reduced renal function is an important risk factor of aminoglycoside induced nephrotoxicity. Demographic, clinical, laboratory and medications administered were obtained from the patients' medical charts. Details collected at baseline included age, gender, previous hospitalization or aminoglyside use, presence of other factors predisposing to renal disease (such as diabetes mellitus, hypertension, peripheral vascular disease, congestive heart failure). Serum creatinine level (S.Cr) was measured at the commencement of the aminoglycoside course in all patients. Uses of potentially nephrotoxic drugs that were given to >10% of the study patients were included in the analysis. The outcome of interest was aminoglycoside induced nephrotoxicity. In this study, nephrotoxicity was defined as an increment in Scr of ≥ 0.5 mg/dL from baseline value. This definition of nephrotoxicity has been used in previous publications and found to be clinically relevant to renal damage [8, 9]

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 Pearson Chi-square or Fishers' exact test for categorical variables and the independent student's t test for continuous variables. Differences in serum creatinine level between consecutive days were tested using paired – samples T test. Data analysis and graphics were carried out using SPSS 16.

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%). The AK and GM group had comparable age, number of co-existing chronic diseases as well as baseline renal function as measured by initial serum creatinine. Nephrotoxicity, defined as an increase of ≥ 0.5 mg/dL in serum creatinine from baseline value was detected in 24 of the 94 patients (25.5%). The GM group received an average of 2.5 ± 0.94 mg/ kg/ day while the AK group received an average of 14.40 ± 6.0 mg/ kg/ day, the difference was significant (P = 0.001), but duration of treatment was similar. Sixteen patients of the GM (35.6%) and 8 patients (16.3%) of the AK group experienced nephrotoxicity; the difference was significant (P = 0.033).

Male and female patients on GM were compared. No significant differences in age ($P = 0.49$), initial S.Cr ($P = 0.25$), dose per kg ($P = 0.063$), frequency of dosing ($P = 0.11$), and concomitant furosemide administration ($P = 0.37$) were found between male and female patients receiving GM. However, males on GM had significantly higher co-existing chronic diseases than females ($P = 0.038$). In the GM group, more males (37%) than females (33.3%) showed nephrotoxicity, but the difference was not significant ($P = 0.8$).

Male and female patients on AK were also compared. No significant differences in age ($P = 0.32$), initial S.Cr ($P = 0.18$), frequency of dosing ($P = 0.55$), dose per kg ($P = 0.42$), number of co-existing chronic diseases ($P = 0.47$), and concomitant furosemide administration ($P = 0.26$) were found between male and female patients receiving AK. Opposite to the GM group, in the AK group, more females (31.6%) than males (6.7%) showed nephrotoxicity and the difference was significant ($P = 0.043$).

GM and AK – induced changes in s.cr during the six-day follow up were compared as stratified with gender. Figure 1 shows GM induced a steep and similar rise in s.cr among males and females after the fourth day of treatment. However, the AK induced changes in s.cr were uprising and steep in females but not in males. Actually, the s.cr level in females was significantly higher than the corresponding s.cr in males at day 6 (1.3 ± 0.38 versus 1.1 ± 0.3; $P = 0.035$) despite that they both started with in-significantly different initial s.cr. However, this was not observed with GM.

Table 1. Baseline demographic, clinical and laboratory data of male and female patients receiving either gentamicin or amikacin.

Variable	GM group			AK group		
	Male N = 27	**Female N = 18**	***P***	**Male N = 30**	**Female N = 19**	***P***
Age (years)	67.7 ± 10.1	64.8 ± 15.7	0.49	63.03± 18.2	58.74 ± 11.61	0.32
Initial S.Cr (mg/dL) at day 1	1.01± 0.166	0.94± 0.22	0.25	0.92± 0.23	0.81± 0.33	0.18
No. of co-existing chronic diseases	2.5 ± 0.9	1.7 ± 1.3	**0.038***	1.6 ± 1.22	1.9 ± 1.6	0.47
Dose (mg/ kg)	2.3 ± 0.95	2.8 ± 0.86	0.063	14.94 ± 6.1	13.52 ± 5.94	0.42
Frequency of Dosing Single Multiple	 10 (37) 17 (63)	 11(61.1) 7 (38.9)	0.113	 12 (40) 18 (60)	 6 (31.6) 13 (68.4)	0.55
Concomitant Furosemide Yes No	 16 (59.3) 11 (40.7)	 13 (72.2) 5 (27.8)	0.373	 14 (46.7) 16 (53.3)	 12 (63.2) 7 (36.8)	0.26
Nephrotoxicity No Yes	 17 (63) 10 (37)	 12 (66.7) 6 (33.3)	0.8	 28 (93.3) 2 (6.7)	 13 (68.4) 6 (31.6)	**0.043***

* Significant at P < 0.05.

Discussion

The impact of gender on GM and AK induced nephrotoxicity among hospitalized patients was investigated in this study. Our results indicated that there was no gender difference in susceptibility of hospitalized patients to gentamicin induced nephrotoxicity. However, a small but statistically significant “gender differences” in the vulnerability of hospitalized patients to amikacin was found. In this study, hospitalized male patients had similar susceptibility to gentamicin as female patients despite that male patients had more predisposing factors to nephrotoxicity as being elder and having significantly higher number of co-existing chronic diseases. In the case of Amikacin, hospitalized female patients were significantly more susceptible to nephrotoxicity than male patients despite that female patients were younger than male patients. It might be argued that elevation of serum creatinine could be due to co-administration of other medications known to elevate serum creatinine, however, such medications were present in less than 5% of the investigated patients and were present in both males and females. This strengthens our conclusion that serum creatinine elevation was mainly due to aminoglycosides rather than interfence from co-administered medications.

Previous studies on animals and humans had no conclusive findings regarding impact of gender on aminoglycoside induced nephrotoxicty. For example, it was found that male Fischer 344 (F 344) rats are more sensitive to the toxic effects of gentamicin or tobramycin than their female counterparts [10]. In contrast, in the isolated perfused rat kidney of the F 344 strain, no sex-related intrinsic differences were found to the nephrotoxic response to gentamicin [11]. Surprisingly, sex differences in the magnitude of gentamicin or tobramicin-induced nephrotoxicity were not present in Sprague-Dawely (SD) rats [10, 12]. Another study concluded that there are small sex-related differences in the susceptibility of SD rats to gentamicin nephrotoxicity and that treatment with testosterone in castrated rats and estradiol in ovarectomized animals did not significantly alter the toxicity [13]. In humans, females were reported to be affected by gentamicin nephrotoxicity more than males [14]. Other workers, however, have found that male humans are more susceptible than females to the morphologic and functional effects of gentamicin nephrotoxicity [15].

The mechanisms underlying gender differences in aminoglycosides induced nephrotoxicity are difficult to explain. However, such difference could be ascribed to hormonal and/or pharmacokinetic differences between both sexes. In some experimental studies, testosterone was not involved in the mechanism of aminoglycoside- induced nephrotoxicty, but estrogen exaggerated it [16]. In another study on SD rats, treatment with testosterone in castrated rats and estradiol in ovarectomized SD rats did not significantly alter the toxicity suggesting minor role of hormones on aminoglycoside induced nephrotoxicty [13]. It was suggested that the mechanism of aminoglycoside nephrotoxicity may be attributable to extra-renal factors such as pharmacokinetics [11]. However, in a study of small sample of critically ill patients, gentamicin and amikacin displayed similar two-compartment pharmacokinetics and produced a similar incidence of nephrotoxicity. Pre-renal hepatic metabolism has also been suggested as a necessary component of aminoglycoside nephrotoxicity [17] and there could be gender differences in this metabolism. However, aminoglycosides are extensively metabolized which raises doubts regarding this explanation. Several correlations between renal brush border membrane binding affinity of aminoglycoside and aminoglycoside nephrotoxicity have been cited including the greater binding affinity in male versus female rats [18]. However, this correlation contradicts our finding that females were more susceptabile to nephrotoxicity than males. In conclusion, more investigation is needed to study the impact of gender on aminoglycide induced nephrotoxicity.

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