

DIABETES MELLITUS TYPE 2 IS NOT A RISK FACTOR FOR AMINOGLYCOSIDE INDUCED RENAL INJURY

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SUMMARY

The aim of the study was to investigate the extent and time course of aminoglycoside (AG)-induced serum creatinine elevation in patients with and without type 2 diabetes mellitus (DM2). This prospective study included patients with and without DM2 who were administered AG parenterally. The outcome of interest was the extent and time course of serum creatinine elevation suggestive of renal injury during AG therapy. Data were entered and analyzed using a statistical package for social sciences (SPSS 16). Of 94 patients included in the study, there were 42 DM2 and 52 non-DM2 patients. There was no significant between-group difference in initial ($P=0.18$) and final serum creatinine ($P=0.15$). Furthermore, no significant difference in serum creatinine elevation was observed between patients with and without DM2 during the course of AG therapy. Eleven (26.2%) of 42 DM2 patients and 13 (25%) of 52 non-DM2 patients had an increase of $\geq 44.2 \mu\text{mol/L}$ in serum creatinine

level during therapy ($P=0.89$). In DM2 group, a significant rise ($P=0.04$) in serum creatinine level was evident on day 4 and maximum rise (28%) from baseline value was evident on day 6 of therapy. Similar extent and time course of serum creatinine elevation was observed in non-DM2 group. In conclusion, type 2 diabetes mellitus is not a risk factor for AG-induced renal injury.

INTRODUCTION

Diabetes mellitus (DM) is a global health problem. The total number of people with DM is projected to rise to 366 million in 2030 (1). Chronic DM is known to be associated with vascular complications such as diabetic nephropathy, which is a common cause of end stage renal disease (2). Clinical investigation in diabetic patients clearly demonstrated consistent defects of neutrophil chemotactic, phagocytic and microbicidal activities, which contributed to high susceptibility and severity of infections in DM (3). A study carried out in Ontario, Canada by Shah and Hux showed that the risk ratio for infectious disease-related hospitalization was up to 2.17 (99% CI 2.10-2.23) for diabetic *versus* non diabetic patients (4). Therefore, it is common for diabetic patients to be administered antimicrobial agents to treat infections as a comp-

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lication of chronic diabetic state. The rise of multi-drug resistant gram-negative pathogens has thrust aminoglycoside (AG) antimicrobial agents back into the spotlight. However, AGs are considered among the most nephrotoxic drugs available although their nephrotoxicity in small mammals and humans is reversed when AG dosing is decreased or stopped (5,6).

The presence of DM as a risk factor for AG-induced renal injury is still contradictory. Streptozotocin-induced diabetic animals were protected against renal injury induced by AG and this protection was attributed to osmotic diuresis, which decreased tubular absorption of AGs and, consequently, their concentrations in the renal cortex (7,8). When these diabetic animals were treated by insulin, the animals lost their protection against AG-induced renal injury (8). In a clinical study involving 86 elderly patients, 9.3% of the patients receiving AG developed renal injury, and DM was identified by logistic regression as a risk factor for AG-induced renal injury (9).

To better understand the impact of DM and status of renal function on AG-induced renal damage, we carried out this observational study to investigate the extent and time course of AG-induced serum creatinine elevation in patients with and without type 2 diabetes mellitus (DM2).

PATIENTS AND METHODS

Settings and study design

The study was conducted at Al-Watani governmental hospital. It was a non-interventional prospective study of all patients receiving AG treatment in the internal during a 12-month period. There is no specific infectious unit in the hospital and patients with suspected infections are treated in the internal medicine department. Aminoglycosides are commonly used in the hospital as an empiric therapy and in infections caused by gram-negative bacilli. The study was approved by medical Ethics Committee and health authorities. The screened patients were those hospitalized due to infections that had to be treated with antibiotics of AG group by intravascular route. Patients were considered to have DM if they had a

positive history of hyperglycemia, had documented diagnosis of DM and were currently on antidiabetic medications. Different markers were reported to assess AG-induced renal damage. Serum creatinine elevation is considered the easiest, most accessible and has been reported to be clinically relevant to renal damage (10). In this study, AG-induced renal injury was monitored using serum creatinine levels, which were measured by Jaffe method (11). Since we are looking at the extent and time course of serum creatinine elevation, a similar pattern of hemodynamics will be obtained if creatinine clearance or glomerular filtration rate (GFR) measurements were used instead. Therefore, all data were presented using serum creatinine rather than creatinine clearance.

Selection criteria

Inclusion criteria for this study were: patients with initial serum creatinine level $\leq 106 \mu\text{mol/L}$, administration of AG iv daily for not less than six days, daily availability of serum creatinine measurements, and finally, having received no AG in the previous month. Serum creatinine measurements were usually done every day at about 10 a.m. for any patient receiving AG therapy. Aminoglycosides encountered in the hospital were either gentamicin or amikacin. Gentamicin is usually given in a dose range of 160-240 mg daily, whereas amikacin is usually given in a dose range of 500-1500 mg daily. Administration of the AG more than once within 24 h is considered multiple dosing. Exclusion of patients with high serum creatinine level was made to avoid misinterpretation of data.

Data extraction

Demographic, clinical, laboratory and medication data were obtained from the patient medical charts. Information collected included age, sex, previous hospitalization or AG use, presence of DM, hypertension, and congestive heart failure. Administration of AG every 24 h was considered as single daily dosing, while administration every 8-12 h was considered as multiple daily dosing. The decision to use single or multiple dosing was made by the

physician in charge based on the clinical status of the patient and severity of the condition. Serum creatinine level was measured at the commencement of AG course in all patients. Potentially nephrotoxic drugs like non-steroidal anti-inflammatory analgesics, furosemide and any others that were given to >10% of the study patients were included in the analysis.

Statistical analysis

Continuous variables were described using mean \pm standard deviation, while categorical variables were expressed as frequency and percentage. Comparison of serum creatinine levels between categorical groups was carried out using independent sample t-test, while comparison of serum creatinine on different days of

treatment was carried out using paired sample t-test. Association between categorical variables was carried out using χ^2 -test. Comparison of serum creatinine levels on any day and baseline serum creatinine value was carried out using one sample t-test. Data analysis and graphics were done by use of the Statistical Package for Social Sciences (SPSS 16).

RESULTS

During the study period, 94 patients met the inclusion criteria. A total of 24 (25.5%) patients had an increase of >44.2 $\mu\text{mol/L}$ (0.5 mg/dL) in serum creatinine during AG therapy, suggestive of a renal injury. Univariate analysis of total data showed that gentamicin ($P=0.03$) and multiple frequency dosing

Table 1. Demographic, clinical and laboratory data of DM2 and non-DM2 patients

Variable	Total N=94	DM2 patients N=42	Non-DM2 patients N=52	P
Age (yrs)	63.84 \pm 14.59	63.92 \pm 13.97	63.77 \pm 15.21	0.96
Sex (male)	52 (55.3%)	27 (64.28%)	25 (48.07%)	0.63
Body weight (kg)	77.88 \pm 15.96	85.74 \pm 14.25	71.54 \pm 14.47	<0.01
Initial serum creatinine ($\mu\text{mol/L}$)	85.7 \pm 18.6	88.4 \pm 15.9	83.1 \pm 21.2	0.18
Serum creatinine on day 6 ($\mu\text{mol/L}$)	107.8 \pm 27.4	113.2 \pm 25.6	104.3 \pm 29.2	0.15
Type of AG:				
gentamicin	45 (47.9%)	22 (52.38%)	23 (44.23)	0.47
amikacin	49 (52.1%)	20 (47.62)	29 (55.77)	
Concomitant furosemide	39 (41.5%)	19 (45.2%)	20 (38.5%)	0.63
Number of chronic diseases	1.98 \pm 1.3	2.95 \pm 0.82	1.2 \pm 1.06	<0.01
Patients with 44.2 $\mu\text{mol/L}$ rise in serum creatinine during therapy	24 (25.5%)	11 (26.2%)	13 (25%)	0.89

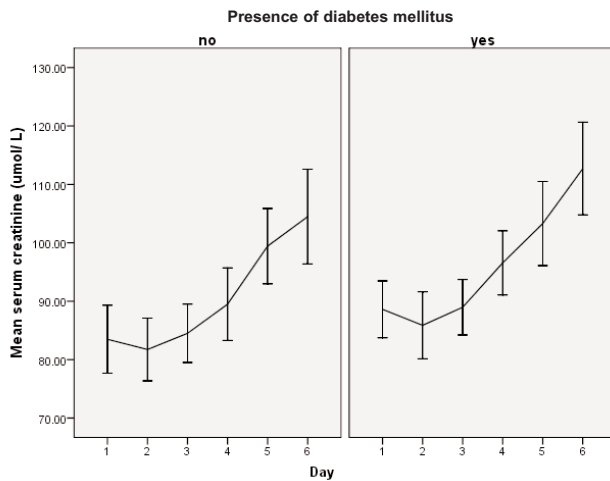
$P \leq 0.05$ is considered significant; DM = diabetes mellitus; AG = aminoglycosides

Table 2. Time course and extent of aminoglycoside-induced elevation of serum creatinine in DM2 and non-DM2 patients

Day	DM2 patients			Non-DM2 patients			
	Mean serum creatinine ($\mu\text{mol/L}$)	% change in serum creatinine	P	Day	Mean serum creatinine ($\mu\text{mol/L}$)	% change in serum creatinine	P
1	88.4	0	0.99	1	83.1	0	0.99
2	85.7	-3	0.38	2	82.2	-1	0.61
3	88.4	0	0.81	3	84.9	2	0.573
4	96.4	9	0.04*	4	89.3	7	0.044*
5	103.4	17	<0.01*	5	99.0	19	<0.01*
6	113.2	28	<0.01*	6	104.3	26	<0.01*

*statistically significant at $P < 0.05$ from the initial reference value (day 1).

Figure 1. Time course of aminoglycoside-induced serum creatinine elevation in DM2 and non-DM2 patients from day 1 until day 6.



($P=0.02$) were significantly associated with this cut-off increase in serum creatinine. However, sex ($P=0.2$), age ($P=0.8$) and presence of DM ($P=0.8$) were not significantly associated with such an increase. We further investigated the impact of DM2 on AG-induced renal injury. Of the total of 94 study patients, 42 (44.7%) of them had DM2, all of them on oral hypoglycemic agents. Baseline demographic, clinical and laboratory data of DM2 and non-DM2 patients are presented in Table 1. Univariate analysis showed that DM2 and non-DM2 patients had similar baseline characteristics except that DM2 patients had significantly higher body weight ($P<0.01$) and a higher number of chronic diseases ($P<0.01$). An increase of $44.2 \mu\text{mol/L}$ (0.5 mg/dL) in serum creatinine levels was detected in 24 (25.5%) patients during treatment with AG: eleven (26.2%) of 42 DM2 and 13 (25%) of 52 non-DM2 patients ($P=0.89$). The similarity between DM2 and non-DM2 patients in AG-induced serum creatinine elevation was independent of the frequency of AG dosing ($P=0.65$) or concomitant administration of furosemide ($P=0.63$) or type of AG administered (gentamicin *versus* amikacin) ($P=0.47$). No significant differences were observed in initial and final (day 6) serum creatinine levels between DM2 and non-DM2 patients (initial: 88.4 ± 15.9 *versus* $83.1 \pm 21.22 \mu\text{mol/L}$; $P=0.18$; final: 113.15 ± 25.64

versus $104.3 \pm 29.17 \mu\text{mol/L}$; $P=0.15$) (Table 2). In DM2 patients, significant ($P=0.04$) serum creatinine elevation was observed on day 4 of treatment. The maximum rise in serum creatinine levels was 28% from baseline levels and was seen on day 6 of treatment (Table 2 and Fig. 1). Similar findings were observed in non-DM2 patients.

DISCUSSION

Our results indicated that DM2 with normal baseline was not a risk factor for AG-induced renal injury evident by an increase in serum creatinine $>44.2 \mu\text{mol/L}$. Other researchers have reached similar conclusions. A study of 249 elderly patients receiving amikacin or gentamicin did not find DM2 to be a risk factor for renal injury, based on logistic regression analysis (12). Similarly, a stepwise discriminant analysis of 214 patients treated with gentamicin or tobramycin did not identify DM2 as a risk factor for AG-induced renal injury (13).

The normal baseline renal function in this sample of patients who have a long standing history of DM2 could be one reason. Aminoglycosides are toxic to the kidney because a small amount of AG is retained in the epithelial cells of the proximal tubule after renal elimination (14). This localized AG is believed to cause extensive lysosomal and mitochondrial damage in tubular proximal cells leading to non-oliguric renal failure. In our study, patients had normal renal function, which suggests that cellular uptake of AG into proximal tubular cells was similar between the two groups of patients. Besides uptake, it is possible that the AG degradation and removal also play an important role in normal renal function. A third possible reason is the relatively older age of patients that made patients in both groups equally vulnerable. There is a case report of a patient aged 55, with a long history of DM2 and hypertension, who was treated with gentamicin and showed signs of oliguric renal insufficiency on the third day and anuric renal insufficiency on the fifth day (15). Therefore, patients with DM2 who require AG therapy need an initial assessment of renal function before initiation of AG

therapy. The proper dose of AG in patients with DM2 will differ from patient to patient, based on creatinine clearance.

Our results showed that the time course and extent of serum creatinine elevation among DM2 and non-DM2 patients were similar. In both groups, the significant rise started as early as day 4 of therapy. Animal studies have shown that at least several days of AG administration are needed before evidence of nephrotoxicity occurs (16). A study in 25 patients using urine N-acetyl-D-glucosaminidase (NAG) activity as a marker of renal tubular injury has also demonstrated that significant injury to proximal tubules occurred in the very early days of AG treatment, although the most significant injury occurred following day 7 of therapy (17).

Limitations

This study had some limitations. The sample size used in the study was smaller than those reported in similar studies. Furthermore, the use of serum

creatinine instead of N-acetyl-D-glucosaminidase as a marker might have affected our conclusion regarding the impact of DM2 on AG-induced renal injury. Finally, the lack of information regarding blood urea nitrogen, blood glucose levels at the time of serum creatinine measurement, concomitant medications that could affect the levels of serum creatinine, and lack of control over fluid intake in study patients might have affected the interpretation of our data.

CONCLUSION

In conclusion, the similar extent and time course of serum creatinine elevation between DM2 and non-DM2 patients suggest that there is nothing unique in the diabetic state that would alter the AG pattern of renal adverse effects. Studies regarding the effect of diabetic state and osmotic diuretics on molecular transport of AGs into tubular epithelial cells are needed.

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