KIDNEY INJURY MOLECULE-1 AS AN EARLY AMIKACIN-INDUCED NEPHROTOXICITY MARKER IN PATIENTS WITH SEPSIS HOSPITALIZED IN THE INTENSIVE CARE UNIT

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ABSTRACT

Objective: This study sought to determine the correlation between trough plasma amikacin concentrations and urinary normalized kidney injury molecule-1 (KIM-1) concentrations as an early biomarker of nephrotoxicity in patients with sepsis who are hospitalized in an intensive care unit.

Methods: In this pilot study, 12 patients with sepsis were treated with amikacin 1000 mg/day between May 2015 and September 2015. The correlation between trough plasma amikacin concentrations measured after the third dose and the elevation of urinary normalized KIM-1 concentrations after the third amikacin dose relative to the first/second dose was evaluated.

Results: In total, three patients had trough plasma amikacin concentrations exceeding the safe level (>10 µg/ml). Furthermore, eight patients displayed higher normalized KIM-1 concentrations after third dose than after the first/second dose; however, there was no correlation between trough amikacin concentrations and the elevation of urinary normalized KIM-1 concentrations (r=0.3, p=0.3).

Conclusion: The study results illustrated that short-term treatment with an amikacin dose of 1000 mg/day was generally safe in patients with sepsis.

Keywords: Amikacin, Kidney injury molecule-1, Nephrotoxicity

INTRODUCTION

Sepsis is a common cause of mortality, and severe sepsis results in death in up to 50% of patients [1]. Aminoglycosides, especially amikacin, are the most commonly used antibiotics in patients with sepsis due to Gram-negative bacterial infections even though these drugs can induce nephrotoxicity in 10–20% of patients [2].

Amikacin has a different structure than other aminoglycosides; therefore, it is not inactivated by enzymes that commonly inactivate gentamicin [2]. An adequate plasma level of amikacin is needed to kill the bacteria that cause sepsis. The target amikacin concentration for treating bacterial sepsis is 20–40 µg/ml, whereas the trough level to avoid nephrotoxicity is less than 10 µg/ml [3,4].

Acute kidney injury (AKI) is traditionally diagnosed by measuring blood urea nitrogen and serum creatinine levels; however, these parameters are neither sensitive nor specific for establishing a diagnosis of AKI. A more specific AKI biomarker is kidney injury molecule-1 (KIM-1) [5]. KIM-1 is a tubular protein that is induced by ischemic reperfusion injury or exposure to proximal tubule toxins. KIM-1 can be produced at the site of injury, and it can be measured quantitatively, rapidly, and easily in urine or blood [6].

Currently, the dose of amikacin used in the intensive care unit (ICU) of Cipto Mangunkusumo Hospital (RSCM) is 1000 mg/day, compared to a recommended dose of 15 mg/kg BW [7,8]. It is unknown whether the currently used dose would generate a trough amikacin level exceeding the minimum level known to cause nephrotoxicity. This study examined trough plasma amikacin levels in patients with sepsis hospitalized in the ICU of RSCM who were treated with amikacin 1000 mg/day, and the relationship between trough amikacin and urinary KIM-1 levels was analyzed.

METHODS

Trough plasma amikacin levels and urinary normalized KIM-1 levels were measured in patients with sepsis who received amikacin 1000 mg/day in the ICU of RSCM. All patients in this study had good renal function. Trough plasma amikacin levels were measured after the third dose (immediately before the fourth dose was administered), whereas urinary normalized KIM-1 levels were measured after the first/second and third doses. The correlations of the difference of normalized KIM-1 levels between the first/second and third doses and the third-dose trough amikacin levels were evaluated.

Blood samples were obtained from patients 5 min before the fourth dose of amikacin was administered to measure trough amikacin levels. Plasma samples were transferred to the pharmacokinetics laboratory after centrifugation and stored at −20°C before analysis. Plasma amikacin levels were measured through liquid chromatography-tandem mass spectrometry using a Waters Alliance 2695 high-performance liquid chromatography system and Quatro Micro Triple Quadrupole MS detector with the lowest limit of quantification of 1 µg/ml. To measure absolute urinary KIM-1 levels, 1 ml of a 24-h urine sample (starting immediately after administration of the first or second dose of amikacin until immediately before the next dose) was used. The urinary samples were analyzed through enzyme-linked immunosorbent assay using a KIM-1 kit (R and D Systems DKM 100). The remainder of the urinary samples was transported to the clinical pathology laboratory of RSCM to quantify urine creatinine levels.

The correlation between trough plasma amikacin levels and the increase of normalized KIM-1 levels was verified using Spearman's test. The differences between the first-/second-dose and third-dose urinary normalized KIM-1 levels were analyzed using Wilcoxon's test.

RESULTS

Subject selection was performed from May 2015 to September 2015. Among 20 targeted patients, only 15 could be recruited. Of these subjects, one died before the sample for trough amikacin and third-dose KIM-1 level measurements were obtained. A second subject could not provide

the day 3 urinary creatinine measurement sample. Another subject was excluded due to prior continuous renal replacement therapy. Thus, data were analyzed for 12 subjects. The basic characteristics of the subjects are shown in Table 1.

The administration of amikacin 1000 mg/day resulted in varied trough amikacin levels after the third dose (Table 2). In total, three subjects had trough levels exceeding 10 µg/ml.

In this study, 8/12 subjects (66.7%) exhibited elevated normalized urinary KIM-1 levels after the third dose compared to those after the first or second dose.

The Spearman correlation test revealed no correlation between trough amikacin levels and changes of urinary KIM-1 levels among the 12 subjects (r=0.3, p=0.3). Meanwhile, patient 7 was excluded from Pearson's correlation test because this patient's trough amikacin level differed by >2 standard deviation from the median trough level of the subjects. However, the result also revealed no correlation between trough amikacin levels after the third dose and the difference of the

urinary normalized KIM-1 levels between the third and first/second doses (p=0.478; r=0.24).

Eight subjects in this study exhibited higher 3rd-day normalized KIM-1 levels compared to the 1st/2nd-day levels; however, the increase was not statistically significant (Wilcoxon's test, p=0.19, Table 3). Varied urinary KIM-1 levels were also detected among the subjects (Tables 3 and 4).

DISCUSSION

This study evaluated the correlation between the trough level of amikacin following administration at 1000 mg/day and the increase of normalized KIM-1 levels as a marker of kidney damage in patients with sepsis. The failure to obtain a correlation between the variables could be due to the lower-than-expected number of enrolled subjects. This may have reduced the power of the statistical test.

Despite the subjects ranging in weight from 35 to 70 kg, the dose of amikacin is 1000 mg/day for all patients with sepsis in the ICU of RSCM regardless of their weight. Consequently, the trough amikacin level in patient 7, who had the lowest weight, exceeded the recommended level of 15–25 mg/kg [7,8]. This patient received an amikacin dose of 28.6 mg/kg BW, leading to elevated trough amikacin and normalized KIM-1 levels. Based on these findings, this patient may have had an increased risk of developing nephrotoxicity [9].

Conversely, patient 12 (90 kg), who had a body mass index (BMI) of 37, exhibited increased normalized KIM-1 levels after the third dose despite a trough amikacin level below the safe threshold. Determination of amikacin dose for obese patients is based on the ideal body weight rather than the actual body weight, using the formula: ideal body weight + 0.4 (total body weight- ideal body weight)×amikacin dose [10]. The elevation of KIM-1 levels may be related to the condition of the patient, who had septic shock. In line with these data, a study by Balqis et al. [11] found that patients with sepsis and AKI have higher absolute KIM-1 levels (median=2.7 ng/ml, range=0.7–13.4) than those without AKI (median=0.8 ng/ml, range=0–3.4, p<0.001).

Meanwhile, patient 10 had an increased normalized KIM-1 level after the third dose. This patient, who was 60 years old, had a history of AKI that was resolved 2 week before sepsis developed. The risk factors for aminoglycoside-induced nephrotoxicity include age, concurrent disease, hepatic dysfunction, septic condition, and kidney dysfunction [12]. However, a study performed by Boghdady et al. [13] identified no association of KIM-1 levels with age, sex, and BMI in 79 critically ill patients.

This study had a number of limitations. First, the number of subjects was small and fewer than expected. The sample size required according to the obtained correlation value (r) in this study, as determined using the formula $\{(Z\alpha+Z\beta)/(0.5\ln[1+r]/[1-r])\}^2+3$ [14], was 51.

Table 1: Basic characteristics of the subjects

Characteristics	Number of subjects (%)
Sex	
Male	5 (41.7)
Female	7 (58.3)
Age	
18–65 years	12 (100)
Creatinine clearance (ml/min)	
60–90	2 (16.7)
>90	10 (83.3)
Total	12 (100)

Table 2: Trough level plasma of amikacin

No	Patient	C_{min} (µg/ml)
1	Patient 1	1.26
2	Patient 2	4.56
3	Patient 4	6.74
4	Patient 5	4.83
5	Patient 6	3.19
6	Patient 7	27.04
7	Patient 9	3.24
8	Patient 10	12.59
9	Patient 11	8.29
10	Patient 12	8.04
11	Patient 13	13.75
12	Patient 15	4.22

Median=5.78

Table 3: KIM-1 levels in urine

No	Subject	Absolute KIM-1 level after the 1st or 2nd dose (ng/ml)	Absolute KIM-1 level after the 3rd dose (ng/ml)	Normalized KIM-1 level after the 1st or 2nd dose (µg/g)	Normalized KIM-1 level after the 3rd dose (µg/g)	Difference between the 1st or 2nd dose and 3rd dose (µg/g)*
1	Patient 1	1.78	0.45	1.37	0.68	−0.69
2	Patient 2	1.31	1.60	1.74	3.09	1.35
3	Patient 4	0.23	0.04	0.39	0.20	−0.19
4	Patient 5	0.53	0.41	1.06	1.25	0.19
5	Patient 6	0.67	0.54	1.42	1.30	−0.12
6	Patient 7	0.95	1.01	2.97	3.68	0.71
7	Patient 9	0.80	1.48	4.74	6.22	1.48
8	Patient 10	2.08	3.98	5.81	9.31	3.5
9	Patient 11	5.49	3.96	23.13	18.68	−4.45
10	Patient 12	8.56	6.15	25.22	27.72	2.5
11	Patient 13	1.87	0.79	4.68	5.48	0.8
12	Patient 15	9.45	6.80	17.02	17.10	0.08

*The third-dose normalized KIM-1 level was subtracted from first- or second-dose normalized KIM-1 level, KIM-1: Kidney injury molecule-1

Table 4: Urinary KIM-1 levels

KIM-1 category	KIM-1 level		Total number of subjects
	Median	Range	
Absolute KIM-1 level after the first or second dose (ng/ml)	1.54	0.23–9.45	12
Absolute KIM-1 level after the third dose (ng/ml)	1.24	0.04–6.80	12
Normalized KIM-1 level after the first or second dose (µg/g)	3.82	0.39–25.22	12
Normalized KIM-1 level after the third dose (µg/g)	4.58	0.2–27.72	12
Difference in normalized KIM-1 levels between the first or second dose and the third dose (µg/g)*	0.45	−4.45–3.5	12
Total number of subjects			12

*The third-dose normalized KIM-1 level was subtracted from first- or second-dose normalized KIM-1 level, KIM-1: Kidney injury molecule-1

Another limitation was that the initial KIM-1 level before amikacin administration was not measured due to difficulties in finding eligible patients for this study. The initial level was needed to obtain information about the kidney function of the patients before therapy and ensure the absence of other factors affecting nephrotoxicity risk. In addition, KIM-1 levels were not compared between the patients and healthy controls.

CONCLUSION

In this study, no correlation was found between the trough amikacin levels and the elevation of urinary normalized KIM-1 levels after the third amikacin dose. After 3 days of treatment with 1000 mg/day amikacin, the trough levels of the drug in patients with sepsis were generally within the safe limits for avoiding nephrotoxicity (<10 µg/ml).

CONFLICTS OF INTEREST

The authors have no conflicts of interest to be declared.

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