Antibiotics Induced Acute Kidney Injury: Incidence, Risk Factors, Onset Time and Outcome

Hossein Khalili[1], Samaneh Bairami[1], and Mona Kargar[2]

1-Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

[2] Research Center for Rational Use of Drugs, Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

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Abstract- Drug induced acute kidney injury (AKI) has been implicated in 8% to 60% of all cases of in-hospital AKI and as such is a recognized source of significant morbidity and mortality. Evaluation of incidence, risk factors, onset time, and outcome of antibiotics' associated acute kidney injury. During one-year period, all patients who developed acute kidney injury during their hospital stay in the infectious diseases ward of Imam Khomeini hospital were included in the study prospectively. Patients' demographic data, baseline diseases, cause of current hospital admission, history of past and current medications and hemodynamic parameters were collected and monitored closely. Drug induced acute kidney injury was defined based on acute kidney injury network criteria. From 424 admitted patients, 76 (17.9%) developed acute kidney injury. Aminoglycosides (gentamicin and amikacin), amphotericin B, vancomycin, beta-lactam antibiotics (cefazolin and ceftriaxone) in monotherapy and combination therapy were the causes of acute kidney injury in most of the patients. From the co-morbid diseases in patients with acute kidney injury, diabetes mellitus (26.3%) and hypertension (5.5%), were the most frequent ones. Presence of diabetes mellitus as comorbidity (OR=2.6; CI=1.3-5.7, *P*=0.01), dehydration of patients upon admission (OR=3.4; CI=1.9-6.4, *P*<0.001), and administration of nephrotoxic combinations (OR=2.1; CI=1.2-4.1, *P*=0.04) were independent risk factors for antibiotic induced nephrotoxicity in our study. About 18% of the patients developed acute kidney injury during their hospitalization period in the infectious diseases ward. Aminoglycosides, amphotericin B, vancomycin and beta-lactam antibiotics were responsible agents for acute kidney injury in this study.

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Keywords: Acute kidney injury; Antibiotics; Risk factors

Introduction

Drug induced acute kidney injury (AKI) has been implicated in 8% to 60% of all cases of in-hospital AKI and as such is a recognized source of significant morbidity and mortality (1). In-hospital drug use may contribute to 35% of all cases of acute tubular necrosis, most cases of allergic interstitial nephritis, as well as nephrotoxicity due to alterations in renal hemodynamics and postrenal obstruction (2). Antibiotics are among the most widely used drugs, and more than half of hospitalized patients receive antibiotics (3). Frequent episodes of adverse drug reactions (ADR) following antimicrobial therapy were reported (4,5). Kidney injury is the most important adverse reaction that was reported with antibiotics (6,7). The incidence of antibiotic-induced nephrotoxicity alone may be as high as 36% (8). Aminoglycoside nephrotoxicity has been reported in up to 58% of patients who are receiving aminoglycoside therapy, most recent reviews suggest rates of 5% to 15% (9,10).

The kidney is a common target for toxic xenobiotics, due to its specific capacity to clearance of toxic substances (11). Despite recent advances in dialysis delivery and the development of sophisticated continuous renal replacement therapy, AKI continues to have a grim prognosis. Indeed, the occurrence of ARF in critically ill patients carries at least a 50% mortality rate (12).

The goals of this prospective study were evaluation

Corresponding Author: Hossein Khalili
Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran, Postal Code:1417614411
Tel: +98 912 2979329, Fax: +98 21 66461178, E-mail: khalilih@sina.tums.ac.ir

of frequency, characteristics and possible predisposing factors of antimicrobial induced AKI in the infectious diseases ward of Imam Khomeini hospital.

Materials and Methods

All hospitalized patients in the adult infectious diseases ward of Imam Khomeini Hospital during one year period who received at least one antimicrobial agent as a part of their treatment regimen were included in the study. Imam Khomeini Hospital is the biggest tertiary teaching hospital, affiliated to Tehran University of Medical Sciences, Tehran, Iran. This hospital has 1100 beds at all that 60 out of them are allocated for infectious diseases. The study was approved by the local ethical committee of the hospital, and all included patients provided informed consent form.

Patients who were hospitalized for less than one-week in the infectious diseases ward were excluded from our study. Other exclusion criteria of the study were renal dysfunction at hospital admission, hemodialysis requirement within the first 48 hours of hospitalization, under treatment with nephrotoxic agents such as calcineurin inhibitors, recent administration of contrast media agents and known cases with chronic kidney diseases. For each included patient, a specific data sheet was designed and following the patient's information were collected; demographic data (including age, weight and sex), vital signs (temperature, pulse rate, respiratory rate and blood pressure), drug history, co-morbid diseases (such as diabetes mellitus (DM), hypertension (HTN), human immunodeficiency virus (HIV) infection), prescribed antibiotics in the course of hospitalization, other medications that potentially may affect renal function (such as non steroidal anti inflammatory drugs (NSAIDs), angiotensin converting enzyme inhibitors (ACEIs) and diuretics), laboratory parameters (such as serum creatinine (SCr), blood urea nitrogen (BUN), sodium (Na), potassium (K), complete blood count), intake and output and urine volume at patient's hospital admission and every two days thereafter. Also, hydration status of the patients was evaluated and recorded. Patient's dehydration was considered if the ratio of patient's BUN to SCr was greater than 20, urine volume was less than 400ml/day, history of fluid or blood losses was positive, and patient had positive signs and symptoms of dehydration on physical examination. Patients' renal function was evaluated specifically based on creatinine clearance (ClCr) that was calculated by Cockroft-Gault formula; Cockcroft and Gault equation:

CrCl=(140-age) x IBW/ (Scr x 72) [(x 0.85 for females)]

Estimate Ideal body weight (IBW) in (kg):

Males: IBW=50 kg+2.3 kg for each inch over 5 feet.

Females: IBW=45.5 kg+2.3 kg for each inch over 5 feet.

In the classic study of the epidemiology of hospital-acquired AKI, AKI was defined as a 0.5 mg/dL increase in serum creatinine if the baseline serum creatinine was ≤1.9 mg/dL, an 1.0 mg/dL increase in serum creatinine if the baseline serum creatinine was 2.0 to 4.9 mg/dL, and a 1.5 mg/dL increase in serum creatinine if the baseline serum creatinine was ≥5.0 mg/dL (13). Most recent studies referred to the definitions and classifications of AKI of RIFLE and AKIN criteria (14,15). The RIFLE criteria (acronym indicating Risk of renal dysfunction; Injury to kidney; Failure of kidney function; Loss of kidney function; and End-stage kidney disease) classify AKI into three categories of severity (Risk, Injury and Failure) and two categories of clinical outcome (Loss and End-stage kidney disease). The AKIN criteria (Acute Kidney Injury Network) classify AKI into three stages of severity (Stages 1, 2 and 3) based on levels of serum creatinine and patient's urine output. We used AKIN criteria for detection and staging of antibiotics induced AKI in this study. Base on AKIN criteria, increase in serum creatinine of more than or equal to 0.3 mg/dL or increase to more than or equal to 150 to 200 percent (1.5- to 2-fold) from baseline (or urine output Less than 0.5 mL/kg per hour for more than 6 hours), increase in serum creatinine to more than 200 to 300 percent (>2- to 3-fold) from baseline (or urine output Less than 0.5 mL/kg per hour for more than 12 hours), and increase in serum creatinine to more than 300 percent (>3-fold) from baseline (or urine output Less than 0.3 mL/kg per hour for 24 hours or anuria for 12 hours) was considered as stage 1, 2 and 3 of AKI respectively.

We used AKIN criteria for detection and categorization of the antibiotics associated AKI in this study. For patients who developed antibiotic associated AKI, time onset of AKI with respect to initiation of responsible agent and predisposing factors for AKI were recorded. Also, outcomes of the patients regarding to AKI were followed during the hospitalization course up to the hospital discharge.

Statistical analysis of the results was performed using SPSS 16. All continuous measurements are expressed as mean±standard deviation. Paired sample t-test was used for comparing of parameters before and after AKI. Pearson's chi-square test applied for evaluation of correlations. Multivariate analysis was used for determination of possible risk factors of AKI.

Statistical levels less than 0.05 were considered significant.

Results

In the study period, 466 patients were evaluated. From these patients, 19, 10, 8, 3 and 2 out of them were excluded from the final analysis due to the duration of hospitalization less than one week in the Infectious Disease Ward, did not receive antibiotic during hospitalization course (these patient were hospitalized for diagnostic evaluations), history of preexisting renal diseases or raised of serum creatinine at hospital admission, recent (during 24 hours of hospital admission) administration of contrast media agents, and patient's preference (did not provide informed consent form) respectively. Finally, 424 patients fulfilled the inclusion criteria and were monitored closely during their hospitalization course for occurrence of AKI. Seventy six (17.9%) of the patients developed AKI during their hospitalization period. Demographic and baseline data of patients with and without AKI was summarized in table 1.

The most commonly used antibiotics for the patients either as monotherapy or as a part of the combination therapy regimen were ceftriaxone (54.9%), cefazolin (31.9%), gentamicin (29.7%), vancomycin (22%), amikacin (18.7%), cloxacillin (17.7%), imipenem (15.4%), ceftazidim (13.2%) and amphotericin B (6.6%). Number of patients who received these antibiotics, number of the patients who developed AKI following antibiotic therapy, time onset of the AKI, number of patients with diabetes mellitus, number of patients with dehydration at the time of AKI and number of patients who concomitantly received other nephrotoxic agents has been shown in table 2. In patients who developed antibiotic induced AKI, 30.3% of them had a positive history of current use of other nephrotoxic agents such as NSAIDs, ACEIs or diuretics. Also, forty-one (53.9%) of patients who developed AKI in their hospitalization course were dehydrated at the time of hospital admission.

AKI was developed within 12.1±9.6 days of the antimicrobial therapy. The mean±SD of patients' baseline SCr was 1.1±04 mg/dl. In patients with AKI SCr was raised to 2.6±1.5 mg/dl that was significantly increased from baseline values (P<0.001). Mean baseline sodium (Na) and potassium (K) was 136.9±6.3meq/l and 3.9±0.6meq/l respectively and at the time of AKI, these values were 138.9±6.7meq/l and 4.2±0.9meq/l correspondingly which did not show significant differences.

Table 1. Baseline characteristics of patients with AKI and without AKI*

Parameter	Patients with AKI	Patients without AKI	*P* value
Sex			
Male/Female	35/41	160/188	0.4
Age (years old)	44.3 ±17.8	48.7 ±18.1	0.3
Baseline diseases			
DM (%)	26.3	17.3	0.02
HTN (%)	5.5	2.6	0.01
Concomitant Drugs			
NSAIDs (%)	17.1	11.3	<0.001
ACEI (%)	7.9	3.4	<0.001
Diuretics (%)	5.3	2.6	<0.001
Cause of hospital admission			
Endocarditis	28.5	24.8	0.1
Cellulites	12	13.9	0.4
Diabetic foot	9.8	8.6	0.5
Sepsis	9.8	10.9	0.7
Meningitis	8.7	7.4	0.5
Osteomyelitis	6.6	6.2	o.2
Brain abscess	5.5	4.2	0.1
Mucormycosis	4.4	5.6	0.6
Other infections	9.9	11.1	0.9
Mortality rate	2.2	0.6	<0.001

*Baseline characteristics of patients with and without Acute Kidney Injury (AKI) have been summarized in this table.

Table 2. The most commonly used antibiotics in the Infectious Diseases Ward*

Antibiotic	Number of patients who received this antibiotic	Number of patients who developed AKI	Time onset of AKI (day) (mean ±SD)	Number of patients with diabetes mellitus	Number of patients with dehydration	Number of patients with concomitant nephrotoxic agents therapy
Ceftriaxone (1-2g q12h)	153	2	15.1±1.6	0	3	0
Cefazolin (1-2g q8h)	85	1	13.2±1.1	0	1	0
Gentamicin (1-1.7mg/kg q8h)	15	3	6.1±3.1	0	1	0
Vancomycin (15mg/kg q 12h)	27	2	18.6±5.7	0	2	0
Amikacin (7.5mg/kg q12)	29	3	4.3±1.9	0	2	0
Cloxacillin (1-2g q4-6h)	40	1	12.9±1.5	0	0	0
Imipenem (500 mg q 6h)	10	0	11.2±2.5	0	0	0
Ceftazidim (1-2g q8-12h)	46	1	13.1±3.6	0	1	0
Amphotericin B (0.5-1 mg/kg/daily)	13	10	2.7 ±1.5	1	5	0
Ceftriaxone + Gentamycin	35	6	4.6±1.9	1	2	1
Cefazolin + Gentamicin	40	8	5.1±2.6	3	3	3
Vancomycin+Ceftriaxone	33	6	14.5±4.1	2	3	4
Vancomycin+Amikacin	10	4	4.2±1.3	1	4	4
Vancomycin+Imipenem	25	5	13.4±2.8	2	2	3
Imipenem +Amikacin	30	5	6.4±3.3	2	3	2
Cloxacillin+Gentamicin	35	5	5.6±1.1	2	2	2
Ceftazidim+Amikacin	10	2	6.4±2.5	0	0	1
Amphotericin + Ceftriaxone	7	5	3.3±2.6	2	2	1
Amphotericin +Vancomycin+Ceftriaxone	5	5	2.2±1.7	3	2	
Amphotericin+Vancomycin	3	3	3.6±1.3	1	1	

*In this table incidence of each antibiotic induced AKI, times of onset of AKI and possible risk factors of AKI have been categorized.

Table 3. Categorization of antibiotic-associated AKI based on AKIN criteria*

Antibiotic	% of patients with stage 1 AKI	% of patients with stage 2 AKI	% of patients with stage 3 AKI
Ceftriaxone	92	8	0
Cefazolin	93	7	0
Gentamicin	75	12	3
Vancomycin	83	12	5
Amikacin	71	24	5
Cloxacillin	94	6	0
Imipenem	92	8	0
Ceftazidim	99	1	0
Amphotericin B	70	19	11
Ceftriaxone + Gentamycin	74	15	11
Cefazolin + Gentamicin	75	16	9
Vancomycin+Ceftriaxone	82	19	9
Vancomycin+Amikacin	70	25	5
Vancomycin+Imipenem	81	18	1
Imipenem +Amikacin	70	29	1
Cloxacillin+Gentamicin	88	11	1
Ceftazidim+Amikacin	86	12	2
Amphotericin + Ceftriaxone	56	35	9
Amphotericin +Vancomycin+Ceftriaxone	52	44	4
Amphotericin+Vancomycin	50	40	10

*In this table, antibiotic induced AKI was categorized based on the Acute Kidney Injury Network (AKIN) definitions. Frequency of different stages of AKI has been reported for each antibiotic that used by patients.

Based on the AKIN criteria, 76%, 26% and 8% of detected antibiotics induced AKI was categorized as stage 1, 2 and 3 respectively (table 3).

From the baseline diseases in patients with AKI, DM (26.3%) and HTN (5.5%) were the most frequent ones. Presence of DM as co-morbidity (OR=2.61; CI=1.35-5.77, *P*=0.01), dehydration of patients upon admission (OR=3.45; CI=1.95-6.44, *P*<0.001), and concomitant nephrotoxic medications (OR=2.01; CI=1.02-4.19, *P*=0.04) were risk factors for antibiotic induced AKI in our study. Responsible antibiotics were stopped in the 86.5% of occasions and antibiotics dose adjustment was done in 13.5% of episodes. After dose adjustments or drug discontinuation, the patients' SCr was decreased to 1.1±0.3 mg/dl during a median of 5 days (range of 1 to 34 days) that was not significantly different from baseline values (*P*=0.826). None of the patients needed renal replacement therapy. Mortality rate in patients who experienced AKI during hospitalization course was 2.2% that was significantly higher than non-AKI group that was 0.6% (*P*<0.001).

Discussion

Drug-induced AKI is a commonly encountered renal injury in the hospitalized patients (16). Currently clinical evidences showed that AKI can be an independent risk factor of mortality in the hospitalized patients (17-18). Prevalence of drug induced AKI was reported in up to 20-30% of the hospitalized patients in intensive care units and 6% of them required renal replacement therapy (19). In our study, the incidence of antimicrobial induced AKI was 17.9%. In a similar study that have investigated the prevalence of adverse drug reactions in a one-year period, the incidence of AKI was 16.3% (20).

We have excluded patients who developed AKI within 24 hours of hospital admission. AKI in this time may be related to baseline diseases, current infections and consequent hemodynamic changes and physiological responses, or dehydration of patients. Most of the AKIs in this study were induced by aminoglycosides, vancomycin, beta lactam antibiotics and amphotericin B when used in combination with other agents, however, vancomycin, amphotericin B and aminoglycosides were the causes of AKI even when used as monotherapy.

Several conditions including concomitant vancomycin therapy (21), furosemide use (22) and volume depletion (23) were reported as predisposing factors of aminoglycosides induced AKI. In the intensive care unit setting, aminoglycoside-associated nephrotoxicity occurred frequently and was associated with a high rate of mortality (18). They found that DM, hypertension, the concomitant use of nephrotoxic drugs are as an independent risk factors for development of aminoglycosides nephrotoxicity. Also in our study, DM and concomitant other nephrotoxic agents were predisposing factors of antibiotics induced AKI. Incidence of gentamicin induced AKI was reported between of 8 to 26% (24,25) and commonly has manifested within 5 to 10 days after initiation of therapy (26). Gentamicin (6.1±3.1 days) and amikacin (4.3±1.9 days) induced AKI also presented within this range of time in our study.

Vancomycin as monotherapy may cause reversible renal dysfunction in 5% of patients (27). The incidence of vancomycin induced AKI when used as monotherapy was 7.4% in the present study. Ingram *et al.,* (28) found that hypertension, concomitant aminoglycosides therapy, loop diuretics and steady-state vancomycin concentration are predisposing factors of vancomycin induced AKI in an outpatient setting. In another study, vancomycin induced AKI has been reported in 10.9% of patients, at least 12 days after vancomycin administration (29). In our study patients who received vancomycin developed AKI after 18.6±5.7 days that is compatible with the previous study. Data regarding the increase in vancomycin induced nephrotoxicity when adding aminoglycosides are controversial. Rybak *et al.,* reported AKI in 5%, 11% and 22% of patients who received vancomycin monotherapy, aminoglycoside monotherapy, and combination of vancomycin and an aminoglycoside, respectively (21). Also, Goetz and Sayers indicated that nephrotoxicity occurred more frequently in patients given combination of vancomycin and aminoglycoside (13.3%) than in patients treated with vancomycin monotherapy (4.3%) (30). In contrast, Huang *et al.,* found no significant difference between the nephrotoxicity of vancomycin alone or in combinations with an aminoglycoside (31). Furthermore, Cimino *et al.,* failed to demonstrate a significant increase in nephrotoxicity in patients receiving aminoglycosides and vancomycin concurrently (32). Four out of 10 (40%) patients who received vancomycin in combination with aminoglycosides developed AKI that is significantly (p<0.001) more common than vancomycin monotherapy (7.4%). AKI was developed sooner (4.2±1.3 days) in vancomycin and aminoglycoside combination therapy compared to vancomycin alone (18.6±5.7 days) (*P*=0.03).

Beta-lactam antibiotics are the most common

administered antibiotics in our hospital Although ceftriaxone induced acute kidney injury is not a major concern, low molecular weight proteinuria after its administration was reported in the previous study (33). Ceftriaxone induced AKI when administered concomitantly with aminoglycosides was reported (34). Also crystalluria and frank nephrolithiasis with ceftriaxone has been noted in the literature (35,36). Ceftriaxone induced AKI was detected in 1.3% of patients on monotherapy and in 17% of patients in concomitant with aminoglycosides in the present study.

Amphotericin B was the other agent that precipitated AKI when used as monotherapy or combination therapy in this study. Nephrotoxicity is a major dose-limiting toxic effect of amphotericin B. In 80% of patients receiving a complete course of amphotericin B therapy, rises of BUN and SCr were reported (37). In another study, a doubling raise in SCr was reported in 40-60% of patients following a full course of amphotericin B treatment (38). Risk factors for amphotericin B renal toxicity include preexisting renal insufficiency, concomitant nephrotoxic agents, cumulative doses, and volume depletion (32). Wingard and colleagues evaluated 239 immunosuppressed patients receiving amphotericin B and found that the creatinine level doubled in 53% of patients and exceeded 2.5 mg/dL in 29% of them. From these patients, 14.5% required dialysis and 60% of them died. Underlying hemodialysis, duration of amphotericin B therapy, and use of nephrotoxic agents were associated with greater risk of death (39). In our study 77% of patients in amphotericin B monotherapy and 100% of patients in concomitant with vancomycin developed AKI.

In the present study, we also evaluate the hydration status of the patients. More than half of patients with AKI suffered from dehydration upon admission. The noteworthy of this evaluation comes from the point that one of the considerable risk factors associated with developing renal side effects of antimicrobial agents is volume depletion (40). Diuretics along with ACEIs and NSAIDs may have an additive effect in the occurrence of AKI in approximately one third of the patients. ACEIs have the potential of inducing or worsening AKI by inhibiting angiotensin II–mediated efferent arteriole vasoconstriction (19). As a result, by decreasing interglomerular pressure, AKI may precipitate (19). Administration of NSAIDs should be with caution in patients with decreased renal perfusion since they may further reduce renal blood flow (19). Risk factors for NSAIDs induced AKI include pre-existing renal dysfunction, severe cardiovascular or hepatic failure, or the concomitant use of nephrotoxic medications, such as aminoglycosides, and ACEIs (41,42). The use of NSAIDs in these circumstances should be balanced against potential adverse events including AKI.

In spite of large sample size, this was a single center study and did not have a control group. Due to the wide range of infectious diseases that caused hospital admission, we could not evaluate the effects of infections on the occurrence of AKI. Differentiation of the main cause of AKI in combination regimens is another limitation of the study. Furthermore, we did not have the facilities to measure the level of antibiotics to assess whether patients with AKI had higher blood concentrations of implicated agents) or not.

In conclusion, AKI is common in the Infectious diseases ward especially with aminoglycosides, vancomycin and amphotericin B in monotherapy and combination therapy. Diabetic and dehydrated patients and patients who received concomitant non-antibiotic nephrotoxic agents are more vulnerable to antibiotic-associated AKI. Most antibiotic associated AKI are categorized in stage 1 based on AKIN criteria. Monitoring of volume status of patients by preparing and implementing a protocol for fluid management as well as avoiding administration of medications form other therapeutic classes with known renal toxicity in this situations when it is possible is justified.

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