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Drug-Induced Acute Kidney Injury in Diabetes Mellitus

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Abstract

Background: Drug-induced acute kidney injury is a common situation in clinical practice. Many treatments are involved and they are even more aggressive when associated with a predisposing factor such as diabetes. We aimed to investigate clinical features of acute drug-induced kidney injury in diabetics in order to clarify renal prognosis. Methods: This was a descriptive and analytical retrospective study including diabetics who presented drug-induced acute kidney injury, conducted in our department during the period from 1986 to 2015. Acute kidney injury was classified according to Kidney Disease Improving Global Outcomes criteria. We analyzed medical records of patients. Results: 31 patients were included with mean age of 65.41 years and gender ratio M/F at 0.93. Diabetes was type 2 in 97% of cases. Mean previous creatinine clearance was 39.33 ml/min/1.73 m^2. Drugs involved were blockers of renin-angiotensin system (35%), aminoglycosides (16%), non-steroidal anti-inflammatory (16%), diuretics (13%), lipid-lowering agents (10%), rifampicin (6%) and ifosfamide (3%). Extracellular dehydration was present in nine cases (29%). Main drug combinations were with diuretics in 16 cases (52%) and with ACE inhibitor or ARB in eight cases (26%). Oligo anuria was observed in 5 cases (16%). Proteinuria with urine strips was objectified in 25 cases (81%). Acute kidney injury was grade 3 in 24 cases (77%), grade 2 in three cases (10%) and grade 1 in four cases (13%). Renal survival at 102 months was 57%. Identified renal prognosis factors were serum phosphorus >1.47 mmol/l ($p = 0.01$), proteinuria at urine strips ($p = 0.042$), dehydration ($p = 0.013$), oral antidiabetic treatment ($p = 0.038$), intravenous rehydration ($p = 0.021$) and insulin ($p = 0.006$). Conclusion: Drug-induced acute kidney injury is potentially serious in diabetics. Prevention is essential to improve the prognosis of this renal damage.

Keywords

Renal Failure, Nephrotoxicity, Drugs

1. Introduction

Drug-induced acute kidney injury (AKI) is frequent in clinical practice [1]. Indeed, the kidney is an organ particularly vulnerable to drug toxicity in the body by its own functions of filtration, concentration and disposal as well as its rich vascularization [2].

Involved drugs are numerous with multiple mechanisms. Drug nephrotoxicity may be related either to a specific effect of treatment, or to the induction of hypovolemia or by altering intrarenal hemodynamics. Treatments involved are even more aggressive when associated with one or more predisposing factors including diabetics [3].

Drug-induced AKI represents iatrogenic adverse events, mostly preventable, whose prognosis is typically better than other etiologies of AKI. They are potentially serious since they are associated with high morbidity and mortality and the risk of progression to end stage kidney disease (ESKD) [4].

Knowledge of risk factors and mechanisms of drug-induced nephrotoxicity are the basis for improved prevention and also for a better management of these patients [5]. Pre-scription of potentially nephrotoxic drugs should be carried out in compliance with therapeutic indications. It must also take into account drug interactions and field of patients.

Diabetes mellitus is the single largest contributor to the growing prevalence of chronic kidney disease (CKD) worldwide and is one of the major risk factors for development of AKI [6]. Meanwhile, literature is poor about prognostic factors of this condition in diabetic patients.

We conducted an analytic study with the purpose to establish prognostic factors of drug-induced AKI in these patients.

2. Patients and Methods

We performed a retrospective data analysis by reviewing the medical records of diabetic patients hospitalized at our department from January 1986 to June 2015 who presented an AKI after taking a drug with a compatible timeline from discovery of the AKI and drug intake.

We excluded individuals who were ≤18 years of age, critically ill patients and those who received iodinated contrast agents.

We collected data on demographics and past medical history, including baseline kidney function, hypertension, coronary artery disease, diabetic neuropathy, diabetic retinopathy and peripheral artery disease.

We noted dose, duration and frequency of administration of offending drug prior to AKI.

We also recorded the use of all other drugs administrated concomitantly with drug in

question. The clinical and para-clinical data were collected from medical records.

Outcomes included renal recovery, length of hospital stay and mortality.

We defined complete renal recovery by a decrease in serum creatinine with return to baseline creatinine.

Local ethics committee had no objections against this study. Written consent was waived because of the retrospective observational nature of the study.

Glomerular filtration rate was evaluated according to Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Stages of CKD were defined according to the International Foundation Kidney disease Improving Global outcomes (KDIGO) [7].

AKI was defined as 26.5 µml/L or 1.5-fold increase in creatinine relative to baseline serum creatinine. Severity of AKI was classified on the basis of peak creatinine increment into three stages according to KDIGO criteria [8].

When baseline creatinine was unknown, it was estimated by the CKD-EPI equation assuming a glomerular filtration ratio of 75 ml/min/1.73 m^2 as validated by Bagshaw *et al*. [4] [9].

ESKD has been defined by renal creatinine clearance below to 15 ml/min requiring maintenance dialysis.

3. Statistical Analysis

Statistical analyses were performed using SPSS 19. The results were presented as means ± SD for continuous variables and percentage for categorical variables.

Differences between groups were evaluated by Chi 2 test for percentages. In case of significance of chi-square test with non validity we used Fisher's bilateral test.

Comparison of independent groups was performed using the Student's t test for independent groups.

A p value less than 0.05 was considered statistically significant.

Quantitative variables were transformed into qualitative variables with two modalities. To determine the threshold at which it must "cut" quantitative variable, we have established ROC (Receiver Operating Characteristics) curve. After verifying that the area under the curve was significantly >0.500, we have chosen the threshold value of the variable as corresponding to the best couple "sensitivity-specificity".

A Kaplan-Meier method was used for comparison of survival.

4. Results

Among 182 diabetic patients presenting an AKI during the period of the study, we identified 31 cases of drug induced AKI (17%).

Thirty one patients were then included. The average age of patients was 65.41 years (39 - 79 years). The age was over 65 years in 17 cases (55%). Gender ratio M/F was 0.93.

Diabetes was type 2 in 30 cases (97%). Median duration of diabetes was 165.45 months (2 - 480 months).

Ten patients (32%) were dependent to insulin therapy and 21 patients (68%) were on

oral antidiabetic treatment. Hypertension was present at diagnosis in 25 cases (81%). Diabetic retinopathy was identified in 15 cases (48%).

Baseline serum creatinine was available in 28 cases (90%) with median baseline creatinine at 205.48 µmol/L (58 - 453 µmol/L) and median creatinine clearance at 39.33 ml/min/1.73 m^2 (8.4 - 92.9 ml/min/1.73 m^2). Twenty three patients had a creatinine clearance less than 60 mL/min/1.73 m^2 (74%). Table 1 summarizes the baseline patient demographics along with clinical and biochemical parameters.

Initial symptoms were vomiting in 11 cases (35%) and asthenia with anorexia in 11 cases (35%).

Table 1. Clinical and biological parameters of patients.

Parameter	Average value	Range
Age (years)	65.41	39 - 79
BMI (kg/m²)	27.45	19.4 - 35.7
SBP (mmHg)	133.55	70 - 180
DBP (mmHg)	73.87	40 - 100
Diuresis (ml/24h)	1033.33	0 - 2000
Urea (mmol/l)	33	11 - 56
Creatinin (µmol/l)	631.52	157 - 1158
Glycemia (mmol/l)	8.68	2.96 - 23.69
Hb (g/dl)	9.74	7.4 - 12.4
WBC	10237	3900 - 23900
Platelets	297166	126,000 - 447,000
AR (mmol/l)	18.69	7.9 - 29
Calcemia (mmol/l)	2.25	1.8 - 2.57
Phosphatemia (mmol/l)	1.76	0.58 - 3.88
ASAT (U/l)	29.38	8 - 100
ALAT (U/l)	23.33	6 - 72
GGT (U/l)	34.37	13 - 172
CPK (U/l)	377.2	19 - 2970
AP (U/l)	104.92	42 - 345
Bilirubin (mg/l)	19.77	4.2 - 78
LDH (U/l)	583.1	165 - 2817
CRP (mg/l)	17.9	0.8 - 188
SA	32.11	15.5 - 45
24-hour Proteinuria (g/24h)	1.42	0 - 8.8

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, Hb: hemoglobin, WBC: white blood cells, AR: alkaline reserves, ASAT: aspartate aminotransferase, ALAT: alanine aminotransferase, GGT: gamma glutamyl transferase, CPK: creatine phosphokinase, AP: alkaline phosphatase, LDH: lactate dehydrogenase, CRP: C-reactive protein, SA: serum albumin.

Drugs involved were blockers of renin-angiotensin system (BRAS) (35%), aminoglycosides (16%), non-steroidal anti-inflammatory drugs (NSAIDs) (16%), diuretics (13%), lipid-lowering agents (10%), rifampicin (6%) and ifosfamide (3%) (Table 2).

Intercurrent factor to drug intake was identified in 16 cases (52%). We found extracellular dehydration in nine cases (29%) and infectious episode in seven cases (23%). Main drug combinations were with diuretics in 16 cases (52%) and with angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blockers (ARB) in eight cases (26%) (Table 3). Gentamicin was associated with an ACEi or ARB and a diuretic (furosemide) in two cases. NSAIDs were associated with a diuretic (furosemide) and an ARB in one case.

Oligo anuria was observed in 5 cases (16%). Proteinuria with urine strips was noted in 25 cases (81%) with hematuria in seven cases (22%).

Median maximum serum creatinine reached was 631.52 µmol/L (157 - 1198 µmol/L).

AKI was grade 3 in 24 cases (77%), grade 2 in three cases (10%) and grade 1 in four cases (13%). Hyperkalemia was noted in 6 cases (19.5%). Metabolic acidosis was present

Table 2. Type and dose of drugs.

Offending drug	Average dose (mg/day)	Average duration (days)	Number of patients	Percentage (%)
Gentamicin	160	7	5	16
ACEi	22	60	7	23
ARB	187	30	3	10
ARB + hydrochlorothiazide	160/25	10	1	3
Furosemide	250	-	1	3
Triamterene + Methyclothiazide	150/5	-	3	10
Rifampicin	450	8.5	2	6
Statin	20	-	2	6
Fibrate	200	-	1	3
NSAIDs	100	5	5	16
Ifosfamide	10,000	3	1	3

ACEi: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blockers, NSAIDs: non-steroidal anti-inflammatory drugs.

Table 3. Combination of drugs in our study.

Drug	+ ACEi/ARB	+ Furosemide
Gentamicin	2 (6%)	3 (10%)
NSAIDs	3 (10%)	2 (6%)
ACEi/ARB	-	8 (26%)
Triamterene + Methyclothiazide	3 (10%)	-

NSAIDs: non-steroidal anti-inflammatory drugs, ACEi: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blockers.

in 11 cases (35%) with lactic acidosis in one case that was under metformin. Elevated liver enzymes were noted in five cases (16%). Among these patients, three were under lipid lowering treatment and the others under rifampicin.

Rhabdomylosis was noted in two cases under lipid lowering treatment. Aseptic leukocyturia was observed in four cases (13%).

Renal ultrasound was made in 26 cases (84%) and has not found stenosis of renal artery in all cases.

AKI was probably prerenal in 20 cases (65%), due to acute tubular necrosis in seven cases (23%), by acute immunoallergic interstitial nephropathy in two cases (6%) and by rhamdomyolysis in two cases (6%).

Kidney biopsy was performed in one case presenting acute tubular necrosis after taking chemotherapy for cutaneous sarcoma without renal recovery after the usual time. It confirmed diagnosis of acute tubular necrosis with chronic interstitial nephritis associated with diabetic glomerulosclerosis.

Offending drug has been stopped in all cases. Oral antidiabetics were stopped when taken and insulin was prescribed in 28 cases (90%). Rehydration was conducted in 19 cases (61%). That was oral in 7 cases (23%) and intravenous in 12 cases (42%).

Hemodialysis was needed in 13 cases (42%).

Complete recovery was noted in 11 cases (35%) after a median period of 12.18 days [7 - 23 days]. Partial recovery was observed in 16 cases (52%) and dialysis dependence in two cases (6%). Evolution depending on the offending drug is summarized in **Table 4**.

Median follow up time was 25.5 months [2 days - 102 months]. Six patients (12%) reached finally ESKD after median period of 14.5 months [4 - 24 months].

Death occurred in three cases. Causes of death were hyperkalemia in one case and septic shock in two cases.

Renal survival at 102 months was 57%. To identify renal prognostic factors we made comparison between patients with complete recovery of renal function with the others (**Table 5**). Identified renal prognosis factors were then serum phosphorus >1.47 mmol/l ($p = 0.01$), proteinuria at urine strips ($p = 0.042$), dehydration ($p = 0.013$), oral antidiabetic treatment ($p = 0.038$), intravenous rehydration ($p = 0.021$) and insulin ($p = 0.006$).

5. Discussion

Drug induced AKI represents 20% of all etiologies of AKI [10]. Its incidence is increasing due to the emergence of new potentially nephrotoxic molecules and growing drug prescription. Pathophysiologic mechanism of drug-induced nephro toxicity is complex depending on type of drug involved [10]. This is a serious event that is associated with increased morbidity and mortality [9].

Preventive measures require mainly understanding patients and drug-related risk factors. Diabetes which is currently expanding in the world is a major predisposing factor [11] [12].

Our study focused on clinical aspects of drug induced AKI in diabetic patients.

Table 4. Prognostic factors of drug-induced acute kidney injury.

Parameter	Group 1	Group 2	p
Age ± SD (years)	69.45 ± 6.876	63.20 ± 10.144	0.079 (NS)
gender (M/F)	0.37	1.5	3.04 (NS)
Duration of diabetes ± SD (months)	163.82 ± 105.574	166.35 ± 128.882	0.956 (NS)
Initial creatinin ± SD (µmol/l)	205.00 ± 138.399	205.76 ± 127.439	0.988 (NS)
Cl creat CKD-EPI ± SD (ml/min/1.73m^2)	36.590 ± 24.5463	40.947 ± 23.8722	0.654 (NS)
BMI± SD (kg/m^2)	26.4943 ± 5.51768	27.8482 ± 3.93298	0.502 (NS)
SBP ± SD (mmhg)	121.82 ± 35.726	140.00 ± 21.764	0.088 (NS)
DBP ± SD (mmhg)	68.18 ± 16.011	77.00 ± 13.416	0.113 (NS)
Proteinuria (dip stiks)	5 (16%)	16 (52%)	0.042
HT	10 (32%)	15 (48%)	1.114 (NS)
P TTT oral AD	7 (22%)	12 (39%)	0.038
DR	5 (16%)	10 (32%)	0.059 (NS)
DN	8 (26%)	10 (32%)	1.457 (NS)
PVD	2 (6%)	1 (3%)	1.365 (NS)
Coronary Disease	3 (10%)	3 (10%)	0.663 (NS)
Associated diuretic	6 (19%)	10 (32%)	0.059 (NS)
Associated ACEi	2 (6%)	6 (19%)	0.501 (NS)
Dehydratation	7 (22%)	3 (10%)	0.013
Infection	2 (6%)	6 (19%)	0.618 (NS)
TTT:insulin	10 (32%)	18 (58%)	0.006
TTT:IV rehydratation	8 (26%)	5 (16%)	0.021
Need to dialysis	3 (10%)	10 (32%)	1.457 (NS)
Urea ± SD (mmol/l)	28.914 ± 14.4125	34.526 ±11.6163	0.315 (NS)
Creatinine ± SD (µmol/l)	567.27 ± 253.568	666.85 ± 277.771	0.333 (NS)
Uricemia ± SD (µmol/l)	546.00 ± 150.408	602.79 ± 228.637	0.519 (NS)
Natremia ± SD (mmol/l)	131.56 ± 6.023	134.05 ± 6.510	0.341 (NS)
Kalemia ± SD (mmol/l)	4.773 ± 1.3222	4.630 ± 1.3095	0.774 (NS)
Serum chloride ± SD (mmol/l)	95.64 ± 9.277	95.87 ± 6.937	0.943 (NS)
AR ± SD (mmol/l)	18.738 ± 5.6778	18.618 ± 6.4346	0.967 (NS)
calcemia± SD (mmol/l)	2.3310 ± 0.17960	2.2120 ± 0.25549	0.215 (NS)
Phosphatemia ± SD (mmol/l)	1.3200 ± 0.59353	2.0713 ± 0.75124	0.01
Hb ± SD (g/dl)	9.618 ± 1.7904	9.805 ± 1.2412	0.735 (NS)
CRP ± SD (mg/l)	33.082 ± 55.5428	23.150 ± 39.6787	0.624 (NS)
SA± SD (g/l)	34.210 ± 7.8614	30.720 ± 6.1603	0.226 (NS)
Glycemia ± SD (mmol/l)	9.080 ± 5.1270	8.470 ± 3.0653	0.680 (NS)
24-hour Proteinuria ± SD (g/l)	0.8656 ± 1.14212	1.7560 ± 2.24910	0.136 (NS)

Group 1: patients with complete recovery of renal function, group 2: all the other patients, SD: standard deviation, NS: non-significant value, CL creatinine: clearance of creatinine, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, HT: hypertension, P TTT: previous treatment, AD: antidiabetic, DR: diabetic retinopathy, DN: diabetic neuropathy, PVD: Peripheral vascular disease, ACEi: angiotensin converting enzyme inhibitor, TTT: treatment, IV: intravenous, Hb: hemoglobin, AR: alkaline reserves, SA: serum albumin, CRP: C-reactive protein.

Table 5. Evolution of patients depending on the drug type.

Drug	Mean Previous Cl Creat (ml/min)	CR	PR	Stabilization Of GFR	Dependance to dialysis
Number		11	16	2	2
Percentage (%)		35	52	6	6
Gentamicin	54.14	1	4	-	-
NSAIDs	47.5	3	2	-	-
ACEi/ARB	33.33	5	3	2	1
Statin/fibrate	27.8	1	2	-	-
Diuretic	46	1	3	-	-
Rifampicin	72.35	-	2	-	-
Ifosfamide	75	-	-	-	1

Cl Creat: clairance creatinine, CR: complete recovery, PR: partial recovery, GFR: glomerular filtration rate, NSAIDs: non-steroidal anti-inflammatory drugs, ACEi: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blockers

Among risk factors known over literature, our population was mainly female and aged over 65 years with a preexistant renal failure in 74% of cases. Hypovolemia was present in 29% of cases.

Indeed, some patient characteristics can predispose to drug-induced nephrotoxicity. Older age and female gender are associated with reduced muscle mass and lower total body water which can impact on drug dose [13] [14]. Risk of drug nephrotoxicity is increased in the patient with CKD. Patient who is on diuretic therapy or has vomiting resulting in extracellular volume depletion is vulnerable also to toxic drug effects on the kidney [13].

BRAS were main causes of AKI in our study. AKI due to BRAS is increasing due to their large use in diabetics to slow progression of diabetic nephropathy. Furthermore, there are actually many evidence based indications for use of these molecules and several guidelines recommend their use for a number of chronic conditions like hypertension or CKD with proteinuria [15].

Our findings are consistent with other studies which have demonstrated an increasing incidence of AKI from treatment with BRAS. There is usually presence of an intercurrent illness and it is more common in patients with known renal failure [15]. We found in our study an intercurrent factor in 52% of all cases.

AKI due to BRAS has been described primarily in patients with bilateral renal artery stenosis or with a single kidney and unilateral stenosis, and in some conditions like severe congestive heart failure and concomitant diuretic therapy [16]. In our cases, renal ultrasound excluded renal artery stenosis but concomitant use of diuretics was present in 26% of all cases. Discontinuation of BRAS leads generally to recovery of renal function meanwhile exceptions has been reported [16].

Aminoglycosides and NSAIDs were either frequently observed in our study. Aminoglycosides are typically the most common drugs involved in the literature [17]. They

are responsible for about 25% of AKI [18]. In our study, they were found in 16% of cases. That was gentamicin in all reported cases.

The inhibition of prostaglandin synthesis by NSAIDs causes a reduction in renal blood flow and glomerular filtration [19]. It is essentially in some pathological situations where renin-angiotensin system is strongly stimulated that the effect of NSAIDs promotes the onset of AKI. Then combination of BRAS with NSAIDs should be avoided especially in pre-existing renal insufficiency or extracellular volume depletion.

Lipid-lowering agents may lead to AKI via rhabdomyolysis [20]. This risk is particularly increased in elderly diabetics. We reported two cases of rhabdomyolysis.

The other drugs found in our study were diuretics, rifampicin and cancer chemotherapy. Antituberculosis agents can induce AKI by immunoallergic mechanism [21] [22]. Hepatonephritis due to rifampicin was found in two cases in our study.

The presence of diabetes poses certain particular problems in the management of AKI. Rapid institution of dialysis is important as the diabetic patient may tolerate uraemia less well [11].

Diabetes must be well controlled as uncontrolled ketosis may worsen hyperkalemia and metabolic acidosis, with increased risk of adverse effects of antidiabetic treatment. Indeed, we reported one case of lactic acidosis in our study due to the use of metformin.

Patients with diabetes are then at increased risk of developing AKI [23]. This condition carries a high mortality and management may be more complicated by the presence of diabetes. Some cases may be avoidable by reducing exposure of the diabetic patient to nephrotoxic agents.

Preventive measures are essential by assessing baseline renal function before initiation of therapy, adjusting the drug dosage and avoiding use of nephrotoxic drug combinations [5].

Non-recovery or incomplete recovery of renal function can translate into a need for long-term dialysis which is associated with low quality of life and representing a major burden for healthcare systems [24] [25].

Presence of factors such as elevated serum phosphorus, dehydration and proteinuria were associated with a poor prognosis in our study.

It is now well established that proteinuria is a progression factor of CKD. The degree of proteinuria is one of the most important predictors of progression of kidney disease, as well as the response to antiproteinuric treatment in almost all studies on CKD.

Dehydration and intravenous rehydration were identified as prognostic factors in our study.

Indeed, improvement of the hemodynamic status of patient with AKI and especially perfusion pressure has a beneficial effect on kidney function and helps to minimize the effect of further attacks on the already injured kidney.

AKI increases the risk of progression to advanced CKD in patients with diabetes regardless of the major risk factors for progression of CKD and each episode of AKI dual this risk. These data suggest that even moderate AKI in diabetics with preserved renal

function should be considered as a serious event [25] [26].

Our study has some limitation such as the retrospective nature of the study and the number of patients included quite low given the frequency of this condition. It is probably underestimated in our study due to the selection criteria we adopted since we included only hospitalized patients.

6. Conclusions

Drug-induced AKI is potentially serious in diabetics due to the high risk of progression to ESKD, especially in case of pre-existing renal insufficiency.

Prevention is so crucial. The measures consist mainly in determination of baseline renal function before initiation of treatment, with adjustment of drug dosage. Prescription of potentially nephrotoxic drugs should be carried out in strict compliance with therapeutic indications. It must take into account drug interactions and patients related risk factors. Correction of intravascular depletion to maintain renal perfusion before initiation of nephrotoxic agents is also essential.

Declaration of interest:

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Ethical Approval

All procedures performed in our study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration.

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