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(CASE REPORT)

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A Case series on Utilization of N-Acetylcysteine for Acute Kidney Injury in patients with Diabetes Mellitus

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Abstract

N-Acetylcysteine is commonly used for paracetamol overdose. It has also been used for acute kidney injury and slowing the progression of CKD. Here we portray three cases that use N-Acetylcysteine in IV and Oral forms for treatment of the Acute kidney injury in patients with Type 2 Diabetes Mellitus. The case series focuses on the need for guidelines to be implemented for the use of IV N-Acetylcysteine in these patients.

Keywords: N-Acetylcysteine; Acute kidney injury; Type 2 Diabetes Mellitus

1. Introduction

N-acetyl cysteine (NAC), a safe and affordable drug, has been on the market for a very long time [1]. Although cysteine can be found in some foods such as chicken and turkey meats, garlic, yogurt, and eggs, this medication is unavailable in natural sources [2]. NAC is an effective mucolytic that improves glutathione S-transferase activity while reducing sticky mucus secretions. When taken orally, NAC undergoes a deacetylation process as it travels through the small intestine and liver, reducing its bioavailability to 4–10%. In addition to promoting detoxification and free radical scavenging directly, NAC also boosts glutathione production. It is a potent antioxidant and a possible therapy for conditions where free oxygen radicals are produced [3]. Studies have revealed that NAC therapy has no negative effects on the mother or the fetus. This dietary supplement is a top-notch supplier of sulfhydryl groups. NAC decreases mitochondrial membrane depolarization and intracellular glutathione levels to stop apoptosis and oxygen-related genotoxicity in endothelial cells [4]. With varying degrees of success, it has also been tried for the prevention of acute kidney damage (AKI) in a variety of contexts, including postoperative AKI and contrast-induced AKI (CI-AKI) [5]. The major endpoint used in these studies was the difference in blood creatinine levels before and after NAC administration. A potential reason for the discrepancy between the effect of NAC on serum creatinine and clinical outcomes may be assay interference from the effect of NAC on serum creatinine measurement. An initial report suggested that NAC lowers serum creatinine, without having any effect on cystatin C. It is yet unclear how NAC safeguards the kidneys [6]. Through the direct antioxidant effect and indirect antioxidant effect of glutathione, it may protect the renal tubules from injury, reduce renal cell apoptosis, promote cell repair, and increase expression of nitric oxide synthase (NOS), thereby reducing vasoconstriction, improving renal flow, and reducing renal injury [7].

2. Case presentation

2.1. Case 1

A 57-year-old female patient was admitted with complaints of fever, and cellulitis right lower leg. She has a medical history of Dyslipidemia, Type 2 DM, and a history of cellulitis one month back. Her past medications include

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Tab.Atorvastatin (5 mg) and Tab.Glimepiride (5 mg) + Metformin (500 mg) BD. On examination her vitals were normal. The lab parameters such as Hb (9.4 g/dL) were declined. The elevated parameters include total count (18160 cells/microliter), polymorphs (79.8%), ESR (134mm/hr), HbA1C (7.3%), urine albumin (faint trace), pus cells (40-35%), RBCs (4-5%), urea (123mg/dL), creatinine (2.3mg/dL). She was diagnosed with acute kidney injury, and varicosities in the left lower leg on the left lower limb venous Doppler study with no evidence of DVT at present. Her blood culture showed the presence of *E coli*. She was treated with Inj. Ceftriaxone 1g BD, Tab. Cilnidipine 10 mg 1-0-1, Inj. Pantoprazole 40 mg BD, Tab Atorvastatin 10 mg HS, Tab Ferrous ascorbate + Folic acid 1-0-0, Tab Sodium Bicarbonate 500 mg BD, Tab. N acetylcysteine 600 mg 1-0-0. Since the sensitivity pattern exhibited was resistant to ceftriaxone and the antibiotic was changed to Cefoperazone/Sulbactam. She was given Insulin Human Actrapid to control her blood sugar levels

The patient received 9 doses of 600 mg N- acetylcysteine and her creatinine levels lowered to 1.1mg/dL and D dimer to 2573ng/ml from 6511ng/ml.

Table 1 Diabetic Chart of Case 1

DAY	PARAMETERS	VALUES	TREATMENT
DAY 1	PRE-DINNER	186mg/dL	20 UNITS HUMAN ACTRAPID S/C
DAY 2	FASTING BLOOD SUGAR	88mg/dL	10 UNITS HUMAN ACTRAPID S/C
	PRE-LUNCH	97mg/dL	10 UNITS HUMAN ACTRAPID S/C
	PRE-DINNER	136mg/dL	14 UNITS HUMAN ACTRAPID S/C
DAY 3	FASTING BLOOD SUGAR	135mg/dL	14 UNITS HUMAN ACTRAPID S/C
	PRE-LUNCH	111mg/dL	14 UNITS HUMAN ACTRAPID S/C
	PRE-DINNER	153mg/dL	16 UNITS HUMAN ACTRAPID S/C
DAY 4	FASTING BLOOD SUGAR	114mg/dL	12 UNITS HUMAN ACTRAPID S/C
	PRE-LUNCH	154mg/dL	16 UNITS HUMAN ACTRAPID S/C
	PRE-DINNER	130mg/dL	14 UNITS HUMAN ACTRAPID S/C
DAY 5	FASTING BLOOD SUGAR	121mg/dL	14 UNITS HUMAN ACTRAPID S/C
	PRE-LUNCH	176mg/dL	18 UNITS HUMAN ACTRAPID S/C
	PRE-DINNER	101mg/dL	10 UNITS HUMAN ACTRAPID S/C
DAY 6	FASTING BLOOD SUGAR	113mg/dL	10 UNITS HUMAN ACTRAPID S/C

Table 2 Renal function test of case 1

PARAMETERS	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6
UREA (mg/dL)	123	120	89	57	42	30
CREATININE (mg/dL)	2.3	2.3	2.0	1.5	1.3	1.1
CREATININE CLEARENCE (CrCl)	29mL/min	29mL/min	33.3mL/min	44.4mL/min	51.3mL/min	60.6mL/min

2.2. Case 2

A 52-year-old male patient was admitted with complaints of left leg pain and edema for one week. He has a history of CAD - PCI on irregular follow-up, Type 2 DM. His past medications include:

- Tab. Losartan (50 mg) + Hydrochlorothiazide (12.5 mg) 1-0-0
- Tab. Metoprolol (50 mg) + Amlodipine (10 mg) 0-0-1

- Tab. Glipizide (5 mg) + Metformin (500 mg) TDS

On examination his vitals were normal. His elevated lab parameters include HbA1C (7.9%), CRP (25 mg/dL), Urea (55 mg /dL), Creatinine (1.7mg/dL), Sodium (131meq/L), ESR (130mm/hrs), Urine albumin (trace)and declined parameter include Hb (8.6g/dL). He was diagnosed with Cellulitis Left Lower Limb and Acute Kidney Injury resolving. He was treated with Inj. Amoxicillin /Clavulanic acid 1.2 g BD, Cap VIBACT DS 1-0-0, Tab Sodium bicarbonate (500 mg) TDS, Tab Tramadol (37.5) + Acetaminophen (325mg), Tab Diosmin (400 mg) + Hesperidin (50 mg) BD, Inj. N- acetylcysteine (1.2 g) BD for four doses, Tab Glipizide/Metformin (500 mg) twice daily on the second day and thrice daily from the third day, Tab Teneligliptin (20 mg) 1-0-0. He was discharged with creatinine lowered to 1.3mg/dL.

Table 3 Diabetic chart of case 2

DAY	PARAMETERS	VALUES	TREATMENT
DAY 1	PRE-DINNER	128mg/dL	12 UNITS HUMAN ACTRAPID S/C
DAY 2	FASTING BLOOD SUGAR	205mg/dL	10 UNITS HUMAN ACTRAPID S/C
	PRE-LUNCH	190mg/dL	10 UNITS HUMAN ACTRAPID S/C
	PRE-DINNER	91mg/dL	NOT GIVEN
DAY 3	FASTING BLOOD SUGAR	70mg/dL	NOT GIVEN
	PRE-LUNCH	227mg/dL	10 UNITS HUMAN ACTRAPID S/C
	PRE-DINNER	73mg/dL	NOT GIVEN
DAY 4	FASTING BLOOD SUGAR	79mg/dL	NOT GIVEN
	PRE-LUNCH	96mg/dL	NOT GIVEN
	PRE-DINNER	89mg/dL	NOT GIVEN
DAY 5	FASTING BLOOD SUGAR	125mg/dL	10 UNITS HUMAN ACTRAPID S/C
	PRE-DINNER	83mg/dL	NOT GIVEN
DAY 6	FASTING BLOOD SUGAR	120mg/dL	NOT GIVEN

Table 4 Renal function test of case 2

PARAMETERS	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5
UREA (mg/dL)	55	52	46	45	40
CREATININE (mg/dL)	1.7	1.5	1.5	1.6	1.6
CREATININE CLEARANCE (CrCl)	39.5mL/min	44.8mL/min	44.8mL/min	42mL/min	42mL/min

2.3. Case 3

A 64-year-old male patient was admitted with complaints of cough with expectoration, tiredness, breathing difficulty, and decreased appetite for 3 days. He has a medical history of dilated cardiomyopathy for 2 years, Type 2 DM diabetic nephropathy and retinopathy, Hypertension, and Hypothyroidism. His sleep pattern was normal. He has a medication history of Tab. Levothyroxine (12.5mcg) 1-0-0, Tab. Aspirin (75mg) OD + Atorvastatin (10mg) 0-0-1, Tab. Ivabradine (5 mg) 1-0-0, Tab Torsemide (10 mg) 1-1-0, Tab. Dapagliflozin (10 mg) 0-1-0, Tab. Isosorbide dinitrate (20mg) + (37.5mg) 1/2-0-1/2, Inj. Human insulin 20-0-15 units. On examination, his BP was 180/88 mmHg, and right-side bilateral crept were heard on auscultation. Other vitals were normal. His abnormal lab parameters include Urine albumin (trace), Urine sugar (1%), RBCs (1-2), Creatinine (2 mg/dl), Urea (68 mg/dl), Polymorphs (79.1%), TSH(9.83mu/L), ESR (116mm/hr), HbA1C (9.2%) CRP (69.4mg/L). His tissue culture shows Enterococcus faecalis sensitive to Linezolid and left lower limb arterial Doppler showed monophasic flow in distal PTA, ATA, and DPA, and Infra popliteal atherosclerotic narrowing. He was treated with Inj. Cefoperazone plus sulbactam 1.5 g BD for 5 days, Inj. Pantoprazole 40 mg BD, Neb. Duolin Q8H, Neb. Budecort Q12H, Syp. Rapitus 5 ml TDS, Tab. Montelukast plus Desloratadine HS, Tab. Vildagard (50mg)

+ Metformin (500mg) BD from the third day after stopping Dapagliflozin, Tab. Levothyroxine dose was escalated to 25 mcg 1-0-0 from the third day, Inj. N- acetylcysteine (1.2) g BD was given for 6 doses from the third day, Tab. Sodium bicarbonate (500mg) TDS from the third day. Based on the tissue culture report Tab. Linezolid (600) 1-0-1 was added and his past medicine was continued during the hospital stay. His creatinine levels were 2.2mg/dL on the third day and declined to 2.0mg/dL on day 4 which does not show a significant improvement in creatinine clearance. He was discharged with Linezolid for 5 more days, Tab. Levothyroxine (25mcg) 1-0-0 and continued own medications.

Table 5 Diabetic Chart of Case 3

DAY	PARAMETERS	VALUES	TREATMENT
DAY 1	FASTING BLOOD SUGAR	185mg/dL	8 UNITS HUMAN ACTRAPID S/C
	PRE-LUNCH	231mg/dL	15 UNITS HUMAN ACTRAPID S/C
	PRE-DINNER	271mg/dL	15 UNITS HUMAN ACTRAPID S/C
DAY 2	FASTING BLOOD SUGAR	170mg/dL	20 UNITS HUMAN ACTRAPID S/C
	PRE-LUNCH	364mg/dL	30 UNITS HUMAN ACTRAPID S/C
	PRE-DINNER	185mg/dL	20 UNITS HUMAN ACTRAPID S/C
DAY 3	FASTING BLOOD SUGAR	177mg/dL	30 UNITS HUMAN ACTRAPID S/C
	PRE-LUNCH	200mg/dL	30 UNITS HUMAN ACTRAPID S/C
	PRE-DINNER	154mg/dL	20 UNITS HUMAN ACTRAPID S/C
DAY 4	FASTING BLOOD SUGAR	105mg/dL	30 UNITS HUMAN ACTRAPID S/C
	PRE-LUNCH	265mg/dL	30 UNITS HUMAN ACTRAPID S/C
	PRE-DINNER	118mg/dL	20 UNITS HUMAN ACTRAPID S/C
DAY 5	FASTING BLOOD SUGAR	171mg/dL	30 UNITS HUMAN ACTRAPID S/C

Table 6 Renal function test of case 3

PARAMETERS	DAY 1	DAY 2	DAY 3	DAY 3
UREA (mg/dL)	54	51	45	41
CREATININE (mg/dL)	2.0	2.2	2.3	2.0
CREATININE CLEARENCE (CrCl)	38mL/min	34.5mL/min	33.04mL/min	38mL/min

3. Discussion

According to several studies, N-acetylcysteine may be able to slow the progression of renal function decline by lowering serum creatinine, increasing endogenous creatinine clearance, and improving podocyte ultrastructure [8]. The patient's creatinine level in the first case was 2.3 mg/dL, and the Cockcroft-Gault equation predicted that the patient's creatinine clearance was 28.97 ml/min. Participants with an eGFR of fewer than 60 ml/min and blood creatinine levels greater than 1.3 mg/dL were included in a systematic review and meta-analysis of N-acetylcysteine for CKD. Patients with stage 3 CKD were included in a randomized controlled trial to investigate the impact of N-acetylcysteine on serum creatinine and renal function. They were assigned to receive 4 doses of oral N-acetylcysteine, each of which was administered at a 24-hour interval. N-acetylcysteine was administered orally in 10 studies for the meta-analysis previously described at doses and frequencies of 1200 mg daily, 1200 mg twice daily, and 600 mg twice daily. In five studies administration of N-acetylcysteine was intravenously within 4 hours during hemodialysis that is N-acetylcysteine 5g in 500ml 5% glucose or 500ml normal saline [9] [10] [11] [12]. Here we do not have any patients on hemodialysis therefore the need for an IV dose of NAC was not necessary. The duration of 1 month of oral N-acetylcysteine vs less than 1 month was considered and it was identified from a study that both groups have similar effects without regard to time. The highest rate of adverse

events was seen with IV N-acetylcysteine such as tachycardia, gastrointestinal discomfort, and hypotension. It is evident from the studies that patients, GI side effects were more common in patients not on dialysis after receiving IV N-acetylcysteine [13] [14]. In the first case 600mg oral N-acetylcysteine was used but in case of second case IV N-acetylcysteine 1.2g was administrated which is given in 4 doses, but it was started on the 4th day of admission when the creatinine was 1.6mg/dL. This increase may be the result of metformin being taken three times daily starting on the third day. This patient was already on Metformin and Glimepiride, which was stopped on day one due to decreased clearance, started as BD on day two, and was increased to its former dose of three times daily on day three, which may have contributed to the elevated creatinine levels in the next day. The patient's medication needed to be adjusted based on their creatinine clearance to reduce adverse events. The third case involves a patient with creatinine 2mg/dL which raised to 2.3mg/dL on the third day. This patient was already on Dapagliflozin this drug was stopped suspecting acute kidney injury and Metformin and Vildagliptin (500mg+50mg) twice daily were added. Based on the patient's creatinine clearance the dose of metformin and vildagliptin should not exceed 500mg OD and 50mg OD respectively. The patient was treated with N-acetylcysteine 1200mg BD for 6 doses.

In a study conducted to find the effect of high N-acetylcysteine concentration on antibiotic activity, it was found that N-acetylcysteine decreases the activity of Ceftriaxone and increases the antibiotic activity of Penicillin and Linezolid [15]. In order to produce a synergistic effect, here both the drugs, N-acetylcysteine and antibiotic need to be started on the same day. Therefore, the rationale for adding IV N-acetylcysteine 1200mg BD cannot be justified in the 2nd& 3rd cases.

The cost of N-acetylcysteine injection was higher as compared to oral N-acetylcysteine. Therefore, there is a need to implement certain guidelines for the use of N-acetylcysteine IV in the patient with elevated creatinine. This could help in reducing the economic burden on patients as well as improve the outcomes.

4. Conclusion

N acetylcysteine has been used in different dosage forms and doses in these patients with comparable levels of creatinine. RCTs have shown the use of oral N-acetylcysteine in creatinine elevation, and IV N-acetylcysteine was given only in a study conducted on dialysis patients. Therefore, a guideline need to be developed to determine at which level of serum creatinine N-acetylcysteine should be started and at which dose and dosage forms. This could reduce the adverse effects as well as the financial burden on the patient.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict of interest for the concept.

Statement of ethical approval

The present research work does not contain any studies performed on animals/human subjects by any of the authors.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study."

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