Case Report

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Acute Kidney Injury in a Patient with Darifenacine Overdose

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Abstract

Darifenacin is a medication that has anticholinergic and antimuscarinic effects and is used in the treatment of overactive bladder. Adverse and overdose effects of the medication such as dry mouth and eyes, headache, nausea, constipation, urinary retention, and dyspepsia have been reported. An overdose effect on acute kidney injury (AKI) has not been reported in the literature, and no dose adjustment is recommended in patients with renal impairment. A 24-year-old male patient applied to the emergency department with a declaration of taking 25 drugs containing darifenacin active ingredient for suicidal purposes. The patient had complaints of nausea and difficulty urinating. The patient's physical examination was normal. In laboratory, creatinine was 2.09mg/dL, and hemoglobin (+++) and protein (++) were found in urine test. Renal ultrasonography revealed a grade 1-2 increase in echogenicity of both kidneys. The patient was followed up with intravenous fluid replacement therapy, and the patient whose creatinine levels regressed was discharged with the recommendation of nephrology outpatient control. Any molecule taken in overdose can cause AKI via acute tubular necrosis should not be ignored by emergency physicians. The fact that such a side effect or undesirable situation has not been reported with Darifenacin so far doesn't mean that the molecule is safe for this situation. An overdose of Darifenacin may cause AKI in patients.

Keywords: Acute kidney injury, darifenacine, drug overdose, emergency medicine, kidney tubular necrosis, suicide

Introduction

Acute kidney injury (AKI), which was previously called acute renal failure (ARF), was redefined by the KDIGO clinical guidelines in 2012, and an increase in serum creatinine level by more than 0.3 mg/dL within a 48-hour period and/or increase in serum creatinine level to ≥1.5 times baseline, which was obtained 1 week ago constituted the first 2 items of the new definition (1). Darifenacin is a medication that has anticholinergic and antimuscarinic effects and is used in the treatment of overactive bladder (2). Adverse and overdose effects of the medication (Emselex® 15 mg tablet) such as dry mouth and eyes, headache, nausea, constipation, urinary retention, and dyspepsia have been reported (2). An overdose effect on AKI has not been reported in the literature, and no dose adjustment is recommended in patients with renal impairment (2).

We present a 24-year-old male patient, who we followed up with the diagnosis of AKI, who drank 25 pieces of his father's medication with active ingredient Darifenacin (Emselex® 15 mg tablet) for suicide and presented to the emergency department with the complaint of difficulty urinating 3 days later.

Case Report

A 24-year-old male patient was admitted to the emergency department with complaints of nausea and difficulty in urinating. The patient drank 25 pieces of his father's medication with the active ingredient Darifenacin (Emselex® 15 mg tablet) 3 days ago for the purpose of committing suicide. The patient, who did not apply to any health facility during that period, did not have any complaints such as vomiting, abdominal pain, oral inability, syncope, palpitations. The patient, who had difficulty in urinating and complaining of constipation at first, stated that his urine output improved and he returned to normal. On examination, the patient's vital signs were stable, general condition was good, consciousness was clear, cooperation was complete, the abdomen was relaxed, mucous membranes and skin turgor were normal. There was no pretibial edema. There was no globe vesicale. There were no additional diseases in the medical history. The patient had no history of smoking, alcohol, or any other medication use. In the biochemical examinations, creatinine was detected as 2.09mg/dl (N: <1.2mg/dl). There was no metabolic acidosis. Bicarbonate and lactate levels were normal. Electrolyte

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values were found to be normal. His hemoglobin level was normal. A urinary catheter was inserted into the patient and treatment was started with the preliminary diagnosis of post-renal ARF and/or acute tubular necrosis (ATN) due to the antimuscarinic/anticholinergic side effects of the medication. Hemoglobin (+++) and protein (++) were detected in the complete urinalysis. The patient had urine output and it was normal, and intravenous (IV) salin hydration at a dose of 150 cc/hour and volume replacement was started. The patient was consulted with Internal Medicine and Urology with the preliminary diagnoses of ATN and post-renal ARF, and Psychiatry due to the suicide attempt, and was taken to the emergency critical care unit and followed up.

Hydronephrosis was not detected in both kidneys in the abdominal ultrasonography (USG) of the patient, and it was reported that the echogenicity of both kidneys increased by grade 1-2. No acute pathology was detected in the unenhanced abdominal computed tomography (CT) examination. The urology department did not consider the post-renal ARF in the patient who had urine output and did not have hydronephrosis. The patient's creatinine values, which were taken once every 6 hours and then twice a day, were found to be 2.19mg/dl, 2.85 mg/dl, 2.70 mg/dl, 2.78 mg/dl, 2.6 mg/dl, and 2.2 mg/dl, respectively. Nephrology did not plan emergency hemodialysis for the patient and did not (could not) perform scintigraphy, elective USG or renal biopsy to diagnose or rule out ATN because they could not hospitalize the patient. Our opinion that the patient, whose follow-up was performed by us, might have ATN was not shared by the Nephrology department together with poison counseling on the grounds that Darifenacin-induced ATN is not a highly anticipated clinical picture. Due to regression in creatinine level, good general condition, and good urine output, the patient was discharged to come for outpatient follow-ups by the Nephrology department after 3 days of emergency critical care hospitalization. We observed that the patient's creatinine level requested by the Nephrology department was 1.5mg/dl 3 days after discharge and was at normal level thereafter.

Discussion

Acute kidney injury is characterized by a sudden decrease in renal function. Causes can be prerenal, renal, or post-renal. AKI is observed in approximately 10% of hospitalized patients (3). We did not consider a pre-renal cause in our patient, since there was no condition that would cause real volume loss such as nausea, vomiting, diarrhea, bleeding, and burns, and hypotension, or third space loss did not develop. About 70% of AKI is caused by prerenal conditions and ATN. In a very small group of patients, the cause is urinary tract obstruction (approximately 10%) (4).

The medication has antimuscarinic and anticholinergic side effects (2), but unlike the nephrology department, we did not consider a post-renal cause in our patient due to the normal amount of urine output at the patient's admission, the absence of a condition such as a globe vesicale, the continuation of urine output after insertion of the bladder catheter, and the lack of condition such as hydronephrosis in renal imaging (USG and CT).

Darifenacine is rapidliy an almost completely absorbed (%97) from the gastrointestinal tract with maximum plasma levels being reached after 7 hours. The elimination half-life of darifenacine is approximately 3h. Darifenacine is lypophilic, exhibits high protein binding (%98). About %58 of the dose is excreted in the urine and %42 in the feaces. Only a small percentage (%3) is excreted in the form of unchanged drug. Metabolism is mediated by hepatic cytochrome P450 2D6 and 3A4, the main metabolic routes being monohydroxylation in the dihydrobenzfuran ring, dihydrobenzfuran ring opening, and *N*-dealkylation of the pyrrolidine nitrogen (5).

In our opinion, the basic condition in the patient is medication-induced ATN. Many endogenous and exogenous toxins can cause ATN, and the main ones have been reported as vancomycin, aminoglycosides, iron pigments, cisplatin, radiocontrast material, pentamidine, foscarnet, mannitol, IV immunoglobulins, and synthetic cannabinoids (6,7). We think that Darifenacine metabolites may also cause this toxic effect.

Since our patient could not be hospitalized by the Nephrology department, the inability to perform further investigations (fractional excretion of sodium and urinary sodium concentration, advanced imaging, renal biopsy, etc.) in terms of differentiation and definitive diagnosis is an important limitation for this case, however, medication overdose (8), exposure to the agent within 24 hours, return of creatinine level to normal after elimination of the agent and the increase in renal echogenicity on USG are strong evidence suggesting the cause as ATN. In our era, side effects of the medications can be detected to a large extent after these molecules start to be sold. One of the conditions that increase the risk of medication-related nephrotoxicity is the high dose (7). Our patient also drank 25 pieces of this medication belonging to his father 3 days before his application. However, medication-induced AKI can be dose-dependent or idiosyncratic (6).

Conclusion

Since we know that technology has not produced perfect medications without side effects until now, the fact that any molecule taken in overdose can cause AKI via ATN should not be ignored by emergency physicians. The fact that such

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a side effect or undesirable situation has not been reported with Darifenacin so far does not mean that the molecule is safe for this situation. An overdose of Darifenacin may cause AKI in patients. We believe that our case will be clarfy for emergency medicine physicians in revealing the possibility of AKI in Darifenacine overdose.

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