LITHIUM INTOXICATION FOLLOWING CO-ADMINISTRATION OF TRANDOLAPRIL AND HYDROCHLOROTHIAZIDE

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ABSTRACT

***Background**: Lithium is a drug used to treat mood disorders-in particular, bipolar disorder. Due to lithium's narrow therapeutic dosage range, the potential for toxicity associated with its use is very high. Herein we report a patient with lithium intoxication following co-administration of trandolapril and hydrochlorothiazide.*

***Case presentation**: A 52-year-old male that had been treated with lithium for bipolar disorder since 1994 was admitted to the intensive care unit for the treatment of a high serum lithium level. Two weeks earlier he began taking trandolapril 2 mg o.p.d. and hydrochlorothiazide 25 mg o.p.d. for hypertension. He then began to experience nausea, vomiting, loss of balance, slurred speech, difficulty walking, hand tremor, and swollen feet in the morning of his presentation to the emergency department. The patient underwent a 4-h hemodialysis treatment, which lowered the serum lithium level. He was discharged on d 5 of hospitalization.*

***Discussion and conclusion**: Concomitant use of trandolapril and hydrochlorothiazide may cause the serum lithium level to increase and hemodialysis can be used to treat lithium intoxication.*

***Key words**: Lithium Intoxication, trandolapril and hydrochlorothiazide.*

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Introduction

Trandolapril is an angiotensin-converting enzyme inhibitor, whereas hydrochlorothiazide is a diuretic drug. Both drugs are used together for the treatment of hypertension. Use of trandolapril or hydrochlorothiazide together with lithium can increase the serum lithium level. Lithium is a medication used to treat mood disorders-in particular, bipolar disorder[1,2]. Because of lithium's narrow therapeutic dosage range (0.6-1.2 mmol L^{-1}), the potential for toxicity is high[3]. Serum lithium levels below 2.5 mmol L^{-1} cause mild toxicity, levels 2.5-3.5 mmol L^{-1} cause severe toxicity, and levels above 3.5 mmol L^{-1} are life-threatening. American Association of Poison Control Centers, Toxic Exposure Surveillance System poison control data for 2000-2004 show that there were 3960 suicidal lithium ingestion cases, the use of the critical care unit was 47%, and there were 2 fatalities[4].

The early signs of lithium intoxication include diarrhea, vomiting, drowsiness, muscular weakness, and lack of coordination when the serum lithium level is below 2.0 mmol L^{-1}, at serum levels between 2.0 mmol L^{-1} and 3.0 mmol L^{-1} giddiness, ataxia, blurred vision, tinnitus, and output of a large volume of dilute urine can occur, and at levels >3.0 mmol L^{-1} multiple organ failure can occur[5,6]. Acute lithium intoxication is observed in patients that have taken it voluntarily or accidentally, and in those without a history of lithium use. In addition, acute intoxication may occur while taking daily dose of lithium. High doses of lithium or low elimination rates can cause toxicity. Acute intoxication in most cases is associated with short-term exposure to high concentrations, because of the widespread distribution of lithium in the total body water compartment. In contrast, chronic toxicity is associated with long-term lithium exposure and, therefore, higher tissue concentrations.

Multiple hemodialysis treatment is very effective for eliminating circulating lithium for rebound serum concentrations[7]. Herein we report a patient with lithium intoxication following co-administration of trandolapril and hydrochlorothiazide, as well as a discussion of the symptoms of chronic lithium intoxication when lithium is used to treat bipolar disorder, medicinal approaches, and the importance of hemodialysis in its treatment.

Case presentation

A 52-year-old male patient with a 20-year history of using lithium 1200 mg d-1 for bipolar disorder was brought to the emergency department with imbalance, difficulty talking and walking, nausea, and vomiting then he was transferred to the intensive care unit. The patient began taking trandolapril 2 mg o.p.d. and hydrochlorothiazide 25 mg o.p.d. 2 weeks earlier. The patient regularly monitored his lithium level, which he had done 3 months before presentation and it was normal. According to the patient's family, his complaints began two weeks after starting trandolapril and hydrochlorothiazide to treat hypertension. At the time of presentation the patient's serum lithium level was 4.9 mmol L^{-1}.

Initial blood biochemical findings were, as follows: Na: 135 mmol L^{-1}; urea: 100 mg dL^{-1}; creatinine: 2.3 mg dL^{-1}; glomerular filtration rate: 33 mL·min-1·1.73 m-2. Neurological examination showed that his awareness was clear, he was cooperative, and he was orientated, but his speech was slurred. Physical examination of his extremities showed that there was no loss of sensation or motor ability, he was able to walk taking small steps, and that he mild hand tremor. ECG findings were indicative of sinus arrhythmia. Normal saline infusion was initiated for volume resuscitation.

The patient underwent a 4-h hemodialysis treatment based on a nephrologist's recommendation, after which the patient's nausea and vomiting were ameliorated. As the patient's urea and creatinine levels decreased, and his glomerular filtration rate and blood bicarbonate level returned to normal at the third day of his admission, hemodialysis was not repeated. The patient's volume of urine output and serum lithium concentration on d 1-4 of lithium intoxication treatment are shown in the Table 1. With a reduction in complaints, and a return to normal urine output and kidney function, the patient was discharged from hospital on d 5.

	1st day	2nd day	3rd day	4th day
Urine volume (mL)	3400	3800	4100	2900
Serum lithium concentration (mmol L^{-1})	2.69	1.6	1.08	-

Table 1: Urine volume and the serum lithium concentration on d 1-4 of lithium intoxication treatment.

Discussion

The therapeutic dosage range of lithium is narrow; therefore, the serum level should be monitored frequently in patients using the medication. Even within the therapeutic dosage range side effects can be observed. Medicines used together with lithium, including non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors (ACE inhibitors), and diuretics, and comorbid diseases that causes dehydration and, infections increase the risk of lithium intoxication[8]. In the presented case co-administration of trandolapril and hydrochlorothiazide with lithium might have caused lithium intoxication.

Trandolapril and hydrochlorothiazide are frequently used together, and their combined effects may cause an increase in the serum lithium level. In cases of lithium overdose the treatment is symptomatic. Activated carbon is not used to treat lithium intoxication because it does not capture lithium, but is used if multiple medicines in addition to lithium have been taken[9]. In most cases kidney function disorders that do not respond to fluid treatment are in the foreground[10]. Lithium is eliminated via the kidneys and under normal conditions is reabsorbed through the proximal tubules. The elimination of lithium may be reduced due to 2 causes: kidney dysfunction or concomitant use of medications, which reduces elimination of lithium via the kidneys[7]. In the presented case kidney function returned to normal following fluid replacement and hemodialysis.

Kidney perfusion with an infusion of normal saline must be provided in patients with lithium intoxication, and the glomerular filtration rate and an increase in lithium elimination must be the primary goals of treatment[11]. The urine output should be observed and electrolyte disorders should be corrected. There is no consensus concerning the use of progressive elimination techniques or when to use them in cases of lithium intoxication.

Hemodialysis is recommended when the serum lithium level is >4.0 mmol L^{-1} in patients

with acute intoxication or >2.5 mmol L^{-1} in patients with chronic intoxication[9]. For the elimination of lithium hemodialysis is more effective than any other technique[7,12]. In the presented case the serum lithium level was 4.9 mmol L^{-1} and hemodialysis was performed once, resulting in a progressive decrease in the serum lithium level; a repeat hemodialysis treatment was not necessary.

Lithium together with the concomitant use of trandolapril and hydrochlorothiazide can cause an elevated serum lithium level and symptoms of lithium toxicity, as in the presented case. The presented case shows that these drugs should not to be co-administered, but if they are the serum lithium level must be monitored closely. Hemodialysis can be effective for treating lithium intoxication in patients that are also taking trandolapril and hydrochlorothiazide.

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