Lithium Intoxication in Type 2 Diabetic Patient After Concurrent Use of Lisinopril and Lithium

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Concurrent use of lithium with diuretics, ACE inhibitors and non-steroid antiinflammatory drugs may result in elevated serum lithium levels and lithium intoxication. We present here a case of lithium intoxication in a 75-year-old woman. The patient had type 2 diabetes mellitus and bipolar affective disorder for 15 years. She was hospitalized for hypoglycemia which developed secondary to oral antidiabetic agents. After treating her hypoglycemia with 20% dextrose iv. infusion, her blood sugar was regulated with crystallized insulin four times a day and her lithium therapy was continued 300 mg. bid. As microalbuminuria was detected, lisinopril 5 mg. was started for hypertension. On the second day of lisinopril weakness, headache and restlessness developed. The following day nausea, vomiting, polyuria, tremor, rejection of therapy and aggressive behaviour, slurred and illogical speech were observed. Lithium intoxication was suspected and lithium therapy was stopped. Her serum lithium level was 2.17 mEq/L. Fluid replacement was given under electrolyte monitoring and lisinopril was switched to amlodipin 10 mg / day. In the following days her symptoms faded gradually and after normalization of serum lithium levels they completely disappeared.

Key words: Lithium intoxication, ACE inhibitors, type 2 diabetes mellitus

Introduction

Lithium intoxication can develop after a process delaying the excretion of lithium from the kidneys. The signs of toxicity generally appear at serum levels higher than 2 meq/L and urgent intervention may be necessary (1).

As lithium has a narrow therapeutic range, small increments in serum levels can result in serious side effects; combination with drugs that raise serum lithium levels should be avoided. Drugs which decrease glomerular filtration rate such as diuretics, non-steroidal anti-inflammatory agents and ACE inhibitors may alter the pharmacokinetics of lithium which is excreted mainly (95%) from the kidneys with significant reabsorption from proximal tubules (80%). Captopril, enalapril and lisinopril have all been implicated in this interaction.

Here, a type 2 diabetic patient who developed lithium intoxication after the addition of lisinopril to lithium therapy is reported.

Case Report

A 75-year-old diabetic woman was admitted to the Emergency Department with profuse sweating and lethargy. She had been under therapy for type 2 diabetes mellitus, Parkinson’s disease and bipolar affective disorder for fifteen years. Hypoglycemia (24 mg/dL), probably due to the oral hypoglycemic
agents (acarbose 100 mg. tid., metformin 850 mg. bid. and glimepride 2 mg/day), was treated with 20% dextrose iv. infusion. Blood pressure was 130/90 mmHg. and physical examination disclosed static tremor, bradykinesia, rigidity and mask face. Laboratory examination revealed Hb: 13.4 g/dL, Hct 40.3%, WBC: 12700/mm³, Platelet: 299.000/mm³, BUN: 13 mg/dL, creatinine: 0.9 mg/dL, Na: 145 mEq/L, K: 3.9 mEq/L, Ca: 9.7mg/dL, AST: 13 U/L, ALT: 18 U/L, HbA1c: 8.3%, creatinine clearance: 65 mg/dL, albumin/creatinine ratio: 50. ECG and chest X-ray were normal. Her blood glucose was regulated with crystalized insulin and her lithium therapy which had been started for bipolar affective disorder was continued with a dose of 300 mg/day.

As the patient was hypertensive and microalbuminuria was detected, lisinopril 5 mg/day was started. On the second day weakness, headache and restlessness developed. The following day nausea, vomiting, polyuria, tremor, rejection of therapy and aggressive behaviour, slurred and illogical speech were observed. Lithium intoxication was suspected and lithium therapy was stopped. Her serum lithium level was 2.17 mEq/L. Fluid replacement was given under electrolyte monitoring and lisinopril was switched to amlodipin 10 mg/day. On the following day, serum lithium level was 1.85 mEq/L and her symptoms faded. As serum lithium levels normalized in two days, the symptoms completely disappeared.

Discussion

Lithium has a high rate of absorption when given orally and its half life is 18-36 hours (2). In patients receiving lithium therapy, serum levels should be monitored and kept with in therapeutic range (0.6-1.2 mEq/L). Because it is primarily excreted from the kidneys, kidney function tests should be performed before it is prescribed.

Lithium and sodium are managed similarly by the kidney. Thus salt-free diets, hypovolemia and diuretics produce a significant increase in its levels (3). Diuretics are on top of the list of drugs having interaction with lithium. Thiazide diuretics are reported to have the highest potential of increasing lithium levels with 25-40% in concurrent use (4). Also drugs such as methyldopa, tiaprofenic acid, phenylbutazone, indomethaine and naproxen cause increments in serum lithium levels (5).

All ACE inhibitors diminish lithium clearance (6). There are retrospective (6) and prospective (7) studies investigating ACE inhibitor-lithium interaction as well as case reports (8,9,10,11,12) presenting intoxications after concomitant use of these drugs. Finley et al. have added ACE inhibitor therapy for hypertension in 20 patients who are receiving lithium therapy on a regular basis and have stable lithium levels. Serum lithium concentrations increased by 36.1%, lithium clearance decreased by 25.5% and signs of lithium toxicity were observed in 4 patients (6). Moreover, significant interaction between lisinopril and lithium has also been reported (13). Our patient was given lisinopril for hypertension and microalbuminuria, but her lithium therapy was not taken into consideration. Probably, a further decrement of an already existing low glomerular filtration rate predisposed her to lithium intoxication.

ACE inhibitors were reported to predispose to lithium intoxication not only by decreasing lithium clearance, but also by causing renal dysfunction in patients especially on long-term lithium therapy (14). Although no experimental and controlled clinical trials have been performed, activation of the renin-angiotensin system with different pathways by lithium has also been observed (14).

In conclusion, ACE inhibitors should not be used in patients on lithium therapy, since they are frequently used in diabetic patients, both for treatment of microalbuminuria and hypertension. If there is a strong indication to use an ACE inhibitor in a diabetic patient on lithium therapy, the patient should be monitored both for kidney functions and serum lithium levels.

References

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