Hyperkalemia Induced by the Calcium Channel Blocker, Benidipine

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Abstract

A 73-year-old hypertensive, non-diabetic woman without obvious renal dysfunction had frequently been hyperkalemic over four years after receiving antihypertensive drugs including the calcium channel blocker (CCB) benidipine. One week after all medications were accidentally discontinued, the serum potassium level returned to normal. After we obtained the informed consent of the patient, benidipine alone was administered again for over two weeks and hyperkalemia developed once more. This previously uncommon side effect of hyperkalemia induced by benidipine is not very serious but it is apt to be overlooked. Since CCBs are now widely prescribed, the development of hyperkalemia should be considered.


Key words: hyperkalemia, benidipine, calcium channel blocker, potassium, side effect

Introduction

Hyperkalemia, defined as a serum potassium concentration greater than 5.0 mEq/l, occurs as a result of increased potassium release from cells, decreased renal loss or increased potassium intake (1). Drugs can cause hyperkalemia through either of the above mechanisms (2). Antihypertensive drugs such as spironolactone, angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) quite often cause this condition (1-4). Although calcium channel blockers (CCBs) are not known for inducing hyperkalemia, several investigators have reported an association between hyperkalemia and verapamil (5-9) as well as diltiazem (10, 11). However, since most patients who developed hyperkalemia during treatment with CCBs were concomitantly prescribed other drugs (5, 6, 8, 10) and had chronic renal failure (7, 9) or underlying hypoaldosteronism (11), the etiology of hyperkalemia has appeared multifactorial.

The CCB, benidipine, has been widely prescribed for hypertensive patients in Japan since 1991. A few post-market surveys have noted that hyperkalemia is a likely side effect of benidipine in hypertensive Japanese patients (12-14). However, the relationship between benidipine and hyperkalemia has not been clearly defined. Since this side effect is relatively minor, a CCB is apt to be overlooked as a cause of hyperkalemia in clinical situations. We emphasize the need for medical awareness of this side effect of CCB.

Case Report

A 73-year-old hypertensive, non-diabetic woman was treated with 120 mg of verapamil and 0.25 mg of reserpine from 1994. A complete atrioventricular block (CAVB) associated with a heart rate of 45 beats/min developed in May 1996, so verapamil was discontinued and 1 mg of cilazapril and 1.5 mg of rescimanine were administered instead. However, CAVB did not improve and she was admitted to our hospital for pacemaker implantation. Although all drugs except for cilazapril were discontinued after admission, CAVB continued. An electrophysiological study showed an intra-Hissian block and a minimal heart rate of 37 beats/min, so a permanent pacemaker (VVI) was implanted in August 1996. She was treated with 1 mg of cilazapril alone during admission and serum potassium levels during these admission periods ranged from 3.8 to 4.7 mEq/l with controlled blood pressure. The serum levels of sodium, chloride, creatinine (Cr) and blood urea nitrogen (BUN) during these periods were 143-146 mEq/l, 104-108 mEq/l, 0.7-0.9 mg/dl and 14.2-23.7 mg/dl, respectively. Arterial blood pH and bicarbonate values were 7.416 and 23.3 mEq/l, respectively.
However, blood pressure became elevated after discharge, so 4 mg of benidipine and 25 mg of spironolactone in addition to 1 mg of cilazapril were administered from October 1996 by her general practitioner. The initial serum potassium level identified by the physician was 5.0 mEq/l in February 1998, so he discontinued spironolactone and cilazapril and prescribed various antihypertensive regimens with continuous benidipine. The physician also advised her to minimize fruit and vegetable consumption. However, her serum potassium level remained high (4.9 to 6.2 mEq/l) despite the administration of 20 mg of furosemide (Fig. 1). Probucol (250 mg) was initiated from July 1999 because of hypercholesterolemia and 2 mg of azelastine was administered in addition to benidipine and furosemide from July 2000 because of occasional itching. The serum levels of sodium, chloride, Cr and BUN while receiving benidipine were 141–144 mEq/l, 102–104 mEq/l, 1.0–1.1 mg/dl and 18–24 mg/dl, respectively. Liver dysfunction and hemolysis were also absent.

The patient presented flu-like symptoms associated with a severe repetitive cough on August 15, 2001. All medications were discontinued and she was prescribed with a procaterol inhaler for the cough. Her blood pressure was controlled during bed rest without antihypertensive drugs. The serum level of potassium was in the normal range between 3.9 and 4.4 mEq/l during these periods, suggesting that hyperkalemia in this patient had been induced by the drugs prescribed before this episode. Values for plasma aldosterone (171 pg/ml), plasma renin activity (0.53 ng/ml/h), renal function (Cr: 0.7 –0.9 mg/dl, BUN: 13–19 mg/dl) and liver function without medication were normal. Informed consent was obtained from the patient and her family to administer 4 mg of benidipine and 2 mg of azelastine on September 29, 2001. She was also advised to consume a balanced diet to minimize the effects on the serum potassium levels during the trial. Three weeks later, serum potassium levels increased from 4.1 to 5.7 mEq/l. Benidipine alone was administered from October 19 to November 5, 2001. The serum potassium level reached 5.7 mEq/l again on November 5, 2001 then decreased to 4.5 mEq/l three weeks after substituting amlodipine for benidipine. Amlodipine and azelastine were continuously administered without the recurrence of hyperkalemia for up to 8 months of follow-up. These find-

**Figure 1.** Changes in serum potassium levels and prescribed medications during 6 years of follow-up. Serum potassium levels before administration of benidipine and spironolactone were between 3.8 and 4.7 mEq/l. However, the first charted record of serum potassium levels after the initiation of benidipine therapy was 5.0 mEq/l followed by 5.3 to 6.2 mEq/l. The level fell to 4.9 mEq/l only once during benidipine therapy immediately after starting furosemide. After discontinuing benidipine, the serum level of potassium dropped to the normal range. Levels then increased from 4.1 to 5.7 mEq/l three weeks after starting benidipine and azelastine therapy and reached 5.7 mEq/l again after 17 days of manidipine alone. Three weeks after amlodipine was substituted for benidipine, serum potassium levels decreased to 4.5 mEq/l. Amlodipine and azelastine were continuously administered without recurrence of hyperkalemia for up to 8 months of follow-up.
ings indicated that hyperkalemia in this patient was caused by benidipine.

Discussion

A 73-year-old hypertensive, non-diabetic woman without obvious renal dysfunction and hypoaldosteronism had two episodes of hyperkalemia while undergoing benidipine therapy. Both episodes were reversed upon withdrawal of the drug. Several drugs including benidipine were prescribed to the patient over the five years during the first episode and benidipine alone was prescribed for over 2 weeks during the second episode. These clinical courses suggested that the hyperkalemia in this patient was induced by benidipine.

Known drugs that may cause hyperkalemia include ACEI, ARB, beta-blocker, cyclosporin, an overdose of digitalis, heparin, non-steroidal anti-inflammatory drugs (NSAID), pentamidine, spironolactone, succinylcholine and trimetidine (1, 2). Neuromuscular blocking agents such as succinylcholine, beta-blockers and digitalis cause potassium release from cells; heparin, NSAID, ACEI and ARB decrease renal loss because of secondary hypoaldosteronism; and potassium-sparing diuretics and pentamidine decreases potassium secretion because of resistance to aldosterone (1). Calcium channel blockers are not included in this list although increased serum potassium levels have occasionally been found by post market surveys of benidipine in Japan (12–14). However, whether CCB actually induces hyperkalemia in the clinical setting has been controversial (5–11, 15–17). Indeed, CCBs such as diltiazem, nifedipine, verapamil and nitrendipine are generally considered not to affect serum potassium levels (15). Most of the etiology of reported hyperkalemia associated with CCB use could be multifactorial, since most hyperkalemic patients were prescribed with beta-blockers (5, 8, 10) and ACEI (8), anesthetized with intravenous dantrolene (6), or had underlying renal dysfunction (7, 9) or hypoaldosteronism (11). Most of the reported CCB-induced hyperkalemia has been caused by verapamil (5–9) or diltiazem (10, 11). In addition, hyperkalemia associated with CCB has occasionally been related to hepatocellular damage, glucose-related potassium shift, and metabolic acidosis (7). It is also postulated that verapamil-induced hyperkalemia is a result of diminished renal function after an adverse hemodynamic effect on ventricular function (8). Verapamil may also decrease potassium movement from the extracellular, to the intracellular space by blocking calcium channels (18).

Aldosterone is synthesized by glomerulosa cells in the adrenal cortex. Calcium is an important intracellular messenger for the synthesis and secretion of aldosterone in response to the serum potassium concentration, angiotensin II and ACTH (11). Patch clamp methods using bovine adrenal glomerulosa cells have revealed T- and L-type calcium channels (19). The activation of T-type calcium channels by angiotensin II leads to calcium influx into cells and nitrendipine suppresses the function of these channels and aldosterone secretion in response to potassium and angiotensin II stimuli. Although the molecular events relating to cellular calcium entry and aldosterone biosynthesis remain unclear, aldosterone secretion induced by potassium stimulation in vivo is also suppressed by nisoldipine (20). Doses of verapamil far larger than those used in clinical practice non-specifically inhibit at least two steps of the aldosterone biosynthetic pathway in vitro (21, 22). The findings of these in vitro and in vivo studies suggest that benidipine could have inhibited the biosynthesis and secretion of aldosterone in the present patient. However, since the plasma aldosterone level was not measured in this patient while undergoing benidipine therapy, we cannot conclude that the hyperkalemia induced by benidipine is via the inhibition of aldosterone biosynthesis and secretion. Furthermore, the fact that our patient could be unique and that her renal function could be potentially decreased, cannot be completely excluded.

In summary, we described a hypertensive patient who developed hyperkalemia after the administration of benidipine, but which was resolved immediately after discontinuing the drug. We emphasize the need for medical awareness of this side effect, since CCBs are widely prescribed to treat patients with hypertension and angina pectoris.

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References


