

Uncontrolled Hypertension and Hyperkalemia Related to Low Dose Daily Acetylsalicylic Acid Therapy in a Patient with Coronary Artery Disease: A Case Report

Koroner Arter Hastalığı Olan Bir Hastada Düşük Doz Asetilsalisilik Asit Tedavisi ile İlişkili Hiperkalemi ve Kontrolsüz Hipertansiyon: Olgu Sunumu

ABSTRACT

Acetylsalicylic acid (ASA) is a member of the non-steroidal anti-inflammatory drugs (NSAIDs). Thus, it can cause side effects such as fluid, electrolyte and acid-base imbalances through the enzyme cyclooxygenases (COX 1-2). Despite the wide use of ASA and its general good safety profile, sensitivity to ASA should be kept in mind. Here, we reported a patient who presented with hypertension and hyperkalemia after low dose ASA treatment.

KEY WORDS: Hypertension, Hyperkalemia, Acetylsalicylic acid

ÖZ

Asetilsalisilik asit (ASA), steroid olmayan antiinflamatuvar ilaçlar (NSAI) grubunun bir üyesidir. Diğer NSAI'lar gibi ASA da çeşitli sıvı, elektrolit ve asit-baz bozukluklarına siklooksijenaz enzimleri (COX 1-2) üzerinden neden olabilmektedir. ASA sahip olduğu iyi güvenlik profile ile geniş bir kullanımı olmasının yanı sıra ASA duyarlılığı akılda tutulmalıdır. Bu olgu sunumunda, düşük doz ASA tedavisi sonrasında gelişen hiperkalemi ve kontrolsüz hipertansiyon ile gelen bir hasta tanımlanmaktadır.

ANAHTAR SÖZCÜKLER: Hipertansiyon, Hiperkalemi, Asetilsalisilik asit

INTRODUCTION

Acetylsalicylic acid (ASA) is widely used as an anti-inflammatory and anti-thrombotic drug for specific conditions such as stroke, heart attack and rheumatoid arthritis (1,2). ASA, as a member of non-steroidal anti-inflammatory drugs (NSAIDs), inhibits the enzyme cyclooxygenase (COX), resulting in decreased synthesis of prostaglandin, leukotriene and thromboxanes. There are two different types of COX, namely COX-1 and COX-2. ASA appears capable of inhibiting platelet aggregation irreversibly by acetylation of the platelet COX-1. It is known that ASA affects COX-1 more than COX-2 (almost 166 times), thus it can be argued that low doses of aspirin (75 to 150 mg/day) are also safe and effective for preventing vascular events. The anti-inflammatory effects

of ASA mainly emerge at higher doses (500 to 1,500 mg/day) through the inhibition of COX-2 in humans (1,3). NSAIDs can lead to impairment of acid-base homeostasis and electrolyte disorders such as hyperkalemia and sodium retention that results in edema and hypertension in sensitive patients by inhibiting renal prostaglandin synthesis (4). Despite its wide use and generally good safety profile, there are concerns about the side effects of ASA. Here, we report a case of ASA-induced hyperkalemia and high blood pressure.

CASE REPORT

A 51-year-old male with coronary artery disease presented to our nephrology department with hyperkalemia despite treatment. The patient had a 3-year history

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of hypertension and coronary angiography had been performed 3 years ago at another hospital. He was treated with ASA 100 mg/day, clopidogrel 75 mg/day and verapamil 1x80 mg/day. We learned from the patient's history that on account of hyperkalemia (>5.5 mEq/L) which had newly emerged and because the blood pressure of the patient remained uncontrolled in spite of the use of verapamil 1x80 mg/day during follow-up, 15 g polystyrene sulfonate (kayexalate) t.i.d. and doxazosin 4 mg twice a day had been added to his drugs 2.5 years ago. On physical examination, blood pressure was 150/100 mm Hg, and pulse rate was 88 per minute. His heart sounds were normal. There were no murmurs and no evidence of heart failure. All other systemic examinations were normal. On initial investigation, white blood cells, hemoglobin and platelets were normal (7.200/mm³, 14.6 g/dl and 186.000/mm³, respectively). Blood glucose, serum urea and creatinine levels were normal at 94 mg/dl, 24 mg/dl and 0.9 mg/dl, respectively. Serum potassium level was 5.6 mEq/L but no ECG changes due to hyperkalemia were seen. The other serum electrolytes except serum bicarbonate (18 mEq/L) and serum osmolality (289 mosm/l) were also normal. Despite the low serum bicarbonate level, there was a normal pH value in the arterial blood gas evaluation (pH:7.35, pCO₂:35.1 and HCO₃:18.7). Additionally, plasma renin activity and aldosterone concentration of the patient were within the normal range. The twenty-four hour urine test showed the following results; urine sodium-126 mmol/24 hour (40-220 mmol), urine potassium-44 mmol/24 hours (25-125 mmol), urine creatinine 2275 mg/24 hours, and urine microalbumin <20 mg/24 hours. Urine specific gravity (1.020) and urine osmolality (840 mosm/l) were normal.

Higher levels of serum potassium (>5.5 mEq/L) can cause life-threatening conditions. Thus, we decided to hospitalize the patient with persistent hyperkalemia and uncontrolled hypertension to remove external factors (substance abuse, eating habits and misuse of medication). Sodium hydrogen carbonate 500 mg t.i.d. was added to his drugs. Potassium levels remained slightly elevated. However the patient did not have any other symptoms of hyperkalemia. The high levels of serum potassium which had emerged were subsequently considered as iatrogenic hyperkalemia. The low dose ASA therapy was then stopped. Serum potassium levels dramatically decreased to normal range in 48 hours. Hence, the drugs used to reduce the serum potassium level were stopped. The patient returned to eating a normal potassium diet.

It was notable that blood pressure dropped to the normal range after stopping ASA therapy as well. Symptoms of orthostatic hypotension developed in the patient so doxazosin was discontinued. The patient's condition typically improved rapidly within a day. The substantial and significant reduction in blood pressure and serum potassium level remained during hospitalization. The patient was discharged from the hospital with recommended medical treatment including clopidogrel 75 mg/day and verapamil 1x80 mg/day.

At the one month follow-up visit, blood pressure, serum potassium and the bicarbonate level were within the normal range (130/80 mmHg, 4.4 mEq/L and 24 mEq/L, respectively). We monitored the patient without any change in his medical treatment.

Two months later, the patient was referred to our clinic due to persistent hyperkalemia. It was learned that low dose ASA therapy had been added to his therapy by his cardiologist again. The low dose ASA therapy and the drugs used to reduce serum potassium level were stopped. Then, it was seen that the serum potassium value dropped from 5.7 mEq/L to 4.4 mEq/L in 3 days. We classified this event as a probable adverse drug reaction (score of 7 points) using the Naranjo Adverse Drug Reactions Probability Scale (5).

DISCUSSION

ASA is anti-inflammatory at high doses, stemming from the inhibition of cyclooxygenase and proinflammatory signaling pathways including NF-kappaB, but is cardioprotective at lower doses (1). As an anti-inflammatory agent for both acute and long-term inflammation, ASA might induce a variety of renal function abnormalities such as electrolyte complications (notably hyperkalemia) by inhibiting prostaglandin synthesis, particularly in high-risk patients with decreased renal blood flow (6). In particular, blocked production of COX-2-related prostaglandins (PGE2 and PGI2) may result in reduced renal perfusion, hyperkalemia and increased blood pressure, leading to sodium and fluid retention and a decreased GFR (7).

Actually, renal expression of COX-2 has been shown to be up-regulated in progressive renal injury and salt restriction, suggesting that COX-2 derived prostanoids may play an important role in the control of renal blood flow and systemic blood pressure (8). Evidence suggests that specific COX-2 inhibition appears to be associated with abnormal blood pressure response, renal ischemia, electrolyte imbalances and vasoconstriction leading to decreased synthesis of vasodilator PGs (4,9). However, all NSAIDs seem to share these adverse effects. Variable degrees of fluid retention and blood pressure changes are observed depending on the NSAID and the doses taken. Additionally, it has been demonstrated that some NSAIDs can reduce the efficacy of some commonly utilized anti-hypertensive agents (10).

A meta-analysis revealed that use of NSAIDs has controversial effects on blood pressure in hypertensive patients. It was noted that the group consisting of indomethacin, naproxen and piroxicam led to increase in mean arterial pressure, whereas placebo, aspirin, ibuprofen, and sulindac caused a decrease in mean arterial pressure. In short-term use, the most marked increase in blood pressure was found to be associated with both indomethacin and naproxen. However, no effect of drugs including piroxicam, aspirin, ibuprofen and sulindac was seen to make a meaningful difference on blood pressure (11).

In this case report, we presented a patient with worsening underlying hypertension due to low dose ASA. The effect of verapamil and doxazosin may have been antagonized by the low dose ASA, probably due to the patient's susceptibility to adverse renal effects of ASA. Salicylate sensitivity might have appeared by presenting an alteration in COX response to ASA in this patient. Another issue noted in our patient was that hyperkalemia was accompanied by hypertension. It is known that PG synthesis inhibition can lead to hyporeninemic hypoaldosteronism which may cause hyperkalemia/type 4 RTA in susceptible patients (4). However, plasma renin activity and aldosterone concentration of the patient were within the normal range. Furthermore, there were no other factors such as obstructive uropathy and urinary tract infections that may lead to secondary pseudoaldosteronism. Because serum potassium concentration began to increase within several days of the onset of therapy, we stopped ASA. During follow-up visits, a dramatic drop in serum potassium levels accompanied by a rapid decline in blood pressure was observed. Thus we think that the patient is particularly sensitive to aspirin somehow. We therefore believe that patients with hyperkalemia and uncontrolled blood pressure should be questioned about low dose ASA use.

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