Case Report

Reversible Hyperkalemia Induced by Flufenamic Acid in Asymptomatic Hyporeninemic Patient

Isamu Miyamori, MD, Takeshi Sakai, MD, Toshiyuki Ito, MD, Norimichi Sugihara, MD, Masatoshi Ikeda, MD, Yoshiyu Takeda, MD and Ryoyu Takeda, MD

Reversible hyperkalemia induced by flufenamic acid in an asymptomatic hyporenemic patient with IgA nephropathy is reported. Flufenamic acid, 600 mg daily, was given for four months to a 64-year-old woman with biopsy proven IgA-nephropathy. This produced hyperkalemia, hypertension and congestive heart failure with slowly progressive renal impairment. We conclude that a further suppression of the renin angiotensin system causing selective hypoaldosteronism together with the nephrotoxic effects of this drug may have been responsible for hyperkalemia in this patient.

Key Words: NSAID, Renal failure, Hyporeninemic hypoaldosteronism

Hyporeninemic hypoaldosteronism (HH) is known to occur in association with diabetes, various renal diseases with mild to moderate renal impairment or in rare instances after chronic sodium bicarbonate abuse. In previous articles, indomethacin-induced hyperkalemia was reported, and a possible mechanism of prostaglandin (PG) inhibition was presented. With the advent of several nonsteroidal anti-inflammatory drugs (NSAIDs) with different potencies for cyclooxygenase inhibition, it is conceivable that HH could occur more frequently during the chronic administration of these agents.

In hypovolemic states induced either by diuretics or sodium depletion, or under decreased renal blood flow, which occurs in congestive heart failure or liver cirrhosis, NSAIDs cause renal impairment of various degrees. Hence, we are warned against their usage in these conditions. We propose that NSAIDs should be administered with extreme caution in patients with asymptomatic HH with or without underlying renal diseases, since these agents may further aggravate potential HH and cause hyperkalemia.

CASE REPORT

A 64-year-old woman had been afflicted with rheumatoid arthritis for which she underwent treatment with 2400 mg of gold from 1980 to July 1982. She gradually developed proteinuria and hematuria for which she was hospitalized in March 1983. Her blood pressure was 122/80 mmHg. Radiology of the chest and bones was normal, except for mild cardiomegaly. Serum sodium was 142 mEq/L, potassium 4.1 mEq/L, blood urea nitrogen 12 mg/dl, and serum creatinine, 0.6 mg/dl. Arterial pH was 7.39 and plasma bicarbonate was 24 mEq/L. Plasma renin activity (PRA) ranged between 0.1 and 0.3 ng/ml/h (normal; 0.5—2.0) on several occasions. Plasma aldosterone (p-aldo) was 2.2 ng/dl (normal; 4.7—13.1). Renal function at the time was normal. Kidney biopsy performed in April 1983 demonstrated sclerotic changes of the glomeruli, with...
fibrocellular crescent formation of a moderate degree in approximately half of them. Using direct immunofluorescence, a deposit of IgA was demonstrated in the mesangium and capillary loops. On the basis of these results, diagnosis of IgA nephropathy was made. The patient was given 600 mg of flufenamic acid daily from May 11, 1983 and was discharged. She received the same regimen and was followed-up at the outpatient clinic. She was well until May 22, when she noticed breathlessness and edema in her legs. On May 27, she visited her physician because of dyspnea. Her blood pressure was 220/130 mmHg, with marked cardiomegaly and pleural effusion. She was given diuretics and transferred to our emergency department. ECG revealed complete AV block with a heart rate of 36. Diagnosis of congestive heart failure was made and she was readmitted.

On admission, 40 mg of furosemide and 0.125 mg digoxin for heart failure were continued. AV block was temporarily improved by the parenteral administration of isoproterenol. An artificial pacemaker was implanted on July 12, based on ECG diagnosis of sick sinus syndrome. Her clinical symptoms disappeared, and there was an improvement of physical findings after two weeks of hospitalization. Her blood pressure was between 154 and 186 mmHg for systolic and 66 and 80 mmHg for diastolic. Laboratory data revealed serum sodium to be 135 mEq/L, potassium, 6.4 mEq/L, blood urea nitrogen 51 mg/dl, and serum creatinine, 2.0 mg/dl when she was on furosemide, digoxine and flufenamic acid. The serum potassium levels ranged between 4.6 and 7.2 mEq/L on these drugs. PRA was 0.2 ng/ml/h and p-aldosterone was 1.0 ng/dl on a regular diet containing 120 mEq of sodium and 60 mEq of potassium/day. After the patient's physical condition was improved, a clinical investigation was undertaken in order to clarify the cause of hyperkalemia in relation to low PRA and p-aldosterone. Sodium and potassium intake was kept constant during the study. In Figure 1, the results of stimulation of the renin angiotensin system by acute furosemide is shown. Eighty milligrams of furosemide was given orally at 8 a.m., and the patient was kept standing for four hours. This stimulation provoked a two- to three-fold increase in both PRA and p-aldosterone levels under a regular hospital diet in age matched controls. In this patient, however, no appreciable changes in either parameter were seen, despite sufficient volume reduction as evidenced by reduced body weight (−6% reduction from the baseline), and increases in hematocrit (+12%) and urinary sodium excretion. PRA changed from 0.6 to 0.5 ng/ml/h and p-aldosterone from 1.8 to 1.2 ng/dl in response to 80 mg of furosemide given orally.

Adrenal function was tested by acute loading of synthetic ACTH (Cortrocin, Daiichi Pharmaceutical, Osaka, Japan). Two hundred fifty micrograms of ACTH was injected intramuscularly and the responses of plasma cortisol and p-aldosterone were determined. Plasma cortisol showed a normal
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Cortisol
μg/dl

Aldosterone
ng/dl

Normal age-matched control (69±2yrs)

Fig. 2. Changes of plasma cortisol and plasma aldosterone following synthetic ACTH administration. Baseline plasma aldosterone was initially below the detection limit, but responded normally after ACTH.

Hyperkalemia returned to the normal range (4.2–4.6 mEq/L) within two weeks after cessation of flufenamic acid. ECG recording indicated spontaneous recovery of sinus rhythm when congestive heart failure was corrected and serum potassium was normalized. Baseline PRA and p-aldo, however, remained at low levels. The renal function test repeated at this stage demonstrated reduction of glomerular filtration and renal blood flow to one third of the pretreatment levels.

DISCUSSION

The occurrence of reversible hyperkalemia in this patient was most likely induced by flufenamic acid, a derivative of anthranilic acid, used as an NSAID in general practice. Previously, hyperkalemia induced by indomethacin was reported in women with glomerulonephritis or no preexisting renal disease. Extensive studies indicate that renal prostaglandins participate in the renin release and also contribute to the regulation of the renal hemodynamics. Since the therapeutic dose of indomethacin has been shown to reduce urinary PGE excretion, it is considered that the inhibition of the renal PG synthesis by indomethacin is a likely mechanism for hyporeninemia. Besides the effect on renin release, indomethacin and aspirin have been shown to reduce renal function in man, which may also contribute to the hyperkalemia. Flufenamic acid is known to reduce proteinuria and is often used in nephrotic syndrome. However, it is associated with decreased glomerular function. Prolonged suppression of PGE output in the renal papilla was recently demonstrated in the rat ex vivo and in vitro.

Hyperkalemia is a major laboratory finding of HH. In approximately 75% of the cases, hyperkalemia is discovered on routine laboratory screening or during studies for unassociated illness. In the remaining patients, hyperkalemia is found with related symptoms. Although the diagnostic criteria for HH have not yet been defined, hyperkalemia appears essential for the diagnosis. In our patient, hyporeninemia and hypoaldosteronism without hyperkalemia was present before NSAID therapy was initiated. The reasons for the normal serum potassium concentration despite persistently low plasma aldosterone levels in this patient are not entirely clear. The explanation may be that plasma aldosterone secretion was not sufficiently reduced to elevate the serum potassium concentration, or alternatively, that high dietary sodium and/or low potassium intake might have obscured the development of hyperkalemia. The sodium-potassium balance study under a regular hospital diet, which was done after the patient became normokalemic, however, does not support the latter possibility. The presence of IgA nephropathy for the development of hypoaldosteronism appears to be coincidental in our case.

PRA and p-aldo responses to furosemide combined with postural stimulation were negligible in our patient. However, after acute ACTH administration, p-aldo showed an approximately normal response. The responses of the renin angiotensin axis in HH syndrome are not conclusive. Blunted responses to both stimuli have been reported by some, but not by others. The varied responses of p-aldo may reflect the extent and degree of adrenal defect. In 21% of the cases.
of HH, ACTH administration produced normal aldosterone response. We speculate that HH in this patient had been subclinical, and symptomatic hyperkalemia developed only after flufenamic acid was administered which caused further suppression of renin or impaired renal function. Prolonged renal or vascular prostaglandin inhibition may be related to the pathogenesis of hypertension and congestive heart failure without underlying cardiac diseases, probably as a consequence of body fluid retention. ECG abnormality which necessitated the artificial cardiac pacing may also be aggravated by hyperkalemia, since the abnormality was corrected when the drug was withdrawn and the patient become normokalemic. This case demonstrates that the use of NSAIDs in asymptomatic HH patients could result in overt hyperkalemia. These agents, thus, should be used with caution in low renin states even with normal renal function.

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REFERENCES