Minoxidil-Related Renal Function Deterioration and Pulmonary Edema: A Case Report and Literature Review

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Abstract

Minoxidil is a highly effective antihypertensive agent for patients with refractory hypertension. Long-term use of a high dose of minoxidil may cause several side effects. However, the concurrence of acute pulmonary edema and rapid progression of renal function after short-term and low-dose therapy is not common. Herein, we report the case of a 70-year-old woman who had diabetes mellitus and mild impairment of renal function. Low-dose minoxidil (2.5 mg) was prescribed to manage her poorly controlled blood pressure. The dosage was gradually increased to 5 mg/day. In the ninth week after the initiation of minoxidil therapy, the patient experienced weight gain (5 kg), orthopnea, and exertional dyspnea. Physical examination revealed basal crackles in both lung fields. Chest X-ray showed bilateral pleural effusions and pulmonary congestion. One week after the discontinuation of minoxidil, her body weight returned to the previous status and the symptoms of pulmonary edema subsided completely. The pleural effusion resolved gradually two weeks later. However, her renal function deteriorated rapidly and did not return to normal. This case alerts us that minoxidil should be used with caution in patients with impaired renal function. Fluid status and renal function should be closely monitored. Whenever complications develop, minoxidil should be discontinued. (Acta Nephrologica 2011; 25: 33-36)

KEY WORDS: minoxidil, congestive heart failure, renal function deterioration

Introduction

Minoxidil is a potent oral vasodilator that acts directly on arteriolar smooth muscle cells. It is effective in controlling blood pressure in patients with refractory hypertension (1, 2). Its side effects include hirsutism, fluid retention, weight gain, tachycardia, congestive heart failure (CHF), pulmonary congestion, electrocardiographic change, alteration in renal function, and pleural and pericardial effusion. Patients who are complicated with severe fluid overload or pericardial effusion had received large doses of minoxidil for a long time (3-5). The development of severe fluid overload, congestive heart failure and rapid deterioration of renal function in patients who received only a small dose for a very short period is uncommon. In this report, we describe the clinical course as well as radiologic and laboratory findings of a patient who experienced simultaneous weight gain, pleural-pericardial effusions, pulmonary edema, congestive heart failure and rapid deterioration of renal function after short-term low-dose minoxidil therapy.

Case Report

A 70-year-old woman was admitted to our ward with complaints of exertional dyspnea, orthopnea, and leg edema for the past week. She had a history of diabetes mellitus, hypertension, and mild renal function impairment (creatinine around 1.7 mg/dL) for more than ten years. In two months before this admission, her blood pressure was not well controlled (around 170/70 mmHg) (Fig. 1) despite receiving treatment with multiple antihypertensive drugs, including me-
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methyldopa (250 mg, tid), clonidine (75 mcg, tid), bisoprolol (5 mg qd), amlodipine (5 mg bid), valsartan (160 mg qd), terazosin (2 mg bid), and furosemide (40 mg qd). Because the patient refused to take so many antihypertensive drugs, the administration of minoxidil was started at an initial dose of 2.5 mg once daily with reduction in dosage of the other antihypertensive regimens (methyldopa, 250 mg tid; clonidine, 75 mcg tid; bisoprolol, 5 mg qd; terazosin, 2 mg bid; and furosemide, 40 mg qd). At this time, chest X-ray showed borderline cardiomegaly. Retinal examination showed no papilledema, no retinal hemorrhage or exudates, and presented grade II hypertensive retinopathy. There was no evidence of malignant hypertension for this patient.

One month later, her blood pressure became normal (around 134/66 mmHg) (Fig. 1), so the other antihypertensive regimens were further reduced (bisoprolol, 5 mg qd; terazosin, 2 mg bid; and furosemide, 40 mg qd). After tapering other antihypertensive medications, her blood pressure rose again (around 155/68 mmHg) (Fig. 1). Thus, the dose of minoxidil was increased to 2.5 mg twice daily for better control of her blood pressure. Unfortunately, the patient developed leg edema, nocturnal dyspnea, and gained weight (about 5 kg) one week after changing the dose to 5 mg per day. On admission, her blood pressure was 137/51 mmHg and heart rate was 56 beats/min. Physical examination showed pitting edema (+++), grade 3) in lower extremities, basal crackles over bilateral lung fields, decreased breathing sound at lung bases, and an engorged jugular vein. The hemoglobin level was 10.2 gm/dL. The findings of biochemical analysis were as follows: blood glucose, 156 mg/dL; blood urea nitrogen (BUN), 48 mg/dL; creatinine (Cr), 4.0 mg/dL; sodium, 139 mEq/L; potassium, 3.2 mEq/L; total cholesterol, 171 mg/dL; and albumin, 3.3 g/dL. C3 and C4 complements were within the normal range. Anti-double-stranded DNA (dsDNA) and antinuclear antibodies were absent in the serum. A chest X-ray showed enlargement of the cardiac silhouette, pulmonary edema and pleural effusions in both sides. Echocardiography revealed a small pericardial effusion. A diagnostic pleural tapping was performed, and a yellow cloudy fluid was obtained. The pleural fluid-to-serum protein ratio

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<th>2003</th>
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<td>170</td>
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BP: Blood pressure
SBP: Systolic blood pressure
DBP: Diastolic blood pressure

Fig. 1. The creatinine level of the patient rose progressively and irreversibly after the administration of minoxidil although it was discontinued 60 days later. No significant blood pressure drop was noted during the whole course of renal function deterioration.
Renal Deterioration after Minoxidil Therapy

was 0.54, and pleural fluid-to-serum lactate dehydrogenase (LDH) ratio was 0.65. The pleural fluid did not contain malignant cells, or acid-fast bacilli, and both cultures were sterile.

Diabetic nephropathy with severe proteinuria was initially thought to be the cause of our patient's severe edema and fluid overload. However, the analysis of urine collected over a 24-hour period revealed that the amount of protein excreted was 1.0 g/day. The plasma albumin level was only slightly below normal (3.3 g/dL). Thus, diabetic nephropathy with nephrotic syndrome is not likely to be the cause of the observed fluid retention. Furthermore, the liver function test and liver echo study revealed no evidence of liver cirrhosis. Thyroid function and cortisol levels were also normal.

Despite treatment with furosemide (160 mg/day), leg edema and dyspnea did not improve. We suspected that the fluid overload was related to minoxidil. Thus, it was discontinued and hydralazine was administered instead to control the blood pressure. Leg edema, dyspnea, and weight gain improved rapidly and dramatically within a week. No hypotension episode or any evidence of volume contraction developed during the whole course of clinical management. Chest X-ray and echocardiogram repeated one month after discontinuation of minoxidil showed complete disappearance of pulmonary edema, pleural and pericardial effusions. She was feeling well, and her blood pressure (Fig. 1) was controlled with clonidine (750 µg three times daily), amlodipine (10 mg daily), hydralazine (50 mg four times daily), and furosemide (80 mg daily). However, her renal function deteriorated rapidly and irreversibly despite termination of minoxidil therapy (Fig. 1).

Discussion

Hypertension is frequent among patients with chronic kidney disease (CKD). Blood pressure may be difficult to control in some patients with CKD and the use of other powerful drugs such as minoxidil may be required (8, 9). The effective dose of minoxidil for controlling severe hypertension generally ranges from 2 mg to 80 mg per day (6, 8). The usual regimen is 10-20 mg twice daily (6, 17, 18).

The most common side effects of minoxidil are hypertrichosis (60-100%), fluid retention and weight gain (20-65%) (7, 9-12). In their investigation on management of intractable hypertension with minoxidil, Mackay et al. reported that hirsutism was a common side effect of minoxidil therapy (80-100%), and fluid retention (weight gain > 7 kg) occurred in around 20% of the patients (10). Occasionally, side effects such as pericardial effusion (3-10%), tachycardia and pericarditis (1-9%), congestive heart failure (2%), ischemic chest pain (1%), cardiac tamponade (< 1%), pleural effusion (< 1%) and others would occur (7, 10-13). The symptoms usually disappeared after discontinuation of the drug. Although the development of fluid overload or pericardial effusion is common, simultaneous concurrence of severe fluid overload, congestive heart failure and rapid deterioration of renal function after low-dose short-term therapy with minoxidil is rare.

There has been no consensus regarding the impact of minoxidil therapy on renal function (15, 16). Some authors reported that renal function might improve or does not change after minoxidil therapy for hypertension (9, 10, 14). Some groups reported contradictory findings. Wilburn et al. reported worsened renal function in three patients with severe hypertension. These patients had been treated with minoxidil (40-60 mg/day) for 11-13 months (17). Mitchell and Pettinger reported progressive renal failure that required hemodialysis. It developed in patients with severe hypertension who received minoxidil treatment (40 mg/day) for periods ranging from six months to five years (18). In the review from the UpToDate, it is suggested that adverse effects of this drug on renal function is usually transient increase in serum BUN and creatinine, which may return to normal after discontinuation of minoxidil (19). Our patient, however, showed rapid and irreversible deterioration of renal function (from 1.7 mg/dL to 7.4 mg/dL) after the onset of minoxidil administration (5 mg/day) in weeks.

Several factors including diuretic or congestive heart failure, induced kidney hypoperfusion, nephrotoxic drugs, and the de novo effect of minoxidil might have contributed to the development of renal function deterioration in this patient. However, her creatinine level had been rising gradually since the initiation of minoxidil therapy and before the development of congestive heart failure and acute pulmonary edema. In addition, no hypotension episode, no volume contraction, and no nephrotoxic agent administration occurred throughout the clinical course. Although the possibility of diuretics or CHF-related kidney hypoperfusion could be considered, we attributed the irreversible renal function deterioration in the patient to the application of minoxidil.

Diabetic nephropathy with nephrotic syndrome may cause fluid retention and congestive heart failure as seen in our patient. However, her proteinuria was mild, and her serum albumin level was only slightly below normal. Furthermore, the fluid overload resolved quickly and completely after discontinuation of minoxidil therapy. Thus, we believed that the contributory factor for the observed fluid overload was minoxidil rather than diabetic nephropathy.

Our findings indicate that physicians should be careful when prescribing minoxidil to patients with
CKD. The body weight and renal function of patients with CKD receiving minoxidil treatment should be regularly monitored. An apparent weight gain or deterioration of renal function should raise the suspicion of a minoxidil related complication and in such cases, the discontinuation of the drug should be considered.

References

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