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CASE REPORT

Treating proteinuria in a diabetic patient despite hyperkalaemia due to hyporeninaemic hypoaldosteronism

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ABSTRACT

Diabetes mellitus is a common cause of hyporeninaemic hypoaldosteronism that might result in significant hyperkalaemia. We describe a patient with diabetic nephropathy and proteinuria who developed a remarkable hyperkalaemia on treatment with an angiotensin-receptor blocker. The management of hyperkalaemia and the pathophysiological background of hyporeninaemic hypoaldosteronism are discussed.

KEYWORDS

Diabetic nephropathy, hyperkalaemia, hyporeninaemic hypoaldosteronism, ACE inhibitor, angiotensin-receptor blocker

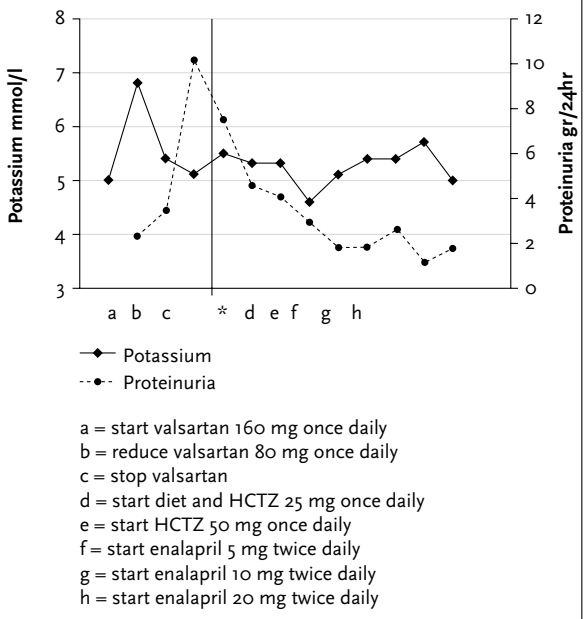
INTRODUCTION

Hyperkalaemia is a common problem in patients with diabetic nephropathy. It usually reflects the seriousness of renal dysfunction and limits the preferable treatment of diabetic nephropathy with angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers.[1,2] As diabetes mellitus itself is a risk factor for hyperkalaemia, even diabetic patients with normal renal function are vulnerable to develop hyperkalaemia as a result of such medication. Hyperkalaemia in these cases is generally mild. However, in patients with concomitant hyporeninaemic hypoaldosteronism this can be serious. We describe a patient with diabetic nephropathy and a normal glomerular filtration rate (GFR), who developed a potentially life-threatening hyperkalaemia during treatment with an angiotensin-receptor blocker.

CASE REPORT

A 55-year-old man had had documented type 2 diabetes mellitus, diabetic retinopathy, and polyneuropathy for three years. During treatment his metabolic control (HbA_{1C} 5.7%, stable body mass index 28.7) and blood pressure (130/70 mmHg) remained good, but he nevertheless developed proteinuria (0.54 to 2.19 g/day). His GFR, electrolytes and urinalysis were normal. Treatment for suspected diabetic nephropathy was started with the angiotensin II receptor antagonist valsartan 160 mg once daily. Other medications for diabetes and benign prostate hypertrophy included metformin 850 mg twice daily, glibenclamide 5 mg twice daily and alfuzosine 10 mg once daily. Hereafter, routine measurement of electrolytes revealed an asymptomatic hyperkalaemia with a potassium concentration of 6.8 mmol/l (*figure 1*). The valsartan was stopped, leading to a decreasing potassium level but escalation of the proteinuria without signs of the nephrotic syndrome. The potassium concentration remained slightly elevated and four weeks after discontinuation of valsartan, this was recognised to be due to hyporeninaemic hypoaldosteronism (*table 1*). The proteinuria was ascribed to diabetic nephropathy. To achieve normokalaemia, dietary measures were taken and hydrochlorothiazide (HCTZ) 25 mg once daily was started. The dosage of HCTZ was later increased to 50 mg once daily and finally the potassium concentration dropped to 4.6 mmol/l. Then, the ACE inhibitor enalapril was gradually started. Potassium levels remained within acceptable margins whereas proteinuria declined significantly but remained high (1.8-2.6 g/day). Further details on the course of potassium and proteinuria after each therapeutic step are shown in *figure 1*. As expected, there was no significant effect on blood pressure. During one-year further follow-up, the patient's proteinuria remained stable (1-2 g/day), while the GFR remained normal. Potassium levels ranged from 5.0 to 5.7 mmol/l.

Figure 1. *Course of potassium concentration in serum and proteinuria after each therapeutic intervention*



a = start valsartan 160 mg once daily
b = reduce valsartan 80 mg once daily
c = stop valsartan
d = start diet and HCTZ 25 mg once daily
e = start HCTZ 50 mg once daily
f = start enalapril 5 mg twice daily
g = start enalapril 10 mg twice daily
h = start enalapril 20 mg twice daily

*** corresponds with table 1. HCTZ = hydrochlorothiazide.**
Note: The periods between each measurement are approximately two weeks except the six-week period between c and d.

Table 1. *Basal data of plasma and urine values four weeks after discontinuation of valsartan.*

	Patient	Normal values
Blood		
Potassium	5.5	3.6-4.8 mmol/l
Sodium	144	136-144 mmol/l
Osmolality	292	260-300 mosmol/kg
Chloride	112	96-107 mmol/l
Bicarbonate	26	22-29 mmol/l
Glucose	7.8	3.5-5.5 mmol/l
Urea	8.3	2.5-7.5 mmol/l
Creatinine	110	70-133 µmol/l
HbA_{1C}	5.7	4.3-6.3 %
Plasma renin activity	0.30	<2.5 µg/l/u
Aldosterone	0.08	<0.35 nmol/l
Albumin	39	40-50 g/l
Total cholesterol	4.58	3.9-7.3 mmol/l
PH	7.38	7.35-7.45
PCO_2	5.9	4.5-6.0 kPa
Urine		
Potassium	132	25-100 mmol/24h (varies with intake)
Sodium	381	100-260 mmol/24h (varies with intake)
Volume	2350	ml, varies with intake
Creatinine	20.64	8.9-17.7 mmol/24h
Protein	7.43	<0.03 g/24h
Bence Jones protein	none	none
Osmolality	487	500-1400 mosmol/kg
Cortisol	203	55-220 nmol/24h
Aldosterone	<0.05	17-70 nmol/24h (normal diet)[a]
Calculated		
Creatinine clearance (GFR)	130	120-170 ml/min
TTKG	6.12	Varies with intake

TTKG = transtubular K^+ gradient = U_{K+} ÷ Uosm / Posm ÷ P_{K+}.
U_{K+}= urine potassium concentration (mmol/l); Uosm = urine osmolality (mosmol/kg); P_{K+} = plasma potassium concentration (mmol/l); Posm = plasma osmolality (mosmol/kg). Creatinine clearance = urine creatinine (µmol/24h) ÷ plasma creatinine (µmol/l) x 0.7
[a]Aldosterone secretion in urine was measured by a solid-phase radioimmunoassay (Coat-A-Count, Diagnostic Products Corporation, Los Angeles, USA.

DISCUSSION

In diabetic patients the incidence of hyperkalaemia is higher than in the general population.[1,3] Exact numbers on its epidemiology are unknown, but one study examined the prevalence of hyperkalaemia in a diabetic population which appeared to be 15% (serum potassium >5.0 mmol/l).[4] Most cases could be explained by impaired GFR or precipitating drugs but proteinuria and retinopathy were also independently associated with higher median potassium levels. In this study, 2.3% of the diabetics had a serum potassium level >5.4 mmol/l while there was no evident cause.[4] In general, 50 to 75% of all cases with initially unexplained hyperkalaemia are due to hyporeninaemic hypoaldosteronism.[3,5] Based on these few studies we estimate that approximately 1% of the diabetic population with normal GFR might suffer from hyperkalaemia (>5.4 mmol/l) due to hyporeninaemic hypoaldosteronism.

The syndrome of hyporeninaemic hypoaldosteronism is characterised by the presence of inappropriately low aldosterone secretion either due to a reduced renin secretion in the kidney, a dysfunctional adrenal zona glomerulosa or a combination of both.[2] Patients typically present with borderline hyperkalaemia or asymptomatic hyperkalaemia precipitated by drugs such as ACE inhibitors, potassium-sparing diuretics and NSAIDs.

The pathophysiology of hyporeninaemic hypoaldosteronism is complex and seems to be multifactorial. In 85% of all patients with hyporeninaemic hypoaldosteronism, renin levels are below the normal margin suggesting a primary defect of renin secretion that causes secondary hypoaldosteronism. Renin is produced by the juxtaglomerular cells of the kidney and its production is influenced by many factors such as prostaglandins.[6] Inhibition of prostaglandins by NSAIDs reduces renin secretion which can induce reversible hyporeninaemic hypoaldosteronism. Other explanations for hyporeninaemia include damage to the juxtaglomerular apparatus, impaired conversion of precursors of renin to the active hormone, insufficient sympathetic stimulation of renin-producing cells by neuropathy, inhibition of renin release by hyperkalaemia, and physiological suppression of renin release by volume overload.[7-11]

In some patients with a normal plasma renin activity, aldosterone secretion can still not be stimulated by infusion of angiotensin, suggesting an intra-adrenal defect of aldosterone secretion.[3] In an attempt to stimulate aldosterone production, the plasma renin level may then rise to normal levels.

The diagnosis of hyporeninaemic hypoaldosteronism should be considered in every patient with an unexplained hyperkalaemia. A first step to establish the diagnosis is to measure the transtubular K^+ (potassium) gradient (TTKG) which gives an estimate on the ability of the kidneys to exchange potassium and sodium by the aldosterone-dependent Na^+-K^+-ATPase pump (for details and formulas see *table 1*). A TTKG below 7 in a hyperkalaemic patient strongly suggests hypoaldosteronism.[2] Further differentiation within the group of hypoaldosteronism (also known as type 4 renal tubular acidosis) can be made by measuring plasma renin activity and plasma aldosterone. Hyporeninaemic hypoaldosteronism is characterised by the combination of a decreased (or sometimes normal) renin level and a decreased aldosterone level while other causes of hypoaldosteronism are characterised by elevated renin levels.

ACE inhibitors or angiotensin-receptor blockers are strongly indicated to reduce proteinuria and progression of diabetic nephropathy.[12] However, in case of hyporeninaemic hypoaldosteronism this treatment is rather limited as it can lead to potentially life-threatening hyperkalaemia as seen in our case. Nevertheless there are some treatment options. Fludrocortisone is in theory the mainstay of therapy, since it corrects mineralocorticoid deficiency, but it should not be used because of its hypertensive effect. The approaches left are focused on decreasing gastrointestinal uptake by a low potassium diet and cation-exchange resin or increasing urinary potassium loss by either loop or thiazide diuretics.

We decided to treat our patient with a low potassium diet combined with increasing dosages of HCTZ until the potassium level became normal. Then an ACE inhibitor was started step by step with frequent control of potassium levels and accepting potassium levels up to approximately 5.5 mmol/l. Finally, full dosage of ACE inhibition could be administered. However, the proteinuria remained significant. Balancing the potential hazard of escalating hyperkalaemia against further reduction of proteinuria, with the addition of an angiotensin-receptor blocker, we decided to accept the proteinuria. The addition of sodium polystyrene sulphonate was not considered to be an option for chronic treatment because of its gastrointestinal side effects.

In conclusion, this report describes a typical case of hyperkalaemia due to (subclinical) hyporeninaemic hypoaldosteronism. The significance of this syndrome in the general diabetic population remains unclear but it is believed to be underdiagnosed by physicians, including internists.[13] We would therefore like to emphasise that it might be a common problem in patients with diabetic nephropathy. Preventive measures should therefore be routinely taken while treating such patients, including measurement of the TTKG in patients with initial borderline hyperkalaemia to detect subclinical hyporeninaemic hypoaldosteronism.

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