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Attenuated Renal Excretion in Response to Thiazide Diuretics in Gitelman's Syndrome
: A Case Report

Gitelman's syndrome is a variant of Bartter's syndrome characterized by hypocalciuria and hypomagnesemia. The administration of thiazide diuretics may induce a subnormal increase of urinary Na^+ and Cl^- excretion in patients with Gitelman's syndrome, consistent with the hypothesis that less Na^+ and Cl^- than normal is reabsorbed by the thiazide-inhibitable transporter in Gitelman's syndrome. Specific mutations of NaCl cotransporter, coupled with mutant NaCl cotransporter expression studies clearly demonstrated that many of the characteristics of individuals with Gitelman's syndrome are explained by lack of function of NaCl cotransporter. We recently diagnosed a patient with Gitelman's syndrome by performing the thiazide and furosemide tests, and it is suggested that the clearance studies by diuretic administration may be of diagnostic help in Gitelman's syndrome.

Key Words : *Gitelman's Syndrome; Bartter's Disease; Furosemide; Nephrons; Diuretics, Thiazide*

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INTRODUCTION

Gitelman's syndrome (GS) is an autosomal recessive inherited disorder first described by Gitelman et al. in 1966 (1). It is, also known as a 'hypocalciuric variant' of Bartter's syndrome (BS) or as 'familial hypokalemia-hypomagnesemia', a primary renal tubular disorder characterized by chronic hypokalemia, hypomagnesemia and metabolic alkalosis of renal origin, hyperreninemia, hypocalciuria not related to hypocalcemia or renal failure, and a normal glomerular filtration rate (GFR) (1-5).

Colussi et al. (6) studied the distal nephron NaCl reabsorption in adult patients with GS by analyzing the paired effects of the two diuretics furosemide (FUR) and hydrochlorothiazide (HCT), and showed that the functional activity of the renal thiazide-sensitive Na^+-Cl^- cotransporter (but not of the furosemide-sensitive carrier) is deficient in patients with GS, in keeping with the recently described genetic link between the syndrome and a wide variety of nonconservative mutations of the gene encoding the protein (7, 8).

Recently we diagnosed a patient as GS by evaluating the distal nephron function with two diuretics FUR and HCT. It is suggested that the dynamic studies with diuretic administration may be of diagnostic help in GS.

CASE REPORT

A 16 yr-old girl was referred to Chonnam National University Hospital for evaluation of hypokalemia. She sometimes had noticed fatigue and muscle weakness during exercise. She was found to be hypokalemic when she visited a private clinic for evaluation of occasional abdominal pain. At the admission to our hospital, she was normotensive (120/80 mmHg) with normal renal function (BUN 12 mg/dL, serum creatinine 0.8 mg/dL). She showed serum potassium levels of 2.7 mEq/L (3.5-5.1 mEq/L), serum magnesium levels of 1.4 mg/dL (1.6-2.1 mg/dL) and urinary calcium levels of 9.0 mg/day (50-250 mg/day). The plasma renin activity was elevated to 63.8 ng/mL/hr (1.3-3.9 ng/mL/hr), albeit plasma aldosterone concentration was 19.2 pg/mL (4-31 pg/mL). She had metabolic alkalosis (arterial blood pH 7.46, $PaCO_2$ 46 mmHg, and HCO_3^- 32 mEq/L) and hyperreninemia, suggesting extracellular fluid volume contraction, but the urinary Na^+ and/or Cl^- excretion was not reduced (268 mEq/day and 283 mEq/day, respectively; normal value, 100-260 mEq/day for both of them). The plasma aldosterone level was not elevated as expected for the degree of hyperreninemia, possibly due to an inhibitory effect of hypokalemia (9). She showed normal serum calcium and phosphorus levels, and the urinary albumin excretion and ultrasonography findings of the

kidneys were normal. No family history of BS or related disorders was found. Her parents had not noticed fatigue or muscle weakness. She denied any past medical history or the medical prescription including diuretics, laxatives, or cathartics. Physical examination showed no abnormality.

All the above mentioned features and exclusion of any surreptitious diuretic intake excluded common causes of renal K^+ loss and metabolic alkalosis such as primary hyperaldosteronism, surreptitious vomiting, and diuretic and/or laxative abuse and were consistent with the diagnosis of a primary tubular disorder. The diagnosis of GS rather than classic BS was favored by patient's age, absence of overt polyuria or the tendency to dehydration, and the presence of hypocalciuria and/or hypomagnesemia (1-5).

She was interrupted from any pharmacological therapy for at least 10 days before the studies and allowed a free-choice diet. FUR and HCT tests were carried out at least 7 days apart, and performed by the study protocol described previously (6). Parameters were calculated as follows: Maximal free water clearance (C_{H_2O})=(1-U_{osm}/P_{osm})×V, Chloride clearance (C_{Cl})=$U_{Cl}\times V/P_{Cl}$, and Distal fractional chloride reabsorption=$C_{H_2O}/(C_{H_2O}+C_{Cl})$, where V=urinary flow (mL/min), U_{osm}=urinary osmolality, and P_{osm}=plasma osmolality.

After FUR administration, the patient showed a marked increase in chloride clearance (C_{Cl}, from 3.05 to 26.71 mL/min/100 mL C_{cr}) and decrease in free water clearance (C_{H_2O}, from 9.19 to 3.83 mL/min/100 mL C_{cr}), although HCT did not significantly change chloride clearance (C_{Cl}, from 1.01 to 1.45 mL/min/100 mL C_{cr}) and free water clearance (C_{H_2O}, from 2.45 to 2.45 mL/min/100 mL C_{cr}). On the contrary, distal fractional chloride reabsorption ($C_{H_2O}/[C_{H_2O}+C_{Cl}]$) was significantly decreased by FUR administration (from 75.1 to 12.54 %), whereas HCT ingestion had little effect on this parameter (from 70.8 to 62.8 %).

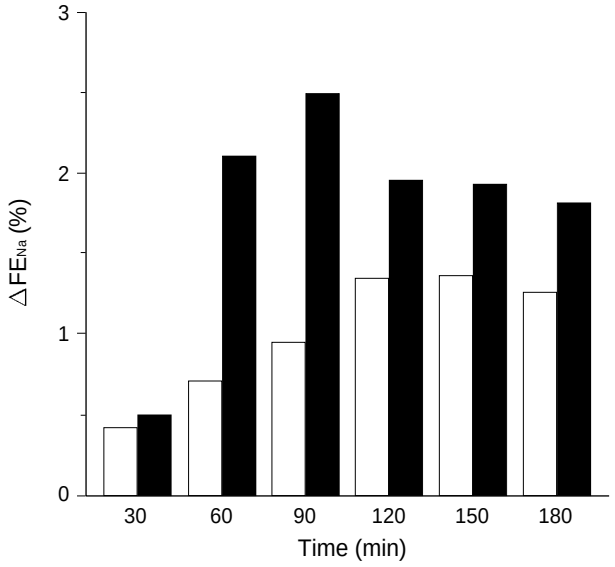

Fig. 1. HCT-induced mean absolute changes above basal levels (mean of the two basal clearances) of fractional excretion of sodium at different times after diuretic administration in our patient (open columns) and controls (closed columns).

HCT test

The patient had lower plasma K^+ levels and similar plasma Na^+, and Cl^- levels (Table 1) and 'basal' excretions of Na^+, Cl^-, and K^+ levels, compared to normal controls published elsewhere (6) (Table 2). However, after HCT administration the patient showed a lower increase of both FE_{Na} and FE_{Cl} (Fig. 1, Table 1), and lower 'cumulative' and 'net' Na^+ and Cl^- excretions (Table 2), while the K^+ excretion was significantly lower only for the 'cumulative' evaluation.

FUR test

The patient showed normal plasma Na^+ and Cl^- levels, lower plasma K^+ level (Table 3), and higher 'basal' urinary excretions of Na^+, Cl^-, and K^+ levels, compared to normal

Table 1. HCT test results: plasma electrolyte levels, creatinine clearance, and fractional electrolyte clearance before (bas) and at its maximal increase over basal levels (max) are shown

	Patient	Control*
pNa (mEq/L)	139	137.3
pCl (mEq/L)	103	103.3
pK (mEq/L)	2.9	4.11
C_{cr} (mL/min)	92.3	119.8
FE_{Na} (bas, %)	0.82	1.2
FE_{Cl} (bas, %)	1.2	1.96
FE_K (bas, %)	14.7	14.8
△FE_{Na} (max, %)	1.43	2.52
△FE_{Cl} (max, %)	1.25	3.64
△FE_K (max, %)	11.27	9.7

FE (bas) is the mean of two pre-HCT clearances; △FE (max) indicates the difference between maximal excretion at any time (max) after HCT administration and FE (bas).
*Control data were mean value obtained from reference 6.

Table 2. HCT test results: quantitative electrolyte excretion

	Patient	Control*
$U_{Na}V$ (bas) μmol/min	114.2	122.3
$U_{Na}V$ (cum) mmol/150 min	39.7	69.4
$U_{Na}V$ (net) mmol/150 min	21.4	47.5
$U_{Cl}V$ (bas) μmol/min	174.2	189.4
$U_{Cl}V$ (cum) mmol/150 min	43.4	69.1
$U_{Cl}V$ (net) mmol/150 min	17.8	40.7
U_KV (bas) μmol/min	59.3	66.4
U_KV (cum) mmol/150 min	7.3	13.8
U_KV (net) mmol/150 min	1.13	3.85

'Cumulative' electrolyte excretion [UxV (cum)] is total electrolyte excretion from 30 to 180 min after HCT administration; 'net' electrolyte excretion [UxV (net)] is calculated by subtracting from 'cumulative' excretion 'basal' excretion multiplied by 150 min.
*Control data were mean value obtained from reference 6.

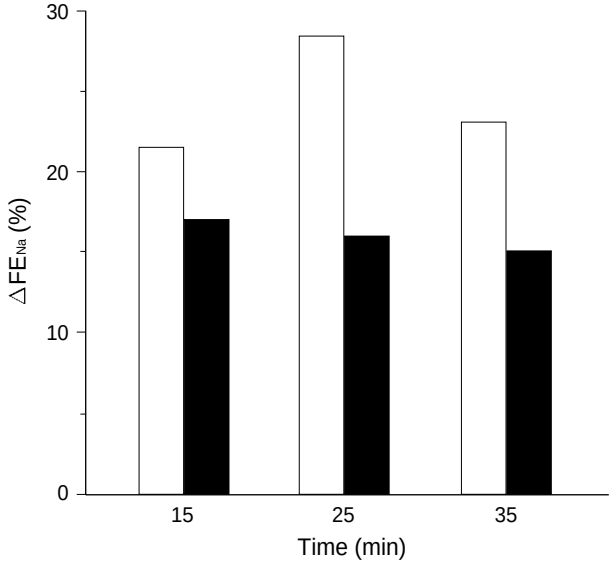

Fig. 2. FUR-induced mean absolute changes above basal levels (mean of three basal clearances) of fractional excretion of sodium at different times after diuretic administration in our patient (open columns) and controls (dark columns).

controls published elsewhere (6) (Table 4). After FUR administration, she showed greater increases of FE_{Na} and FE_{Cl} (Fig. 2, Table 3), higher 'cumulative' excretions of Na^+ and Cl^-, and a higer 'net' Na^+ excretion, while the K^+ excretion was not different from the controls (Table 4).

DISCUSSION

Classic BS and GS are likely to represent distinct tubular disorders: specifically a defect of the loop of Henle in the former and that of the distal tubule in the latter (5), despite common pathogenetic mechanisms. In both of them, the primary tubular defect would imply a reduction of NaCl reabsorption at the involved site, with a secondary increase of NaCl delivery to the distal nephron sites (mostly the cortical collecting tubule), stimulation of electrogenic Na^+ reabsorption, and K^+ and H^+ hypersecretion at these sites, resulting in hypokalemia and metabolic alkalosis.

Two members of an electroneutral Na-Cl cotransporter family predominantly expressed in the kidney (namely, the 'loop'-type diuretic-sensitive symporter expressed in the thick ascending limb of Henle's loop and the thiazide-sensitive symporter expressed in the distal convoluted tubule) have recently been recognized and cloned (7, 8). Indeed, the administration of thiazide diuretics induced a subnormal increase of urinary Na^+ and Cl^- excretions in a few patients with GS studied by different centres (3, 10, 11), an observation consistent with the hypothesis that less Na^+ and Cl^- than normal is reabsorbed by the thiazide-inhibitable transporter in GS.

Table 3. FUR test results: plasma electrolyte levels, creatinine clearance, and fractional electrolyte clearance before (bas) and at its maximal increase over basal levels (max) are shown

	Patient	Control*
pNa (mEq/L)	139	136.7
pCl (mEq/L)	99	103.4
pK (mEq/L)	2.7	4.03
Ccr (mL/min)	81.6	118.8
FE_{Na} (bas, %)	2.31	1.19
FE_{Cl} (bas, %)	4.21	1.75
FE_K (bas, %)	26.63	18.2
$\triangle FE_{Na}$ (max, %)	28.33	17.8
$\triangle FE_{Cl}$ (max, %)	41.10	24.5
$\triangle FE_K$ (max, %)	43.7	39.1

FE (bas) is the mean of three pre-FUR clearances; △FE (max) indicates the difference between maximal excretion at any time (max) after HCT administration and FE (bas)
*Control data were mean value obtained from reference 6.

Table 4. FUR test results: quantitative electrolyte excretion

	Patient	Control*
$U_{Na}V$ (bas, μmol/min)	202.89	167.7
$U_{Na}V$ (cum, mmol/30 min)	89.79	61.4
$U_{Na}V$ (net, mmol/30 min)	83.70	56.4
$U_{Cl}V$ (bas, μmol/min)	297.6	189.6
$U_{Cl}V$ (cum, mmol/30 min)	92.86	65.5
$U_{Cl}V$ (net, mmol/30 min)	78.4	60.0
U_KV (bas, μmol/min)	83.97	73.6
U_KV (cum, mmol/30 min)	6.47	6.1
U_KV (net, mmol/30 min)	3.95	3.8

'Cumulative' electrolyte excretion [UxV (cum)] is total electrolyte excretion from 5 to 35 min after FUR administration; 'net' electrolyte excretion [UxV (net)] is calculated by subtracting from 'cumulative' excretion 'basal' excretion multiplied by 30 min.
*Control data were mean value obtained from reference 6.

In our study, the HCT induced blunted natriuresis and chloruresis as compared with control values, while FUR has a slightly increased effect. The different effects of the two diuretics in our patient were not related to any differences in plasma Na^+ and Cl^- levels (which were normal in GS) or in GFR: in fact, the electrolyte excretion changes were smaller in the patients both in absolute terms and in relation to unit GFR (i.e., in FE values), indicating a blunted diuretic effect at the single-nephron level. Thus, the different diuretic effects in GS patients were likely to represent different effects of the two drugs on the renal tubule itself.

The chloride clearance (C_{Cl}) and the distal fractional chloride reabsorption ($C_{H_2O}/[C_{H_2O}+C_{Cl}]$) showed abrupt change after FUR administration, while HCT induced little effect in our patient. The most likely explanation of our data is that the decreased diuretic effect of HCT in GS patients was the expression of reduced NaCl reabsorption via the thiazide-inhibitable electroneutral Na^+/Cl^- symporter of the distal convoluted tubule, due to some abnormalities of structure or expression in the cell membrane of the carrier protein.

In conclusion, GS is characterized by blunted diuretic effect of the thiazide, but not of the loop diuretics. These observations appear to represent a direct functional 'in vivo' counterpart of the recently described link between GS and a series of genetic mutations of the gene encoding the renal thiazide-sensitive Na^+-Cl^- cotransporter.

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