**Table 1.** Clearance study during hypotonic saline diuresis before and after administration of furosemide and hydrochlorothiazide

<table>
<thead>
<tr>
<th></th>
<th>V (ml/min/100 ml GFR)</th>
<th>Minimal U_{\text{osm}} (mOsm/kg/H_2O)</th>
<th>C_{\text{H}_2\text{O}} (ml/min/100 ml GFR)</th>
<th>(C_{\text{H}<em>2\text{O}} + C</em>{\text{Na}})/C_{\text{Cr}} (%)</th>
<th>C_{\text{H}<em>2\text{O}}/(C</em>{\text{H}<em>2\text{O}} + C</em>{\text{Cl}}) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before F</td>
<td>5.00 (14.4–15.1) (^b)</td>
<td>128 (38.4–76.8) (^b)</td>
<td>2.65 (4.6–14.4) (^b)</td>
<td>4.04 (7–16) (^c)</td>
<td>59.9 (82.5–96.1) (^b)</td>
</tr>
<tr>
<td>After F</td>
<td>19.87</td>
<td></td>
<td>2.34</td>
<td>19.24</td>
<td>9.2</td>
</tr>
<tr>
<td>Before H</td>
<td>2.94 (14.4–15.1) (^b)</td>
<td>105 (38.4–76.8) (^b)</td>
<td>1.79 (4.6–14.4) (^b)</td>
<td>2.23 (7–16) (^c)</td>
<td>75.7 (82.5–96.1) (^b)</td>
</tr>
<tr>
<td>After H</td>
<td>4.53</td>
<td></td>
<td>2.76</td>
<td>3.79</td>
<td>76.7</td>
</tr>
</tbody>
</table>

The clearance study using the two diuretics was performed according to the method described previously [6]. V, fractional urine flow rate; GFR, glomerular filtration rate; C_{\text{H}_2\text{O}}, free water clearance; C_{\text{Cr}}, creatinine clearance; C_{\text{Na}}, sodium clearance; C_{\text{Cl}}, chloride clearance; (C_{\text{H}_2\text{O}} + C_{\text{Na}})/C_{\text{Cr}}, fractional distal delivery of solute; C_{\text{H}_2\text{O}}/(C_{\text{H}_2\text{O}} + C_{\text{Cl}}), distal fractional chloride reabsorption; F, furosemide; H, hydrochlorothiazide. Normal values: \(^a\), \(^b\), \(^c\) data from [7–9], respectively.


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**Atypical Gitelman syndrome with L623P mutation of the thiazide-sensitive Na–Cl cotransporter gene exhibiting lack of hypocalciuria and increased proximal tubule salt reabsorption**

Sir,

Gitelman syndrome (GS) is an inherited disorder caused by loss of function of the thiazide-sensitive Na–Cl cotransporter gene (SLC12A3) in the distal convoluted tubule (DCT). GS is distinguished from classical Bartter syndrome by the presence of hypocalciuria [1]. We report here an atypical GS with a mutation of the SLC12A3.

A 50-year-old Japanese woman was diagnosed with hypokalaemia 30 years ago, but was asymptomatic. In 2002, she was again found to have severe hypokalaemia (2.5 mEq/l) at our hospital. She had no history of renal calculi, vomiting, diarrhoea, or abuse of diuretics or laxatives. Her parents were non-consanguineous. Blood pressure was 104/68 mmHg; the physical examination was normal. Blood tests showed: hypokalaemia (2.5 mEq/l), hypomagnesaemia (1.4 mg/dl), metabolic alkalosis (HCO3: 33.0 mEq/l), high plasma renin activity (7.8 ng/ml/h), creatinine (0.4 mg/dl), albumin (4.3 g/dl), Na (139 mEq/l), Cl (98 mEq/l), Ca (8.7 mg/dl) and inorganic phosphorus (P) (3.5 mg/dl).

In our case, the distal fractional chloride reabsorption during hypotonic saline diuresis was moderately decreased before administration of the diuretics and was further markedly decreased after furosemide administration, but was unchanged after hydrochlorothiazide administration (Table 1). The genetic analyses of the SLC12A3, the thick ascending limb basolateral Cl channel (ClC-Kb) gene, and the ClC-Kb β-subunit gene revealed only a homozygous missense mutation of the SLC12A3, which substitutes proline for leucine at 623 amino acid position (L623P) (Figure 1). Therefore, she was diagnosed with GS.

One of the striking features in our patient was that both urinary Ca excretion rate (140 mg/day) and urinary Ca/creatinine molar ratio (0.35–0.53) were normal. It has recently been reported that some patients with GS do not show hypocalciuria [2,3]. Another striking feature was that proximal tubule solute reabsorption was enhanced in this patient, because both fractional distal delivery of solute and fractional urinary flow rate were decreased during hypotonic saline diuresis before administration of the diuretics (Table 1). This idea is also supported by the reduced fractional excretion of P (3.1%) in the patient, because P is exclusively reabsorbed through Na-coupled carriers located at the apical membrane of the proximal tubule.

The L623P mutation has been previously reported in Japanese patients with GS [4,5], but the renal clearance study using furosemide or thiazide was not performed in those patients. We first demonstrated that the DCT was functionally impaired in this mutation. Furthermore, those cases exhibited marked hypocalciuria and were from the same geographical region in Japan, suggesting that the mutation in these patients might have been introduced by...
The use of lepirudin in haemodialysis complicated with heparin-induced thrombocytopenia type II (HIT II)—dosage monitoring

Sir,

Heparin-induced thrombocytopenia type II (HIT II) is an unpredictable prothrombotic, immune-mediated life-threatening complication that occurs following administration of unfractionated heparin (UFH) or low-molecular weight heparin (LMWH) for a variety of prophylactic or therapeutic applications [1]. The mainstay of HIT treatment consists of the immediate cessation of all forms of heparin therapies and the simultaneous initiation of non-heparin, rapidly acting anticoagulant therapies with direct thrombin inhibitors (DTIs) [1]. DTIs bind directly to thrombin, thus preventing fibrin formation and clotting. The three available DTIs are lepirudin, argatroban and bivalirudin, with only lepirudin and argatroban being currently approved by the U.S. Food and Drug Administration for use in HIT [1].

The major challenges of lepirudin treatment, given by any route, are the lack of an antidote and the extreme care needed when treating patients with any degree of renal insufficiency as it is primarily eliminated through the kidneys. Therefore, dosing must be reduced in patients with impaired renal function [1]. Moreover, its use is currently not indicated in patients requiring haemodialysis [2]. Only anecdotal reports are available on the usage of lepirudin as anticoagulant in haemodialysis [3–5].

Adding one more anecdotal case, we report a 23-year-old female who developed HIT following pre-emptive, living related donor, renal transplantation. The patient was pre-operatively exposed to both UFH and LMWH heparin during five haemodialysis sessions. HIT (diagnosed on the basis of both clinical and serological grounds) caused right common and external iliac vein and renal graft artery and vein thrombosis, resulting in graft loss. Heparin-free haemodialysis was continued using the DTI lepirudin as anticoagulant for both thromboses and haemodialysis. The dose of lepirudin (given as repetitive intravenous bolus) was titrated based on the activated partial thromboplastin time (aPTT) in order to maintain an aPTT value of 70–80s [1]. In detail, the patient received 0.005 mg/kg/h of lepirudin the first day, 0.0024 mg/kg/h the second day, 0.0016 mg/kg/h the third day and for the subsequent 7 days 0.0012 mg/kg/h as a maintenance dose. She was then switched to oral anticoagulation treatment with acenocoumarol after a combined anticoagulation period of 5 days. aPTT values were evaluated every 3h in the first day and every 4h thereafter. The patient underwent four haemodialysis sessions post-operatively without any bleeding complications. Finally, she was accepted into the continuous ambulatory peritoneal dialysis (CAPD) programme.

It should be noted that although lepirudin dose for normal renal function is 0.15 mg/kg/h and for patients with creatinine clearance of 15–29 ml/min is reduced to 0.0225 mg/kg/h, the appropriate dose for patients requiring haemodialysis is almost 125 and 19 times less, respectively, suggesting that extremely cautious dosing adjustments at shorter intervals (i.e. every 4h) should be made in such cases.

Recently, Haase et al. [6] successfully used fondaparinux as an anticoagulant in a dialysis patient with symptomatic HIT II. The pentasaccharides seem to have a promising role in treatment and/or prevention of HIT, since they do not appear to interact with platelets or platelet factor 4. However, fondaparinux, as lepirudin, is eliminated primarily through the kidneys (it is contraindicated in patients with creatinine clearance <30 ml/min), thus leaving the issue of appropriate dosing in dialysis patients in pendency.

We conclude that lepirudin can be used with safety in patients requiring short-term haemodialysis, providing aPTT is closely monitored, especially on the first day of treatment.

Conflict of interest statement. None declared.