reference values <1 mmol/l) and fibrin monomers (1.8 mg/dl, reference values <1.45 mg/dl) were determined, indicating activation of haemostasis. In addition, platelet-related haemostasis was enhanced revealed by remarkably shortened closure times below the 1 percentile with epinephrine/collagen (77 s) and ADP/collagen cartridges (52 s) determined with a platelet function analyser (100). Platelet receptor polymorphisms associated with increased thrombogenicity, particularly the HPA-1b/1b phenotype and the GP Ia 807 TT phenotype, were not found. The patient was negative for the prothrombotic G1691A mutation of the factor V gene (factor V Leiden), the G20210A mutation of the prothrombin gene and the MTHFR 677TT genotype. Two months after these examinations were performed, the patient developed the next episode of TTP and was effectively treated with plasma separation and immunosuppression.

Elevated activities of coagulation factors II, V, VIII:C, X and XI have been identified as risk factors for venous [6] and arterial thrombosis [7]. In addition, elevated activities of coagulation factors VIII:C and increased d-dimer levels have been found to be associated with recurrent events in patients with a history of previous venous thrombosis [8,9]. The relevance of enhanced platelet-related haemostasis, e.g. reflected by shortened closure times determined with a platelet function analyser as risk factor for thrombotic events is less well established. Our findings suggest a potential pathogenic role for enhanced plasmic and platelet-related haemostasis in the pathogenesis of TTP and illustrate that factors other than ADAMTS 13 deficiency might be involved in the pathogenesis of this thrombotic disorder. Although it remains unclear whether the haemostatic abnormalities observed in our patient are a cause or a rather a consequence of this thrombotic disorder, these factors modulate the thrombogenicity and, thus, might predispose not only to the development, but also to the recurrence of TTP. We speculate that reduction of clotting activity by oral anti-coagulants and inhibition of platelet function might reduce the risk for further episodes of TTP in selected patients. The identification and evaluation of abnormalities of haemostatic components as additional risk factors for TTP should be assessed in further studies.

Conflict of interest statement. None declared.


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Artifactual hypocalcaemia after intravenous administration of gadodiamide (Omniscan®)

Sir,

It has been documented that certain gadolinium-based magnetic resonance contrast agents injected for enhancement of magnetic resonance imaging (MRI) or for angiography in selected patients, i.e. gadodiamide (Omniscan®) and gadoversetamide (Optimark®), can cause spurious hypocalcaemia, due to interference with colorimetric assays in a dose-dependent way [1–4]. Three other agents approved for clinical use, gadopentetate dimeglumine (Magnevist®), gadoterate meglumine (Dotarem®) and gadoteridol (Prohance®), do not cause this interference [2].

A 69-year-old female patient underwent contrast-enhanced vascular MRI of the verteobasilar system with gadodiamide (20 ml, 287 mg/ml, intravenous injection) and presented to the outpatient pulmonary clinic ~1 h later for a routine check-up. Afterwards she went home, though was urgently called back 60 min later because laboratory results revealed a total serum calcium level of 2.87 mg/dl (0.7 mmol/l) with an albumin level of 4.47 g/dl (44.7 g/l). Serum calcium was measured by colorimetric method using ortho-cresolphthalein (OCP) (Roche® Diagnostics) as reagent on a Modular P800 Analyzer (Roche® Diagnostics).

The patient had a history of proven Gilbert syndrome [homozygosity for the A(TA)7TAA-sequence in the promoter region of the UGT1A1-gene] and pulmonary arterial hypertension secondary to an atrial septal defect type II. She had moderate chronic renal insufficiency of unknown aetiology with a calculated creatinine clearance (Cockcroft and Gault formula) of 37 ml/min. There was no previous history of chronic hypocalcaemia. Her treatment consisted of fosfomamide 40 mg once daily, spironolactone 50 mg once daily, atorvastatin 10 mg once daily, sitaxsentan 100 mg once daily and fenprocoumon with a target INR of 2.5.

Three hours after the first serum sample, a second sample yielded a total calcium level of 6.9 mg/dl (1.68 mmol/l). The ionized calcium level at that time, measured by ion-selective electrode-technology, was 4.88 mg/dl (1.19 mmol/l). The patient was asymptomatic and there were no clinical signs of hypocalcaemia. No treatment was initiated. She returned home and a control serum calcium level determined 6 days later was 9.05 mg/dl (2.2 mmol/l). Given the relationship in time with the administration of a gadolinium-chelate, her...
normal ionized calcium level and the absence of symptoms, it was concluded that this had to be a laboratory error.

Gadolinium-related spurious hypocalcaemia in colorimetric assays, such as the Arsenazo Dye III and OCP assays, is caused by binding of gadolinium ions to the colorimetric agent, removing the gadolinium from the chelate [3]. The free chelate then binds to serum calcium thereby causing it to be falsely low. The administration of gddiamide or gadoversetamide in higher doses, in particular when given to patients with chronic renal insufficiency, increases measurement inaccuracy and prolongs the duration of artificial hypocalcaemia [4].

Since the use of colorimetric assays to determine total calcium levels is widespread, this laboratory ‘artefact’ is a potentially dangerous cause of unnecessary and possibly harmful medical interventions. Due to the nature of their illness, patients with renal disease face the double risk of being injected with higher doses of contrast agent (i.e. for vascular MRI) while being least able to excrete it. Based on our own experience, we feel that, certainly among clinicians, this cause of spurious hypocalcaemia is still largely unknown. We suggest drawing the attention of clinicians and radiologists to the potential interference of gadodiamide with total calcium measurement, especially when high drug doses are used, or when it is administered to patients with impaired renal function.

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[see related Teaching Point by Mark et al. (doi:10.1093/ndt/gfh836)]

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**Large-pore haemodialysis membranes: an efficient tool for rapid removal of vancomycin after accidental overdose**

Sir,

The usual dosage of vancomycin is 40–60 mg/kg per day divided into four 1 h infusions. Its elimination is mainly renal. An overdose can be responsible for severe ototoxicity and nephrotoxicity, especially if combined with other nephrotoxic drugs such as aminoglycoside antibiotics. As long as renal function remains normal, vancomycin plasma t1/2 is 4–6 h, suggesting forced diuresis alone to reduce drug serum levels rapidly [1].

Renal failure provoked by a vancomycin overdose is responsible for an increase in plasma t1/2 suggesting the necessity of efficient extracorporal drug removal. Standard haemodialysis with cuprophane and cellulose acetate membranes has a limited capacity to remove substances larger than 500 Da. As vancomycin has a molecular weight of ~1500 Da it is only marginally removed by standard HD or peritoneal dialysis [2], whereas continuous haemodiafiltration [3], charcoal haemoperfusion [4] and haemodialysis with high flux polysulfone membranes [5] have been shown to clear vancomycin successfully from the circulation.

The patient, a 9-year-old girl (17 kg, 90 cm), was suffering from cystic fibrosis (homozygous F508del mutation) with chronic airway obstruction and multiple infectious episodes. She accidentally received toxic doses of vancomycin (260 mg/kg/day in four daily doses) over 9 days and usual doses of gentamycin (3 mg/kg/day) in an outside hospital. No controls of vancomycin and gentamycin serum levels were performed until the ninth day. The girl developed progressive malaise and acute generalized exanthematous pustulosis (AGEP) associated with fever of 38°C. On day 10 the vancomycin serum level was 420 μg/ml and antibiotic treatment was interrupted. She developed non-oliguric renal failure. Serum creatinine increased to 650 μmol/l and BUN to 42.6 mmol/l 8 days after discontinuation of vancomycin (Figure 1), whereas serum potassium, phosphorus and calcium levels remained in the normal range. She was then transferred to our hospital. On arrival she presented with weight loss of 2 kg, severe anorexia and irritability. The vancomycin serum level was 96 mg/l (calculated t1/2 = 216 h).

She had normal blood pressure and a constant diuresis without volume overload. Vascular access was obtained via a femoral 9.0 Fr MedComp dual lumen catheter. A Gambr AK-100 haemodialysis machine was used with a high flux large pore-size polymethylmethacrylate dialysis membrane (BK-F 1.3; Toray, Tokyo, Japan) and paediatric lines giving an extracorporal volume of 150 ml. The filter was prepared using NaCl 0.9% containing heparin 1000 UI/l. Low molecular weight heparin (1 mg/kg) was administered at the onset of haemodialysis. Blood flow was 6 ml/kg per min (100 ml/min); duration of treatment was 4 h using standard dialysis baths. Ultrafiltration was 1000 ml/h compensated by a continuous infusion of NaCl 0.9% at 1000 ml/h.