in patients with intra-renal haemosiderin deposits than in subjects without deposits. The frequency of cardiac failure was not different. Therefore, we postulate a probable link between renal haemosiderosis, possibly aggravated by co-existing urinary infection, and late ARF in patients with heart valve replacement, as was the case in our patient.

The pathophysiological mechanism of this association, however, is unclear. The mechanism of iron deposition in intravascular haemolysis is well known [5]. The role of haemosiderin in acute renal toxicity remains controversial. Ferrous iron catalyses the Fenton reaction, which leads to generation of the highly reactive cytoxid hydroxyl radicals. Furthermore, it has also been shown that lipid peroxidation of polyunsaturated fatty acids occurs in the kidneys of experimental animals with iron overload. Peroxidatic alterations of the polyunsaturated fatty acids of membrane phospholipids can result in specific abnormalities of organelle function leading to cell injury or cell death [6].

Since a pathogenetic role for such reactive oxygen species could not be excluded, we attempted a novel medical treatment for renal haemosiderosis. In analogy to contrast media-induced renal failure [7], we administered N-acetylcysteine to the patient.

Conflict of interest statement. None declared.


doi:10.1093/ndt/gfh429

Non-oliguric acute renal failure and abortion induced by metamizol overdose

Sir,

Metamizol is a non-narcotic, analgesic and anti-pyretic pyrazolone derivative which belongs to the non-steroidal anti-inflammatory class of drugs. This drug is used in Germany, Spain and Italy, and in many South American countries. It is prohibited in other countries because of its capacity to induce agranulocytosis and aplastic anaemia. In addition to its effects on bone marrow, metamizol may also cause cutaneous reactions, allergic idiosyncratic reactions such a bronchospasm, anaphylactic shock, toxic epidermal...
necrosis, hepatitis and severe hypotension [1]. We report here a case of non-oliguric acute renal failure and abortion following the ingestion of an overdose of metamizol in an otherwise healthy girl.

Case. A 14-year-old girl, previously healthy and without history of affective disorder, attempted suicide. She was admitted to our hospital ~5 h after ingesting twenty 575 mg metamizol (Nolotil®) capsules (total amount ingested: 11.5 g). At admission, the patient presented with nausea and vomiting. Physical examination revealed a conscious and pale girl. There were no skin eruptions. Weigh was 47 kg, blood pressure was 110/70 mmHg, heart rate was 95 b.p.m., temperature was 36.6°C, and urine output was 100 ml/h. After repeated gastric lavages with medical charcoal, the initial laboratory data showed haematocrit 41%, haemoglobin 14 g/dl, white blood cells 15 500/µl with normal eosinophil count, platelets 237 000/µl, urea 35 mg/dl, glucose 90 mg/dl, creatinine 0.6 mg/dl, sodium 139 mmol/l, potassium 4.2 mmol/l, bicarbonate 24 mmol/l, ionized calcium 5.2 mg/dl and prothrombin time 78%. Eleven hours after admission, the patient was discharged from the hospital and referred to the mental-health unit. She complained of menstrual irregularities and at the time of discharge presented vaginal bleeding. On the second day after metamizol overdose, the patient had persistent vomiting, and was re-admitted to the hospital. Laboratory data showed haematocrit 37%, haemoglobin 12.6 g/dl, white blood cells 11 100/µl, platelets 202 000/µl, urea 41 mg/dl, glucose 96 mg/dl, creatinine 2.2 mg/dl, sodium 139 mmol/l, potassium 3.7 mmol/l, bicarbonate 21.4 mmol/l. Other laboratory data showed aspartate aminotransferase (AST) 91 IU/l, alanine aminotransferase (ALT) 71 IU/l, total bilirubin 0.6 mg/dl and C-reactive protein 4.9 mg/dl protein and 50 red blood cells/µl in the sediment. A urine pregnancy test was positive [rapid enzyme-linked immunosorbent assay (ELISA)]. Abdominal ultrasonography showed normal sized and symmetric kidneys with increased cortical echogenicity. Transvaginal ultrasonography revealed an empty uterus and a left ovarian cyst. The patient received intravenous (i.v.) normal saline, anti-emetic and omeprazole. Her renal function worsened over the course of the next few days despite the fact that urine output was maintained between 2500 and 3500 ml/day. During the third day in hospital, her serum creatinine and urea levels increased to 3.1 and 67 mg/dl, respectively, her creatinine clearance was 22 ml/min and proteinuria was 0.61 g/day. The haematocrit was 33%, haemoglobin was 11.1 g/dl, and the serum β-human chorionic gonadotrophin (hCG) level was <1.2 mIU/ml (normal values at 3–4 weeks of pregnancy, 9–130 mIU/ml). The patient was treated with methylprednisolone (0.5 mg/kg/daily) i.v. for 3 days. This therapy was tapered and withdrawn within 12 days. In addition, she received erythropoetin 3000 IU subcutaneously per week (two doses). She recovered renal function rapidly after 3 days of steroid treatment and was discharged 7 days after hospitalization. At that time, her urinalysis was normal, serum creatinine was 0.8 mg/dl and creatinine clearance was 96 ml/min.

Comments. Metamizol can induce two different forms of acute renal failure. In addition to acute renal failure secondary to loss of counter-regulatory prostaglandins during plasma volume contraction, acute tubulointerstitial nephritis is a well recognized side effect of metamizol [2–4]. Acute tubulointerstitial nephritis has been observed at the usual pharmacological dose of the drug. However, the renal effects may be dose dependent, and large doses of this drug have been associated with acute renal failure in animals. Renal failure may occur because the elimination of this drug and its metabolites is mainly renal or because of acute haemodynamic effects due to inhibition of prostaglandin synthesis [5–7]. A characteristic feature of this form of presentation is a symptom-free interval of several days [2, 4]. In addition, the effects of metamizol on renal function range from moderate to advanced impairment, with most patients having oliguria.

Our patient presented a severe degree of intoxication to judge by the amount of drug ingested (at least six times the average normal daily dose). She developed non-oliguric acute renal failure after a latent period of ~24–36 h. Renal damage probably occurred as a result of toxic tubular necrosis, since it was not reversible despite volume repletion. In addition, she also presented microhaematuria and proteinuria, and renal function was rapidly reversible following steroid therapy. Therefore, on the basis of the time course of the disease, we suggest that the renal damage in this patient might be due to a toxic effect producing a tubular lesion and interstitial nephritis.

The mechanism of abortion with this drug is unknown. Metamizol is a prostaglandin synthetase inhibitor and it is advised to be used with caution in pregnancy. Although normal doses of metamizol have been associated with oligohydramnios [8], only in one case report has a high dose of metamizol been implicated in acute renal failure and oligohydramnios [4]. It has been suggested that oligohydramnios could also be a consequence of fetal toxicity due to prostaglandin inhibition [4]. In our patient, the dose of metamizol was very high; part of the drug probably entered the fetal tissues, and might have induced the abortion by direct toxic effect.

In conclusion, overdose of metamizol may induce reversible acute renal failure and abortion in early pregnancy, suggesting that it has toxic effects per se. Although the role of steroid therapy in acute interstitial nephritis has been questioned, it is reasonable to assume that this therapy could have contributed to the subsequent improvement in renal function of our patient. Additionally, menstrual history and test of early pregnancy should be part of the routine follow-up in adolescent girls with drug overdose.

Conflict of interest statement. None declared.

1Secció de Nefrologia and Ramon Peces1
2Servicio de Medicina Interna Antonio Pedrajas2
Hospital General La Mancha-Centro
Alcazar de San Juan
Ciudad Real
Spain
E-mail: cpeces@varnet.com

4. Sánchez de la Nieta MD, Rivera F, de la Torre M et al. Acute renal failure and oligohydramnios induced by magnesium
Ticlopidine induces lupus in a haemodialysis patient

Sir,

It is widely believed that patients on dialysis are immunocompromised and less commonly affected by autoimmune diseases. However, in our dialysis units we often encounter patients with allergies to particular drugs. Ticlopidine hydrochloride is a platelet aggregation inhibitor, which has been shown to reduce the risk of thrombotic strokes and also shown to reduce the risk of thrombotic strokes and also is used in the treatment of claudication and in patients with cardiac stents [1]. Its uncommon but serious adverse effects are neutropenia, aplastic anaemia, thrombotic thrombocytopenic purpura and cholestatic hepatitis – the latter two being uncommon but serious adverse effects. The release of free circulating DNA has been shown during HD and it has been claimed that antibodies are formed against native DNA and other nuclear antigens in HD patients [6], which might lead to de novo lupus-like syndromes in HD patients. Alternatively, a number of drugs are able to induce a lupus-like syndrome [4]. The real frequency of drug-induced lupus in HD patients remains unknown. Ticlopidine clearance is decreased in patients with renal dysfunction [7], which may have been the pathogenesis of lupus in this patient. In addition, there is a genetic predisposition determined by drug acetylation rates [4]. Individuals with a mutation of the N-acetyltransferase-2 gene have an impaired enzyme function and, thus, are slow acetylators. They have been reported to have a higher incidence of drug-induced lupus. Unfortunately, so far it is uncertain whether drug acetylation in HD patients is slow or normal [8].

It is of interest that our patient took 7 months to manifest symptoms after first exposure to ticlopidine (March 2002). In addition, in contrast to rapid decreases in the serum levels of C-reactive protein, ANA-EIA and anti-dsDNA, his anti-histone antibodies remained high in the serum levels of C-reactive protein, ANA-EIA and anti-dsDNA. The intervals between exposure to the drug and the development of symptoms and clinical signs were >1 year in these patients. All four patients were positive for anti-histone antibodies and in two of them hyperparathyroidism. His serology tests showed 1615 mg/dl immunoglobulin G (IgG), 46 mg/dl IgM, 286 mg/dl IgA, 101 mg/dl C3, 25 mg/dl C4, 33.6 anti-nuclear antibody by enzyme immunoassay (ANA-EIA; normal <20), 26.3 IU/ml IgG class anti-double-stranded DNA antibody (anti-dsDNA; normal <10 IU/ml) and ++ positivity for anti-histone antibody (normal being negative). All of these findings suggested drug-induced lupus.

Comment. Allopurinol, ranitidine, loxoprofen, clarithromycin and ciprofloxacin each sometimes induce allergic dermatitis and bone marrow suppression, but except for ticlopidine none of the medications prescribed to this patient have been implicated in lupus [3–5]. Therefore, although a lymphocyte drug stimulation test was negative, ticlopidine was suspected to be the causative drug and it was stopped immediately. During the following weeks, along with decreases in the serum levels of C-reactive protein, ANA-EIA and anti-dsDNA antibody, fever and arthralgia gradually subsided.

Table 1. Changes in C-reactive protein and autoantibodies

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(normal &lt;0.2)</td>
<td>11.7</td>
<td>2.8</td>
<td>0.7</td>
<td>0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANA-EIA (normal &lt;20)</td>
<td>33.6</td>
<td>24.9</td>
<td>14.9</td>
<td>10.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-dsDNA (IU/ml)</td>
<td>26.3</td>
<td>10.3</td>
<td>5.3</td>
<td>6.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-histone (normal, negative)</td>
<td>++</td>
<td>n.c.</td>
<td>++</td>
<td>n.c.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CRP, C-reactive protein; n.c., not checked.