Prolonged elevation of serum creatine kinase (CK) without renal failure after ingestion of ecstasy

Sir,

We would like to report two recent cases of ecstasy intoxication associated with elevated and prolonged circulating creatine kinase, but without acute renal failure. The first case was a 33-year-old previously fit man on holiday from Australia. Three days before presentation, while at a party, he had taken ¼ tablet of ecstasy and danced for several hours, drinking only alcohol. By the following morning, approximately 7 h later, he developed diarrhoea, passing 1–2 loose stools, and generalized muscle aches and pains. The muscular pains were worse the next day and another day later (3 days after taking ecstasy) he noticed that he was passing dark ‘Coca-cola’ urine, which prompted him to seek medical advice. On examination he looked anxious, but well. He was afebrile, normotensive and had a pulse rate of 100 beats/min. There was no muscle tenderness or firmness. His urine was dark and tested positive for blood and protein, but on microscopy showed only 12 white cells and no red cells per high power field. Blood tests showed normal serum urea, creatinine and electrolyte concentrations, including potassium, phosphate and calcium, but raised aspartate transaminase (AST; 212 IU/l, normal range 11–55 IU/l) and creatine kinase (CK; 9200 IU/l, normal range 24–195 IU/l). An ECG was normal, showing only sinus tachycardia. His CK increased rapidly and peaked at 112 000 IU/l within 24 h of admission. He was treated initially with a forced alkaline diuresis and then maintained on an oral water diuresis, such that he became slightly hyponatraemic. His renal function did not change. However, his CK remained elevated (>96 800 IU/l by next day), decreasing slowly until he was discharged 5 days later. At that time he felt well and his CK was 6500, but had increased 2 days later to 18 860 IU/l, when he was reviewed in the outpatient clinic, 9 days after ecstasy ingestion (Figure 1). He was seen again, 7 days later, with a CK of 1290 IU/l, and finally after another week, when his CK had declined to near normal, 30 days after his original admission, at 210 IU/l.

The second case was a previously fit 25-year-old woman who presented having collapsed at a party after taking one ecstasy tablet with alcohol. Shortly after her arrival she had a grand mal seizure, which required i.v. diazepam. She was also hyperpyrexial with a temperature of 41.9 °C. This was managed with i.v. dantrolene. She was unconscious and transferred to the intensive care unit. She also became hypoglycaemic and required i.v. glucose. An urgent CT scan of her brain was requested because of the uncertain history, but was normal. Within 24 h of admission her platelet count had fallen to <45 000, but there was no evidence of a consumptive coagulopathy, and she was given a platelet transfusion. She was kept well hydrated and her renal function remained normal throughout, although her urine did initially test positive for blood and protein. Her CK peaked at 99 700 IU/l (normal range 24–170 IU/l) 24 h after admission; 8 days later it was still over 11 000 IU/l, and it was just over 300 IU/l 1 week after discharge, 2 weeks after taking ecstasy.

Rhabdomyolysis, usually associated with acute renal failure (ARF), is a well-recognized complication of ecstasy (methylene dioxymethamphetamine) ingestion [1–4]. Recent publicized deaths following the recreational use of ecstasy have highlighted the dangers of this drug. Previous reports of ecstasy-induced rhabdomyolysis indicate that the CK rise typically occurs at about 48 h after ingestion and settles to values of <1500 IU/l within 1 week [5]. In our cases, renal function was completely unaffected, despite very high peak CK and a much slower rate of decline. In both patients, we considered the possibility of an underlying intrinsic muscle abnormality, but we did not proceed to a muscle biopsy.

A CK of >5000 IU/l is thought to reflect significant muscle damage, and when CK is >15 000 IU/l there is a high risk of developing ARF [6]. However, in both our patients renal function remained normal despite CK concentrations over 6 times greater, at 90 000–100 000 IU/l. Values for the mean circulating half-life of total CK vary between 20 and 30 h, being slightly greater in men than women [7], possibly reflecting the increased muscle mass in men, and cell turnover. CK is too large a molecule at 80 kDa to be filtered and excreted in the urine, and like other systemically released enzymes is probably inactivated in the circulation before uptake and catabolism by most tissue cells. Following ecstasy ingestion, the combination of a direct myotoxic effect of the drug, together with vigorous muscle activity and volume depletion, cause significant muscle damage and raised CK levels, often associated with ARF. Alkali therapy to increase urine pH and enhance myoglobin excretion to prevent ARF, also reduces the clearance of weak bases like amphetamines, and may actually prolong their toxic effects [3], which could account for sustained elevations in CK. From Figure 1, estimates of the half-life of CK in each case are 44 and 56 h, respectively. Thus, a prolonged increase in CK following ecstasy ingestion can occur without consequent...
renal damage. Both hyperpyrexia [2] and clotting abnormalities [4] are recognized complications of ecstasy poisoning. We conclude that CK may remain elevated longer than previously recognized following ingestion of ecstasy, and that the CK level per se does not reliably predict the extent of muscle damage and the risk of developing ARF, nor can it be a guide to continuing therapy. However, this does not negate the importance of rapid and aggressive treatment to promote and maintain a diuresis in this setting. In deciding whether to add alkali, and the risk of ARF, perhaps more importance should be attached to the presence of acute hyperkalaemia, hyperphosphataemia and hypocalcaemia, than the level of CK alone. A forced diuresis, without alkalization of the urine and the potential hazards of systemic alkali administration, may be more appropriate following ecstasy ingestion and a raised CK.

Haemolytic–uraemic syndrome in a patient infected by HIV

Sir,

HIV infection-associated haemolytic–uraemic syndrome (HUS) was first reported in 1984 [1]. The HUS/TTP prevalence in 1423 HIV-infected patients was 0.6% [2]. HUS/TTP are two presenting forms of thrombotic microangiopathy (TMA). Whether TTP differs from HUS is still debated. Both diseases have identical clinical features: non-immune haemolytic anaemia, thrombocytopenia, and renal failure. Renal involvement dominates HUS. TTP could be considered as a systemic form of TMA with neurological signs. Management is the same as recommended for non-HIV patients, bearing in mind that drugs with an immunosuppressive effect may increase the opportunistic infection risk and may reduce the survival of these patients. A 36-year-old male with HIV infection presented to our hospital with a 2-day history of congestive heart failure. He was an intravenous drug abuser until 3 years ago, since when he has been inhaling cocaine and heroin. The CD4 count before was 71% neutrophils, haematocrit 16% and platelet count 57 × 10^9 mm^3. Retiucocyte count was elevated and serum haptoglobin was decreased. Red cell morphology included schistocytes and polychromatophilic normoblasts. Coagulation parameters were normal. Abdominal ultrasound revealed normal size kidneys. On the first hospital day dyspnoea worsened progressively, the patient remained anuric and he became agitated and confused. Findings from a computed tomography of the head were normal. Haemodialysis and plasmapheresis were initiated on alternative days. The patient’s dyspnoea resolved after ultrafiltration and he recovered from the neurological disorder over the next 2 days. Renal and haematologic indices improved progressively and plasmapheresis was discontinued on day 15. A few days later the patient had a relapse and plasmapheresis was reinstalled for a month. Haemodialysis was discontinued 3 months after the diagnosis, when the creatinine clearance was 21 ml/min (serum creatinine 2.59 mg/dl). Results of CD4 + cell count was 247/mm.

Del Arco et al. [3] compiled data on 29 HIV-infected patients with TTP/HUS: approximately 50% belonged to Centers of Disease Control and Prevention (CDC) group II or III at the time of diagnosis and the others to group IV. The distribution was different in the study of Bachmeyer et al. [2], with eight of nine patients belonging to group III and one patient belonging to group II. In our case the patient belonged to group II, A3 according to the CDC classification reviewed in 1993. TTP/HUS has been reported in patients whatever the route of transmission of HIV. The clinical and biological features do not differ from those of non-HIV patients. The role of HUS-precipitating factors, such as cocaine abuse, has been advocated. The proposed trigger mechanism is endothelial damage from cocaine-induced vasoconstriction and hypercoagulability [4]. Despite numerous publications, the pathogenesis of HUS/TTP remains to be clarified. The presence of p24 antigen in endothelial cells may be indicative of a direct cytopathic effect of the virus or a functional impairment of the endothelium [5]. Based on the fact that PGH2 activity is deficient in HUS, plasma infusion or exchange was used by Remuzzi et al. in HUS management [5]. The beneficial effect of plasmapheresis with fresh frozen plasma has been attributed to an increase in plasma PGH2 activity, which has been indirectly measured by testing its stable metabolite 6-ceto-PGF1α, which was decreased before the infusion. It returned to normal after plasmapheresis with 3 l of fresh plasma [6].

Prognosis was very poor in the series of Bachmeyer et al. [2] with a mortality rate of 77% within 3 months of diagnosis. However 60% of other previously reported HIV-infected patients with TTP/HUS had excellent response to various treatments [3]. The short-term response rate to plasma exchange (86%) in seven patients with HIV-associated TMA was comparable to the rate (80%) reported in the pooled literature of non-HIV cases, though none of these patients survived more than 2 years after remission [7].

Our patient presented with HIV infection, A3 group, and clinical and biological features of HUS. He was treated with 17 plasmaphereses, exchanging 3 l of fresh plasma on each occasion, and a total of 25 acute haemodialyses. This resulted in complete haematological and neurological resolution with partial recovery of renal function and without impairment of the immunological system.

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**Table 1. Histopathological patterns in lupus nephritis patients with and without acute renal failure (ARF) in relation to gender**

<table>
<thead>
<tr>
<th>WHO classification</th>
<th>With ARF</th>
<th>Without ARF</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Class I</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Class II</td>
<td>4</td>
<td>–</td>
<td>14</td>
</tr>
<tr>
<td>Class III</td>
<td>6</td>
<td>–</td>
<td>11</td>
</tr>
<tr>
<td>Class IV</td>
<td>17</td>
<td>10</td>
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</tr>
<tr>
<td>Class V</td>
<td>5</td>
<td>–</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td>10</td>
<td>59</td>
</tr>
</tbody>
</table>

NS, not significant.

*Significant difference in occurrence of ARF in males compared to females.

**Table 2. Histopathological patterns in 103 cases of lupus nephritis in relation to gender**

<table>
<thead>
<tr>
<th>Class according to WHO classification</th>
<th>F</th>
<th>M</th>
<th>F</th>
<th>M</th>
<th>F</th>
<th>M</th>
<th>F</th>
<th>M</th>
<th>Total</th>
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<tbody>
<tr>
<td>Class I</td>
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<td>18</td>
<td>17</td>
<td>1</td>
<td>42</td>
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<tr>
<td>Class II</td>
<td>1</td>
<td>14</td>
<td>1</td>
<td>25</td>
<td>11</td>
<td>13</td>
<td>1</td>
<td>91</td>
<td>12</td>
</tr>
<tr>
<td>Class III</td>
<td>6</td>
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<td>1</td>
<td>25</td>
<td>11</td>
<td>13</td>
<td>1</td>
<td>91</td>
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<tr>
<td>Class IV</td>
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<td>10</td>
<td>14</td>
<td>2</td>
<td>91</td>
<td>12</td>
</tr>
<tr>
<td>Class V</td>
<td>5</td>
<td>1</td>
<td>8</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>59</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
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<td>30</td>
<td>50</td>
<td>30</td>
<td>50</td>
<td>30</td>
<td>50</td>
<td>30</td>
<td>103</td>
</tr>
</tbody>
</table>

F, female; M, male.

*Significant difference between diffuse proliferative lupus nephritis in male as compared to female patients (P = 0.0155).

Numbers in parentheses are the numbers of patients with membranoproliferative lesions, included in diffuse proliferative morphology and classified as a histological subset of class IV lupus nephritis. This histopathology was found significantly more in male compared to female cases (P = 0.01).

had prerenal azotaemia, obstructive uropathy or chronic renal failure. Histopathological distribution in those with ARF was as follows: four mesangial, six focal, 27 diffuse proliferative including 15 membranoproliferative and five membranous. Diffuse proliferative and membranoproliferative lesions were found more in patients with ARF compared to those without ARF (P = 0.0021 and P = 0.0032, respectively). The results were contrary to the claim that the entry serum creatinine level contributes little to prediction of underlying renal histopathology [5]. ARF was detected more in males, particularly those with class IV lupus nephritis, compared to females (Table 1; P = 0.0007 and P = 0.0014, respectively). In addition, diffuse proliferative and membranoproliferative lesions were seen more in males compared to female patients (Table 2; P = 0.0155 and P = 0.01, respectively). Why ARF and diffuse proliferative and membranoproliferative histopathology are found significantly more in males with lupus nephritis is not clear. It has however been elucidated that sex hormones modify susceptibility to, and expression of SLE [9]. Therefore, it is possible that only a very severe form of SLE is expressed in males.

Lupus nephritis in patients of Iranian origin: differences in clinical and histopathological features at initial presentation

Sir,

In previously published series of biopsied lupus nephritis patients the proportions of pathology types occurring in proposed classification by WHO [1] is different [2–5]. The reason for this is not known. More recently it has been appreciated that genetic factors play an important role in the development and expression of systemic lupus erythematosus (SLE) and its glomerulonephritis [6,7]. Employing the WHO histologic criteria, we prospectively determined the proportion of each class of lupus nephritis and its relation with gender and clinical findings in 103 consecutive Iranian cases. Patients were aged 14–35 years and all fulfilled the American Rheumatism Association criteria for diagnosis of SLE [8]. Kidney biopsy was done in all patients with clinical and laboratory data of renal involvement. Renal tissues with less than seven non-sclerosed glomeruli were considered inadequate and discarded. Biopsied renal tissues were examined by light and immunofluorescent microscopy. The renal biopsy specimens were classed as follow: one normal, 18 mesangial, 18 focal, 52 diffuse proliferative (22 membranoproliferative) and 14 membranous. In the published series of biopsied lupus nephritis patients membrano- proliferative histopathology was occasionally seen [4,5], ranging from 5% to 11.8% of cases. In this study 22 patients (21.35%) had membranoproliferative lupus nephritis, which is remarkably higher than previously reported series. Nephrotic syndrome presenting with proteinuria >3 g/day and the presence of at least two of oedema, serum albumin <3 g/dl and serum cholesterol >300 mg/dl, was found in 73 patients (70.8%). Previous data suggest that nephrotic syndrome occurs significantly more in patients with membranous and diffuse proliferative lesions [3]. In our patients we found no significant difference between histological classes in patients with and without nephrotic syndrome.

Acute renal failure (ARF) with rapid and persistent accumulation of waste products with and without oliguria was evident in 42 cases. Creatinine clearance dropped to less than 50% of its initial value in patients with ARF. None of them...


Reversible hypothryroidism with EDTA chelation therapy in a patient with elevated lead burden and chronic renal insufficiency

Sir,

Lead is a significant metal pollutant in the environment. Previous reports on lead toxicity concerned haematoletic, nephrologic, and hypertensive problems, but there have been few reports [1–4] on lead affecting thyroid function. Whether low levels of environmental lead exposure can affect the thyroid function of persons without previous lead exposure is unknown.

A 68-year-old female housekeeper first visited our out-patient department on 20 February 1992 because of weakness, fatigue, and periboral oedema of several months duration. Tracing back her history, she had suffered from chronic renal disease, gout and hypertension for about 10 years and had not received any regular medication. She denied any history of lead exposure or thyroid disease. She did not drink alcohol or smoke. She did not eat any seafood or sea vegetables. On physical examination, her blood pressure was 140/100 mmHg and her thyroid was normal size without palpable nodules. No anaemia or other abnormalities were found and renal echo showed bilateral borderline small kidneys, compatible with chronic gouty nephropathy. Serum laboratory data were serum creatinine 2.4 mg/dl, creatinine clearance 50.84 ml/min, daily urine protein excretion 1.2 g, uric acid 12.6 mg/dl, and blood lead 12.8 μg/dl. Serum thyrotropin (TSH) was 92.4 μIU/ml and free T4 0.21 ng/dl (normal range 0.73–1.95 ng/dl) were measured by radioimmunoassay (RIA) methods (Amerlex-MAB FT4 Kit & Amerwell TSH Assay; Kodak Clinical Diagnostics, Amersham, UK). Thyroid function has been monitored regularly since then. Anti-thyroglobulin antibody was negative and the antimicrosomal antibody titre was less than 1:100. Thyroid echo was negative. Since the blood lead level was thought to accurately reflect only recent lead exposure, an infusion of 1 g Na₂-Ca-EDTA chelating agent was undertaken to assess the whole body lead burden. Twenty-four-hour urine collection over a 72-hour period measured 223.2 μg lead. No adverse effects were noted during the infusion. Blood and urine lead were quantified by electrothermal atomic absorption spectrometry (Perkin–Elmer 5100PC) with Zeeman background correction and an L’vov platform. In order to investigate the relationship between thyroid function and lead, neither thyroid drugs nor iodine-containing agents were given. After chelation therapy, her hypertension and hyperuricaemia were treated and controlled by atenolol 50 mg q.d., captopril 12.5 mg b.i.d., and allopurinol 200 mg q.d. She was placed on a low-salt (5 g) and low-protein diet (40 g).

EDTA chelation treatment was initiated because body lead burden was higher than normal (90.24±10.6 μg (SD)) [5]. Over the following 2 months, she received 1 g EDTA intravenously every week. She continued her antihypertension and antihyperuricaemia medications during the therapeutic period. An EDTA mobilization test was repeated and 72-h urine lead excretion was 76.2 μg. The serum TSH then fell to 7.32 IU/ml and free T4 increased to 0.72 ng/dl. The patient felt well and had a good appetite after 2 months of chelation therapy. She has been regularly followed up at our nephrological out-patient department since that time.

During a regular examination on 24 October 1992, the serum TSH was found to be elevated to 12.2 IU/ml, but the serum free T4 was still normal (0.84 ng/dl). No history of seafood consumption was noted. An EDTA mobilization test was performed again and revealed the body lead burden was 92.4 μg. We started chelation therapy again and gave her 1 g EDTA intravenously every other week. The body lead burden decreased to 32 μg after 10 weeks of treatment. The serum TSH fell to 2.42 IU/ml again and free T4 further increased to 1.6 ng/dl on 27 February 1993. The treatment course was uncomplicated and renal function remained stable (creatinine clearance 49.6 ml/min).

To further pursue the issue of adult lead poisoning and hypothryroidism, thyroid hormones were measured in lead-exposed workers. Previous investigators [1–4] suggested that commonly encountered levels of occupational or moonshine lead exposure may depress human thyroid function. They suggested lead may contribute to a central depression of the thyroid axis or alter thyroid metabolism. In 176 male workers with occupational exposure to lead, the duration of lead exposure was negatively correlated to free T4 [6].

In our case, normalization of thyroid function was found after the body lead burden had been reduced. To the mechanism involved, we mention that lead reduces thyroidal iodine-131 uptake [7,8]. We can exclude that the patient merely recovered spontaneously from transient hypothryoidism or transient autoimmune thyroiditis. Although several studies [9] claim that patients with chronic renal failure are euthyroid, the serum thyroid hormone levels are subnormal in some of these patients, possibly as an adaption to severe systemic disease.

After excluding possible confounding factors, we conclude that lead was the major aetiologic factor inducing the hypothryoid state in our patient. Our preliminary observation leads to two hypotheses. Either lead itself may play an important role in thyroxine synthesis upon removal of lead by a chelating agent, the thyroid dysfunction disappeared. Or, alternatively, lead may be a non-specific toxin contributing to the hypothryoid state in patients with pre-existing chronic renal insufficiency.
4. Kremer HU, Frank MN. Coexisting myxedema and chronic potassium (mEq/l) 5.15
8. Robins JM, Cullen MR, Connors BB, Kayne RD. Depressed sodium and calcium were normalized (Table 1). Of the subcutaneous administration of calcitriol, had not yet been
9. Chopra IJ, Hershman JM, Pardridge WM, Nicoloff JT. Thyroid function in non-thyroidal illness.

**Table 1. Serum electrolyte and pH changes during haemodialysis (HD)**

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Before HD</th>
<th>After HD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mEq/l)</td>
<td>136±4.4</td>
<td>140±3.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Potassium (mEq/l)</td>
<td>5.15±0.8</td>
<td>3.65±0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>8.5±0.6</td>
<td>9.0±0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ionized Ca (mmol/dl)</td>
<td>1.97±1.12</td>
<td>1.96±0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Magnesium (mg/dl)</td>
<td>2.1±0.2</td>
<td>1.8±0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bicarbonate (mmol/l)</td>
<td>18.5±4.2</td>
<td>25.0±3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>pH</td>
<td>7.35±0.7</td>
<td>7.46±0.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ECG parameters only QTc interval showed a significant lengthening (from 425±31 to 434±43 ms). QTc lengthening was observed in 42 of 50 patients (84%); in 13 of them, QTc interval lengthened significantly (more than 460 ms in women and 440 ms in men). Although there was a small increase during HD in the number of ventricular extrasystoles, no TDP or ventricular tachycardia was observed. No significant correlation was found between the echocardiographic chamber sizes, ejection fraction, serum pH, bicarbonate, sodium or calcium with the QTc lengthening. The only two variables which had a significant effect on QTc were hypomagnesaemia and hypokalaemia (P<0.05).

These data show that during bicarbonate HD, serum Mg and K decrease and QT interval increases. This makes HD patients more vulnerable to TDP as reported by Huynh-Do et al. [2]. Although we did not observe any TDP, this may be due to the fact that none of our patients were using any medication, including antiarrhythmics, that could cause QT lengthening. We conclude that during HD any patient receiving a drug that may cause QT lengthening deserves rhythm monitoring.

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M. E. Korkmaz, M. Kayatas, A. Ertürk


**Is oral intermittent calcitriol more effective than daily calcitriol therapy in suppressing overt secondary hyperparathyroidism in predialysis patients?**

Sir, Watanabe et al. [1] concluded that they are able to assert that intermittent calcitriol is more effective than daily calcitriol therapy in suppressing overt secondary hyperparathyroidism in predialysis patients, because the percentage reduction of PTH was greater in the pulse-treated group than in the conventionally treated group (71% vs 46%). Having recently concluded an extensive review of the literature on that issue [2], we came to the conclusion that the experimental data of Reichel et al. [3], demonstrating clearly the greater suppressive effect of intermittent intraperitoneal administration of calcitriol compared to the continuous subcutaneous administration of calcitriol, had not yet been
confirmed by clinical data. We were therefore particularly interested in the data of Watanabe et al. However, we are not convinced by their results for the following reasons.

1. The study was not randomized and the initial degree of hyperparathyroidism was greater in the pulse-treated group (424 ± 65 vs 239 ± 10 pg/ml of plasma intact PTH). Since there were only 11 patients treated with pulse and 29 treated daily it would be interesting to make the comparison on a group matched for plasma concentration of Ca, PO₄ and PTH to see whether the changes of PTH Ca and PO₄ are actually different.

2. The cumulative weekly dose was dramatically different: 8 µg for the pulse-treated group vs 1.75 µg for the daily treated group.

Therefore the design of the study was not appropriate to demonstrate the superiority of pulse versus daily oral calcitriol therapy.

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Service de Nephrologie, A. Fournier
80054 Amiens Cedex, N. El Esper
France


Reply by author
Sir,
I regret that our study was not randomized and therefore the degree of hyperparathyroidism (HPT) was more severe in the pulse treatment group [1]. In addition, the cumulative weekly dose was completely different between pulse and conventional daily treatment groups, as Dr Fournier points out. I wish to thank Dr Fournier for reminding us of this.

First, I want to explain our motivation for starting pulse treatment in the patients at the predialysis stage, as we were unable to do this in our earlier communication because of space limitations. One case developed an aggravation of HPT despite conventional treatment, and a trial of pulse treatment was effectively done without an aggravation of renal function (Fig. 1). This was the motivation for starting pulse treatment. Failure of conventional low-dose treatment to suppress iPTH was not restricted to patients with overt HPT. In fact, four out of 29 patients (14%) did not respond to conventional treatment in our study. Three of 11 patients who were enrolled into the pulse treatment groups had a history of unsuccessful conventional treatment. To address this problem, we started a pilot study of pulse treatment. Patients with overt HPT tended to be enrolled into pulse treatment in our study. When we add the results of unsuccessful daily treatment of four cases to the group of daily treatment, a suppressing effect on HPT with daily treatment became more weak.

A second problem is the cumulative weekly dose. In a controlled comparison of intermittent and daily treatment using identical doses, Hermann et al. [2] failed to show significant differences in the rate of decline in iPTH. No report is available which shows the superiority of intermittent treatment over daily treatment. Hermann’s study was done in dialysis patients. It is well known that 1.15 µg/day vitamin D (equivalent to 8 µg/week) may be dangerous to predialysis patients, because even low doses tend to increase serum calcium [3]. Therefore, we assume that a design providing identical total doses for pulse and daily administration is difficult in predialysis patients.

Our initial speculation when starting this study was that pulse treatment might influence less serum electrolytes. Though an increase in serum calcium after therapy was found even in the pulse treatment group, the degree of increase during pulse treatment was extremely small in relation to the cumulative weekly dose (pulse 8 µg, daily 1.75 µg).

The duration of biological effects of vitamin D is a controversial issue. Both prolonged stimulation of intestinal calcium absorption even after the return of serum 1,25(OH)₂D to basal level [4] and suppression of iPTH [5] have been reported. Thus, there is a possibility that one could choose even longer intervals for pulse treatment. A pharmacokinetic study done during our study also revealed that some patients did not return to basal level even at 48 h after administration. Based on these results, we now assume that even as few as two pulses per week are too many. We now use one single pulse of 4 µg once a week, with satisfactory results.

Finally, various experimental data suggest that bolus treatment is more effective than continuous treatment. The response of parathyroid glands is correlated to the achieved peak 1,25(OH)₂D concentration, but not to the time-averaged increase of serum 1,25(OH)₂D [6]. Although our study was not randomized, I emphasize that oral pulse treatment was effective and safe even in predialysis patients who had failed to respond to daily treatment. As Dr Fournier correctly pointed out, a study matching dose and patient status will be necessary before one is absolutely certain that pulse treatment is more effective than daily conventional treatment.
Nagoya University School of Medicine, Third Department of Internal Medicine, 65 Tsurumai, Showa-Ku, Nagoya 466, Japan


Fig. 1. The extremely enlarged parathyroid gland (PT) with probably nodular hyperplasia (N), thyroid (T). Longitudinal section, 10 MHz.

Quantitative assessment of erythropoiesis after subtotal parathyroidectomy

Sir, although reduced erythropoietin secretion is the most important cause of anaemia in end-stage renal disease, other factors such as secondary hyperparathyroidism are also implicated. Clinical observations involving excess PTH in the development of anaemia in chronic renal failure have been reported. Thus, an inverse relationship between PTH and haematocrit have been observed by some authors [1], an improvement of anaemia has been obtained in several weeks later, i.e. not after 1 week, as Fukagawa and his group do. Despite some unanswered questions we completely agree with the opinions of Fukagawa and colleagues, that parathyroid sonography is essential for the management of parathyroid hyperfunction in dialysed patients.

Sveti Duh General Hospital, and D. Pavlović Clinical Hospital, University of H. Tomić Brzac Zagreb, S. Čala Zagreb, N. Janković Croatia

Table 1. Time course of haemoglobin (Hb, g/dl), serum transferrin receptor (sTfR, ng/ml), ferritin (Fe, ng/ml) and intact PTH (iPTH, pg/ml). Values are expressed as means ± SD.

<table>
<thead>
<tr>
<th>Before Time after subtotal parathyroidectomy</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>48 h 1 week 2 weeks 4 weeks</td>
<td></td>
</tr>
<tr>
<td>Hb</td>
<td>10.3 ± 2.2</td>
</tr>
<tr>
<td>sTfR</td>
<td>2605 ± 909</td>
</tr>
<tr>
<td>Fe</td>
<td>308 ± 153</td>
</tr>
<tr>
<td>iPTH</td>
<td>1316 ± 191</td>
</tr>
</tbody>
</table>

(ANOVA test.)

Thrombosis of angioaccess in haemodialysed patients treated with human recombinant erythropoietin

Sir,

The association between fistula thrombosis and human recombinant erythropoietin (rHuEpo) remains controversial [1,2]. In a single-centre, 4-year retrospective study, we tried to assess both the incidence of fistula thrombosis and the potential role of rHuEpo in a large cohort of haemodialysed (HD) patients.

All patients dialysed in our centre during the last 4 years were included, except those who underwent less than 30 dialysis sessions and those who received rHuEpo for less than 6 months. The cohort, comprising 177 patients (104
males, 73 females) aged 19–86 years (mean age 56 years), was retrospectively divided into 2 groups: (1) Group 1: 80 patients (45 males, 35 females) aged 19–85 years (mean age 54 years), treated with rHuEpo for more than 6 months. Epo was administered subcutaneously and the initial dose was 25–30 IU/kg thrice weekly. Subsequent adjustments of 30–50% of the previous dosage were made following weekly determinations of haemoglobin (Hb), so as to maintain the 9–11 g/dl target value. The unitary dose of Epo was decreased every time the Hb increased by more than 1 g/dl per week. Treatment was interrupted as soon as two successive Hb values greater than 12 g/dl were recorded. Once a plateau in Hb was achieved (at least two successive values between 9 and 11 g/dl), blood samples were collected and tested monthly.

(2) Group 2: 97 patients (59 males, 38 females), aged 32–86 years (mean age 58 years), none of whom received rHuEpo at any time during the study period.

Both groups appeared to be similar as regards age, gender, duration of dialysis, and type of angioaccess. Thirty-four of the 177 patients, 17 in each group, experienced one or more thrombotic events, such that there was a total of 60 thromboses, 30 in each group. The overall incidence of thrombosis was 0.102 event per patient year in group 1 versus 0.095 in group 2 (non-significant). However, when types of angioaccess were differentiated, the incidence of thrombosis was greater among patients with PTFE grafts (Table 1).

There was no significant difference between patients free of any thrombosis and those who subsequently experienced one or more thrombotic event as regards Hb values (Table 2) or platelet count (215.9 ± 8.6 versus 208.5 ± 14.9 × 10^9/mm³, respectively). The mean unitary dose of rHuEpo over the study period was 1984 ± 194 IU in patients with thrombosis and 2087 ± 172 IU in the others (non-significant). The mean duration of treatment was however significantly longer in the former than in the latter patients (639 ± 83 vs 436 ± 41 days, respectively; P = 0.023).

Early studies have suggested that rHuEpo increases the risk of angiographic thrombosis [3,4], but none of these reports included any control group. The American multicentric study [5] had conflicting results; however, no data concerning the angiographic or the existence of other thrombogenic factors were provided, and the incidence of thrombosis in the control group was strikingly high. A single prospective placebo-controlled study, the Canadian Multicentric Study, has investigated the issue of fistula thrombosis in patients receiving rHuEpo. The overall incidence of thrombosis was 0.28/patient year in Epo-treated patients vs 0.05 in controls; furthermore, patients dialysed with synthetic grafts were at greater risk for thrombosis when receiving rHuEpo [6].

There was no difference in Epo dosage between patients affected and those unaffected by fistula thrombosis. However, the affected patients received treatment for significantly longer, an observation consistent with rHuEpo having a direct thrombogenic effect on the vasculature. rHuEpo has been shown to directly modulate endothelial secretion, reducing prostacyclin and enhancing thromboxane A₂, as well as endothelin-1 production [7]. It must be remembered that the high rate of thrombosis of PTFE grafts is attributed to endothelial cell injury [8]. Anti-aggregant drugs are sometimes prescribed to prevent thrombosis in patients with PTFE grafts. Low-dose aspirin has been claimed to be inefficient in patients receiving rHuEpo, but the type of angioaccess was not taken into account [9]. In a prospective randomized study, aspirin had no effect either as a primary or as a secondary prevention of thrombosis of PTFE grafts, whereas dipyridamole proved efficient in the former case [10]. On the other hand, recent data have shown that the vasoactive effect of rHuEpo can be prevented by antiplatelet drugs [11]. We feel that antiplatelet therapy could be proposed in patients dialysed with PTFE grafts and receiving rHuEpo.

### Table 1. Incidence of fistula thrombosis in EPO-treated and non-treated patients

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>No. thromboses</td>
<td>%</td>
</tr>
<tr>
<td>Total</td>
<td>103</td>
<td>30</td>
<td>29</td>
</tr>
<tr>
<td>Direct AVF</td>
<td>84</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>PTFE grafts</td>
<td>19</td>
<td>17</td>
<td>89</td>
</tr>
</tbody>
</table>

### Table 2. Pre-treatment, plateau and pre-thrombosis/steady-state Hb levels (g/dl) in EPO-treated and non-treated patients

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thrombosis (T⁺)</td>
<td>No thrombosis (T⁻)</td>
<td></td>
</tr>
<tr>
<td>Pre-treatment</td>
<td>8.38 ± 1.06ᵃᵇ</td>
<td>8.46 ± 1.12ᵃᶜ</td>
<td>NS</td>
</tr>
<tr>
<td>Plateau</td>
<td>9.57 ± 0.67ᵇᶜᵈ</td>
<td>9.70 ± 1.02ᵇᶜ</td>
<td>NS</td>
</tr>
<tr>
<td>Before thrombosis</td>
<td>9.81 ± 1.38ᶜ</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>Steady-state</td>
<td>10.33 ± 1.52ᵃᵇ</td>
<td>9.50 ± 1.89ᵇᶜ</td>
</tr>
</tbody>
</table>

P values: ᵃ<0.0004; ᵇ<0.0009; ᶜ<NS; ᵈ<0.0004; ᵉ<0.0001; ᶠ<NS.


Zinc in plasma and platelets in patients on regular haemodialysis

Sir,

Zinc (Zn) is an essential component of a large number of metalloenzymes and is important for normal metabolism in man. Abnormalities of Zn status in patients with chronic renal failure, particularly in those on haemodialysis have been documented [1,2]. The cause and degree of Zn deficiency in dialysed patients are controversial.

Most haemodialysis patients receive erythropoietin (rHuEpo) but still present severe or moderate Zn deficiency [3]. The diagnosis of Zn deficiency, especially if moderate, is an unsolved problem. Only a small part (0.5%) of the total body Zn content is in the blood, 12–22% in plasma and 75–78% in erythrocytes. Erythrocytes have a slow turnover and hence their Zn concentration does not reflect current Zn status. Some investigators have suggested that concentrations of Zn in leukocytes or platelets are more reliable indices of short-term changes in Zn status, because of their relatively short life span [4]. The platelets contain significant Zn pool distributed in the cytoplasm (~60%) and the x-granules (~40%). Zn deficiency impairs platelet aggregation and coagulation process [5]. The duration of dialysis session is 4 h and is appropriate for measuring of short-term Zn changes.

To study whether the dialysis procedure influences Zn homeostasis and to determine Zn status in haemodialysis patients we observed 65 patients (mean age 51.10±13.2 years and mean duration of haemodialysis treatment 62.77±4 months) and 42 healthy controls (mean age 48.88±13.4). Haemodialysis was performed using reverse osmosis.

Table 1. Concentrations of Hb, Hct, albumin, total protein, and plasma Zn pre- and post-dialysis procedure; mean ± SD

<table>
<thead>
<tr>
<th></th>
<th>Pre-HD</th>
<th>Post-HD</th>
<th>r</th>
<th>P &lt; 0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dL)</td>
<td>10.54</td>
<td>11.65</td>
<td>0.903</td>
<td>0.001</td>
</tr>
<tr>
<td>Ht (%)</td>
<td>31.96</td>
<td>35.52</td>
<td>0.882</td>
<td>0.001</td>
</tr>
<tr>
<td>Alb (g/l)</td>
<td>40.42</td>
<td>45.95</td>
<td>0.648</td>
<td>0.001</td>
</tr>
<tr>
<td>Tprot (g/l)</td>
<td>72.02</td>
<td>81.20</td>
<td>0.528</td>
<td>0.001</td>
</tr>
<tr>
<td>Plasma Zn (mmol/l)</td>
<td>10.32</td>
<td>12.08</td>
<td>0.898</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Comparative studies between buffer bicarbonate (BC in 32 patients) and acetate haemodialysis (AC in 33 patients) were done. Forty-five of the patients were on rHuEpo and 22 on calcitriol in controlled doses.

Fasting samples were taken in lithium heparin Vacutainers.

Plasma and platelet Zn concentrations, haemoglobin (Hb), haematocrit (Hct), albumin, and total protein were measured at the start and the end of haemodialysis. To determine dialytic Zn losses during a haemodialysis treatment, spent dialysate was collected in a Zn-free plastic tank.

Zn in plasma, platelets, and dialysate was determined by flame and electrothermal atomic absorption spectrophotometry. Mean platelet volume (MPV) and count were determined by a Serano counter.

The results, given in Table 1, demonstrate that mean plasma Zn in dialysed patients (pre- and post-haemodialysis) is significantly less than in healthy controls. There is no correlation between platelet and plasma Zn. The statistically significant increase of plasma Zn at the end of haemodialysis is probably due to haemoconcentration (mean ultrafiltration is 2746±171 ml; n = 65) confirmed by other investigators [6,7]. The cause and degree of Zn deficiency in dialysed patients are controversial.

This work was financially supported by grant from Bulgarian Medical University Sofia.
### Table 2. Plasma, platelet, and dialytic Zn, platelet count, and platelet volume in pts on HD compared to healthy controls; mean ± SD

<table>
<thead>
<tr>
<th></th>
<th>Plasma Zn (μmol/l)</th>
<th>Platelet Zn (nmol/10⁶ cells)</th>
<th>Platelet count (10⁹/l)</th>
<th>MPV (fl)</th>
<th>Dialysate Zn (μmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-HD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>65</td>
<td>65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-HD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>65</td>
<td>65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P &lt;</td>
<td>0.001</td>
<td>0.001</td>
<td>0.005</td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>13.81</td>
<td>168.98**</td>
<td>219.52</td>
<td>7.76</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>42</td>
<td>42</td>
<td>42</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>p***</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

*Mean dialytic fluid (used) 132.88±1 (105–148).**

**Normal range for platelet Zn concentrations in healthy adults 35.5 (61.5–299.5), 413.6 nmol/10⁶ cells.

***P < compared pre-dialysis levels and healthy controls.

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Drug-related low responsiveness to recombinant human erythropoietin therapy in three patients with end-stage renal disease

Sir,

Anaemia due to chronic renal failure can usually be corrected by recombinant human erythropoietin (rHuEPO), but some patients are poorly responsive or unresponsive [1]. We observed three such patients.

Case 1 (Figure 1) was a 77-year-old female patient who had been admitted on maintenance haemodialysis (HD) since February 1994 due to chronic glomerulonephritis. She had been administering rHuEPO 3000 IU/week, but haematocrit levels failed to increase above 25% despite intravenous Fe supplements and increasing the rHuEPO dose to 9000 IU/week. At that time, occult blood tests were persistently negative. Haematocrit levels rose to 32% with a concomitant increase of reticulocyte count after discontinuation of rHuEPO. Currently, haematocrit levels remain at 30% in spite of a reduced rHuEPO dose (3000 IU/week).

Case 3 (Figure 3) was a 68-year-old male patient who had been on maintenance HD since June 1992 due to chronic glomerulonephritis. Captopril (50 mg/day) had been administered before initiation of HD. Haematocrit levels were around 20% and were unresponsive to the treatment. Cases 1 and 3 both had a history of episodes of infection or other inflammatory processes. All cases reported some discontinuation of the drugs simultaneously administered.

It is generally accepted that the common causes of resistance to rHuEPO are iron deficiency, aluminium overload, episodes of infection or other inflammatory processes, severe hyperparathyroidism, acute or chronic haemolytic conditions, and acute or chronic blood loss [1]. In our cases such causes were not present and anaemia improved soon after discontinuation of the drugs simultaneously administered. This indicates that these drugs may have played a causative role in the poor responsiveness to rHuEPO therapy.

Although the mechanism of allopurinol-induced suppression in haematopoiesis has not yet been well defined, several cases of aplastic anaemia induced by allopurinol have been reported, most of them in cases of renal failure [2,3]. Hunde et al. [4] demonstrated that renal clearances of the major metabolite of allopurinol (oxipurinol) and creatinine are directly correlated. This finding suggested that the dose of allopurinol should be reduced. In our case 1, the dose of allopurinol (200 mg/day) may have resulted in several times greater values of plasma oxipurinol concentration levels than those of normal subjects, which may have caused suppression of haematopoiesis as well as resistance to rHuEPO treatment.

To our knowledge, haematological suppression associated...
with roxatidine acetate, an H2-receptor antagonist, has not been reported, but there have been several reported cases of haematological suppression associated with other H2-receptor antagonists [5,6]. Fitchen et al. [5] demonstrated that high concentrations of cimetidine inhibit myeloid colony formation of human bone marrow in vitro. In our case 2, administration of a relatively high dose of roxatidine acetate (150 mg/day) may have resulted in high serum concentration, leading to poor responsiveness to rHuEPO. Although malabsorption of dietary iron or cobalamine associated with other H2-receptor antagonists has been reported [6], this mechanism may not contribute to poor responsiveness to rHuEPO in our patient because normal iron and cobalamine levels were obtained.

Resistance to rHuEPO due to ACE inhibitors has been postulated by others [7].

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3Saga, Japan


The kinetics of initial gastrointestinal absorption of an aluminium-containing antacid (Tisacid) in patients with various stages of chronic renal insufficiency

Sir,

The use of aluminium (Al)-contaminated water in dialysis and oral administration of phosphate-binding Al salts may lead to encephalopathy, vitamin D-resistant osteomalacia and microcytic anaemia in uraemic patients on haemodialysis [1]. However, their sporadic occurrence has been described in patients with chronic renal diseases also in the absence of haemodialysis, as well as in renal patients not receiving Al salts such as phosphate binders. Hyperacid patients receiving long-term treatment with Al-containing antacids show no sign of Al toxicity [3].

We have previously reported on the kinetics of Al absorption in healthy subjects [4,5]. The aim of this study was to examine the kinetics of Al absorption in patients with moderate or severe renal insufficiency, with a view to obtaining data on the role of kidney function in Al toxicity.

We studied two groups of renal patients. Group I (moderate renal insufficiency) consisted of two men and two women aged 39–54 years with membranous nephropathy, IgA nephropathy or chronic glomerulonephritis of 1 to 20 years’ duration. Serum creatinine varied between 194 and 440 μmol/l (2.2–4.0 mg/100 ml), creatinine clearance between 23 and 42 ml/min (mean 35 ml/min), and P between 0.9 and 1.4 mmol/l (2.8–4.3 mg/100 ml). In Group II (severe renal insufficiency), two men and two women aged 49–74 years with chronic pyelonephritis, chronic glomerulonephritis or nephrosclerosis of more than 10 years’ duration were studied. Serum creatinine was 465–680 μmol/l (5.3–7.7 mg/100 ml), creatinine clearance was 7.1–11.9 ml/min and P was 1.5–2.1 mmol/l (4.6–6.5 mg/100 ml). In Group III (healthy controls), two men and two women aged 29–72 years were studied. Their renal function and urine were normal.

After administration of four tablets of Tisacid (Biogal, Hungary), each tablet containing 58.1 mg Al, the serum Al concentration was determined in each patient and healthy controls using the electrothermic Perkin-Elmer-Zeeman 5000 atomic absorption spectrometer of the National Institute of Hygiene, Budapest. Blood was collected prior to and at 15, 30, 60 and 90 min, and then at 2, 5 and 24 h after ingestion of the four tablets. The results of the determinations are given in μg/l (factor: 0.037 × μg/l=μmol/l). The detection limit of Al was 1.0 μg/l (0.037 μmol/l). Student’s t-test was used to compare the three groups of data.

The results are summarized in Figure 1. In both groups we found an elevated serum Al concentration almost twice as high as the baseline value, even at 24 h after ingestion of Tisacid (P<0.05). However, in healthy controls, a peak was found only at 30 min; the concentration decreased rapidly thereafter and reached the baseline value as early as 5 h post-ingestion. Thus there is a fundamental difference in the kinetics of Al absorption following Tisacid ingestion between healthy controls with normal renal function and patients with moderate or severe chronic renal insufficiency.

These observations lend support to our assumption that reduced renal function must necessarily be associated with an elevated serum Al level. Under such circumstances the likelihood of tissue Al deposition in these patients is much greater than in healthy subjects or in duodenal ulcer patients with intact renal function. If after administration of a single dose of Al-containing antacid a diseased kidney is unable to eliminate Al, one must assume that this inability is much greater in renal patients, who regularly may take such

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been transfused and the other case was transferred from HD in CAPD patients. Absence of seroconversion to hepatitis C virus infection reported two seroconversions; one of them had previously been transfused and the other case was transferred from HD in CAPD patients.

Nagy E, Jobst K. The kinetics of aluminium-containing antacid anti-HCV-negative donor, but he was transfused during the study period or in the previous 16 months, and showed seroconversion in the 13th month of the study.

2. Altmann P. Aluminium toxicity in dialysis patients: no evidence for a threshold serum aluminium concentration.


Abundance of seroconversion to hepatitis C virus infection in CAPD patients

Sir, Some papers have recently been reported in Nephrology Dialysis Transplantation regarding the risk for nosocomial hepatitis C virus (HCV) infection in haemodialysis (HD) patients [1,2], but few prospective studies have been published about the risk for HCV infection in CAPD patients [3,4]. In a very recent report [5] we observed that the prevalence of HCV antibodies (anti-HCV) in CAPD was similar to that detected in predialysis chronic renal failure patients in our region, and it was correlated to events that occurred mainly before starting CAPD treatment, i.e. not related to CAPD technique. From these data, we hypothesized whether CAPD treatment could be considered as a low risk technique against HCV infection.

Our objectives were: (1) to assess the incidence of seroconversion to HCV infection in CAPD patients; (2) to compare these results with those obtained in patients who were transferred to HD or received a kidney graft; and (3) to analyse whether seroconversion was related to previous blood transfusions.

Two hundred and twenty-six anti-HCV-negative patients from five different treatment centres of our region were prospectively studied. Seroconversion was considered when anti-HCV test (ELISA 2 + supplementary test) became positive. The anti-HCV screening was done with ELISA 2. As a supplementary test, we used RIBA-4 in three centres and INNOLIA in two. Anti-HCV test was carried out in the following situations: as a screening every 6 months, after changing the renal replacement modality, and when an increase in serum alanine aminotransferase (ALT) was detected. ALT was measured monthly. Demographic characteristics, seroconversion, change in modality treatment and number of blood transfusions were registered.

Of the 226 patients who began the study, 60 (26%) died and were excluded, 121 (54%) continued on CAPD until the end of study, 27 (12%) were transferred to HD and 18 (8%) received a kidney graft (Figure 1). The study group consisted of 90 (54%) males and 76 (46%) females, with mean age 46.4 years (range 18–73 years). They had been on CAPD for a mean of 27 months (1–113 months). The follow-up period in CAPD patients was 26.5 months (3312 patients/month), in HD 17.8 months (465 patients/month) and in renal transplant (RT) patients, 14.8 months (246 patients/month). The number of blood units received by CAPD, HD and RT patients during the study was 1.1±2.3 (0–10), 1.4±2.2 (0–4) and 0.5±1.0 (0–6), respectively (non-significant difference, ANOVA test).

None of the 121 patients who had been on CAPD seroconverted to HCV, or showed ALT increases. However, three (11%) of the patients that were transferred to HD seroconverted to HCV (Figure 1). One of the three patients who seroconverted had received 6 blood units 10 months before seroconversion (seroconversion in 25th month of the follow-up). The second patient (*) showed anti-HCV RIBA-4 indeterminate during a previous renal transplant, with seroconversion in the ninth month post-transplantation (second month on HD). This patient received a kidney graft from an anti-HCV-negative donor, but he was transfused during the surgical procedure. The third patient was not transfused during the study period or in the previous 16 months, and showed seroconversion in the 13th month of the study.

In our literature review (Medline 1989–August 1996) we found only two studies on seroconversion for HCV in CAPD patients [3,4]. Cendoroglo et al. [3] studied 46 patients and reported two seroconversions; one of them had previously been transfused and the other case was transferred from HD 6 months before. Medin et al. [4] found only one patient who seroconverted, but before starting CAPD.

In contrast to HD treatment, patients on CAPD require neither extracorporeal circulation nor blood manipulation. They are not exposed to other patients since CAPD is performed at home, and they come to the dialysis unit once a month. Therefore, CAPD may reduce the potential risk for HCV infection. Moreover, the increased use of erythropoietin and anti-HCV testing in blood transfusions have dramatically decreased the incidence of HCV infection in dialysis patients. The absence of seroconversion to HCV in our CAPD patients could be due to the fact that there is no environmental exposure in this treatment modality. In our seroconversion cases, transfusions were not associated in all...
cases, suggesting that other routes of transmission were present. Although there are no controlled studies assessing the incidence of HCV infection in patients randomly assigned to different treatment modalities for renal failure (HD, CAPD, RT), based on our results we consider that CAPD could be regarded as a low-risk technique for HCV infection, and should be kept in mind when a renal replacement therapy is chosen.

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6. Hospital Universitario La Fe Valencia M. Lanuza

Spain


Mycophenolate mofetil for rescue therapy in acute renal transplant rejection in children should always be monitored by measurement of trough concentration

Sir,

Birkeland [1] reported the successful treatment of OKT3-resistant rejection in a 2-year-old renal allograft recipient with mycophenolate mofetil (MMF). The report does not describe the pharmacokinetics of MMF in this patient. This is of particular importance because MMF is rapidly converted to mycophenolic acid (MPA) which in turn is converted to the glucuronide metabolite (MPA-G) or excreted unchanged in the urine [1]. MPA-G can be subject to enterohepatic circulation [1]. There is evidence of accumulation of MPA in renal insufficiency, and therefore MMF dosing in adults with a GFR less than 25 ml/min/1.73 m² should not exceed 1 g b.d. (product information guide). MPA trough concentration measurements are possible by HPLC methods [1]. The patient reported by Birkeland almost certainly had very poor renal function because she remained anuric for 8 days after commencement of MMF rescue therapy and therefore MMF was likely to accumulate.

We report here a patient with severe MMF toxicity during rescue therapy of steroid-resistant vascular rejection and severe toxicity. The 15-year-old girl weighed 55 kg, was 163 cm tall, and had a body surface area of 1.57 m². She successfully received a renal allograft in May 1995. Primary renal disease was haemolytic uraemic syndrome. Maintenance immunosuppression consisted of cyclosporin, azathioprine and steroids. On 14 February 1996, an acute rejection was diagnosed by an increase of serum creatinine from 92 to 600 μmol/l, severe metabolic acidosis, mild proteinuria, and doubling of graft volume. Rejection failed to respond to 6 days of intravenous treatment with 10 mg/kg methylprednisolone. A transplant biopsy revealed severe aggressive tubulointerstitial rejection and vascular rejection. Immunosuppression was subsequently altered to MMF 1 g b.d and FK-506 at a dose of 0.15 mg/kg in two divided doses. Initial FK-506 concentrations were low at 4.1–5.5 ng/ml, and the dose was gradually increased to 0.24 mg/kg. At day 4 after switch, a routine MPA trough concentration (HPLC method) was taken and found to be 24.8 μg/ml, exceeding the target range of 2–5 μg/ml. Data on glucuronized MPGA were not available. MMF was discontinued on 4 March. Forty-eight hours later the MPA blood concentration was 16 μg/ml, still markedly elevated.

Sixty hours after discontinuation the patient developed severe bloody diarrhoea, and intestinal salt and bicarbonate loss which necessitated treatment with full parenteral nutrition and water and salt supplementation up to 6 l/day. Ninety-six hours after cessation of MMF the MPA was 2 μg/ml and MMF was readministered at a dose of 250 mg/day. Two days later the dose had to be adjusted to 250 mg every other day, resulting in MPA trough concentrations between 3 and 6 μg/ml. There was no evidence for either viral or bacterial infection: Clostridium difficile tests were negative in the stool. No antibiotics were administered. Improvement was seen on the fifth day after onset of diarrhoea. We regard the profuse diarrhoea as a severe adverse event to MMF. A pharmacokinetics study in the patient performed 4 weeks after the intoxication is shown in Figure 1. It shows the characteristic second recirculation peak of MPA at 12 h. On 13 June, serum creatinine had declined to 185 μmol/l and the patient is now well. MMF dose is 375 mg/day.

To date, we have treated three other patients with MMF for steroid-resistant rejection and one patient with recurrent HUS in the graft. All four are living with functioning grafts. MMF doses ranged from 250 mg/day (in an 18-year-old girl weighing 40 kg and with a serum creatinine of 460 μmol/l).

