Table 1. Comparison of Hb, Hct, ferritin and Epo doses (mean± standard deviation) at baseline, post-bolus (1–2 weeks) and post-study (4 months) in chronic haemodialysis patients receiving i.v. iron saccharate

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post-bolus</th>
<th>Post-study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dl)</td>
<td>7.75±1.41</td>
<td>8.32±1.11</td>
<td>10.6±1.48*</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>23±4.2</td>
<td>26±3.0</td>
<td>31±4.0</td>
</tr>
<tr>
<td>Ferritin (mg/l)</td>
<td>510±42.6</td>
<td>123.5±103.7</td>
<td>206.0±130*</td>
</tr>
<tr>
<td>Epo dose (IU/kg/treatment)</td>
<td>66.17±19.64</td>
<td>72±21.43</td>
<td>73.52±39.94</td>
</tr>
</tbody>
</table>

Compared to baseline: *P=0.0006; **P=0.0006; ***P=0.0001; ****P=0.50.

and the maintenance phase; yet during this time Hb levels rose higher than they were pretreatment. We feel that if the maintenance phase of treatment had been started immediately after the bolus phase, the response would have been much quicker and Epo doses may have been reduced further.

We conclude that i.v. ferrous saccharate is a safe, effective, cost-saving drug and more convenient than oral iron for patients on long-term haemodialysis treatment receiving Epo. In addition, we advocate small weekly doses of i.v. iron in HD patients for better monitoring of iron status and to avoid iron overload.

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Removal of morphine but not fentanyl during haemodialysis

Sir,

The very sick patients in intensive care units frequently require high doses of sedatives/hypnotics, especially when they are maintained on mechanical ventilation. It is not uncommon for these patients to develop different degrees of renal insufficiency, from mild insufficiency to severe oliguric acute renal failure. It has long been known that morphine can cause prolong central nervous system/respiratory depression in patients with severe renal failure, which may last for days after the drug has been discontinued [1–3].

Most of the morphine is glucuronated in the liver to morphine-3-glucuronide, morphine-6-glucuronide, and nor-morphine. In chronic renal failure there is a gradual accumulation of morphine and its metabolites in the central nervous system (CNS). Morphine is concentrated by the choroid plexus, by an active transport mechanism, with CNS effects and toxicity being related to the concentration of free morphine and/or its metabolites in the cerebral grey matter. Approximately 60–90% of the free and conjugated derivatives of morphine are excreted in the urine, about 10% are excreted in the faeces (mainly through bile, gastric juice, and saliva), and some are excreted in sweat [1]. Earlier studies using radioimmunoassay (RIA) suggested that morphine half-life is markedly increased in patients with severe renal failure, resulting in a very prolonged sedation in this patient population [4]. However, subsequent studies have indicated that RIA is non-specific for morphine, since the antisera to some extent also detect the glucuronide metabolites [5–7].

Although there is no evidence that morphine-3-glucuronide has any pharmacological activity, morphine-6-glucuronide has been shown to be pharmacologically active and indeed may be more potent than morphine itself [8,9]. More recent studies using specific high-performance liquid chromatography (HPLC) methods, which accurately measure morphine and its metabolites separately, have shown that the elimination half-life of morphine itself is not prolonged with severe renal failure (mean 2.5 vs 1.7 h, renal failure vs normal kidney function respectively) [10,11]. However, concentration of the glucuronide metabolites rapidly increased to exceed those of morphine and then remained elevated for a prolonged period, with elimination half-life for morphine-3-glucuronide of 41 vs 4 h (renal failure vs normal kidney function respectively) [10]. A very prolonged elimination half-life of the metabolites, some of which are more potent than morphine itself, would explain the prolonged CNS/respiratory depression observed in patients with renal failure. It also explains the high morphine plasma concentration and half-life reported in earlier studies using tests (RIA) that detected both morphine and its metabolites.

In an interesting report, three patients with chronic renal failure were described as having classical signs of intoxication with morphine (CNS/respiratory depression) in the absence of measurable quantities of morphine in the plasma [12]. The observed clinical effect was attributed to the accumulation of the glucuronide metabolites, particularly the pharmacologically active morphine-6-glucuronide, which persisted at very high plasma levels for an average of 7 days after discontinuation of morphine, during which period the patients had remained in severe respiratory depression [12].

In an earlier report on patients treated with continuous arteriovenous haemofiltration (CAVH) using Amicon Dialfilter 20 (Polysulphone membrane, hollow fibre, 0.25 μm) it was noticed that haemofiltration was associated with an increased sedative requirement [13]. In a subsequent study in which i.v. morphine infusion was given to 12 critically ill patients, four of whom had severe oliguric renal failure requiring haemofiltration (Amicon Dialfilter 20) and haemodialysis, morphine could be detected in the ultrafiltrate with a mean extraction efficiency of 47% [14]. With dialysis sessions of 3–5 h using the same Amicon Dialfilters the mean fall in the serum concentration of morphine during dialysis with ultrafiltration was 75% (range 47–100%), and the mean fall during dialysis without ultrafiltration was 48% (24–84%) [14]. Interestingly, they found that the fall in serum morphine concentration was much more than the fall in serum creatinine. This finding was as one would have expected with a water-soluble drug with relatively low plasma protein binding (20–30% plasma protein bound). However, in a widely used reference book on drug prescribing in renal failure it has been indicated that morphine is not haemodialysable and there is no need for supplemental doses at the end of haemodialysis [15].
Table 1. Percentage extraction rate and plasma clearance of morphine with different dialysis membranes

<table>
<thead>
<tr>
<th>Ref</th>
<th>Dialyser</th>
<th>Membrane</th>
<th>Surface area (m²)</th>
<th>Kuf</th>
<th>KoA</th>
<th>Extraction rate (%)</th>
<th>Plasma clearance (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>Amicon Dialter 20 (haemodiafiltration)</td>
<td>Polysulphone (hollow fibre)</td>
<td>0.25</td>
<td>47</td>
<td>-</td>
<td>24–84</td>
<td>48 (24–84)</td>
</tr>
<tr>
<td>14</td>
<td>Amicon Dialter 20 (haemodialysis)</td>
<td>Polysulphone (hollow fibre)</td>
<td>0.25</td>
<td>75</td>
<td>-</td>
<td>47–100</td>
<td>51 (47–100)</td>
</tr>
<tr>
<td></td>
<td>Present study</td>
<td>Polysulphone (hollow fibre)</td>
<td>1.8</td>
<td>81</td>
<td>800</td>
<td>-</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>Present study</td>
<td>Cellulose acetate (hollow fibre)</td>
<td>2.1</td>
<td>10.1</td>
<td>930</td>
<td>-</td>
<td>122</td>
</tr>
</tbody>
</table>

¹Without ultrafiltration; ²with ultrafiltration.

In this report we present two cases with end-stage renal disease (ESRD) who required high doses of morphine for pain management, one of whom additionally required fentanyl i.v. drip. The patients were on maintenance haemodialysis and the one who was conscious always complained of worsening of the pain, in her ischaemic cutaneous ulcers, while she was being dialysed. Morphine serum levels were assayed by gas chromatography/mass spectrometry (GC/MS) in a reference laboratory (ARIP Laboratories, Salt Lake City, Utah). Blood clearance rate (ml/min) was calculated as: (A−V/A) Q B, when A=concentration of the drug in the arterial line (predialyzer), V=concentration of the drug in the venous line (postdialyzer), and Q B=blood flow rate (ml/min). Plasma clearance rate (ml/min) was calculated as: (A−V/A) Q B (1–% HCT).

Case 1
A 32-year-old white female, ESRD secondary to lupus nephritis, S/P renal transplant, developed severe renal allograft failure due to postpartum haemolytic uraemic syndrome (HUS). The hospital course became complicated with severe Clostridium difficile colitis requiring total colectomy. The patient weighed 46 kg. She required morphine infusion at the rate of 5 mg/h while receiving mechanical ventilation. She was on maintenance haemodialysis 3 times a week, with F8 membrane ( Fresenius, Bad Homburg, Germany; polysulphone, hollow fibre, Kuf 8.1, surface area 1.8 m², KoA 800). Dialysis was via a Pernnath through the left internal jugular vein with a blood flow rate of 400 ml/min. Haematocrit at the time of study was 30%. After 2 h on dialysis, in one of the routine dialysis sessions, the arterial (predialyser) serum morphine level was 79 ng/ml while the venous (postdialyser) serum level had declined to 61 ng/ml (23% extraction rate). Calculated blood and plasma clearances of morphine were 91 and 64 ml/min respectively.

Case 2
A 22-year-old white female, ESRD secondary to primary hyperoxaluria type I awaiting combined kidney/liver transplantation, was suffering from severe pain in the lower extremities secondary to multiple cutaneous ischaemic ulcers. Pain management included morphine sulphate contin 60 mg p.o. b.i.d., fentanyl patches 300 µg/h, and fentanyl PCA (patient-controlled analgesia) at 60 µg/h with an additional bolus of 50 µg at the start of haemodialysis. During routine dialysis sessions the patient always complained of marked worsening of the pain in the cutaneous ischaemic ulcers in the lower extremities. She weighed 42 kg and had a haematocrit of 31.7%. She was dialysed with a CA-210 membrane (Baxter Health Care Corp., McGaw Park, IL, USA; cellulose acetate, hollow fibre, Kuf 10.1, surface area 2.1 m², KoA 930) via a Pernnath in the left internal jugular vein, with a blood flow rate of 350 ml/min. During one of the routine sessions, after 2 h of haemodialysis, serum morphine level in the arterial line (predialyzer) was 16 ng/ml, and in the venous line (postdialyzer) was 7.8 ng/ml, with dialyser extraction rate of 51%. The blood and plasma clearance rates were calculated at 179.5 and 122 ml/min respectively. Moreover, predialysis morphine level was 26 ng/ml, which after 2 h of dialysis had declined to 16 ng/ml (38.5% decline over 2 h). Simultaneously, fentanyl concentration in the arterial line was 5.4 ng/ml, while that in the venous line was 5.3 ng/ml, indicating no significant removal of fentanyl with dialysis. Predialysis fentanyl level had been 6.1 ng/ml with non-significant decline over 2 h of dialysis to 5.4 ng/ml; however, the patient had received a bolus dose of 50 µg at the start of haemodialysis.

Our results support the previous report that morphine is significantly removed during dialysis [14]. In our two patients there was 23–51% extraction rate (average 37%) with F8 and CA-210 dialysis membranes. We have also shown a blood morphine clearance of 91–179.5 ml/min (average 135 ml/min) and plasma clearance of 64–122 ml/min (average 93 ml/min) with these two dialysers. The better clearance with the CA-210 membrane may be due to its higher KoA, Kuf, and larger surface area.

In regard to the clearance of fentanyl with haemodialysis, there is currently no information in the literature [15]. Our results indicate that fentanyl is not removed to any significant extent by CA-210 dialyser.

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6. Grabinski PY, Kaiko RF, Walsh TD, Foley KD, Houde RW. Morphine radioimmunoassay specificity before and after extrac-
The effect of dialysis membrane on serum β2-microglobulin in chronic haemodialysis patients

Sir,

One major area of current controversy relates to the question, as to whether membrane biocompatibility modifies the risk of β2-microglobulin amyloidosis. Drs Farrell and Bastani, in a retrospective study on five chronic haemodialysis patients [1], claim that high-flux ‘biocompatible’ membranes (cellulose triacetate and polysulphone) are more effective in reducing serum β2-microglobulin than ‘less biocompatible’ high-efficiency membranes (cellulose acetate), we would like to test the fact that it is very difficult to prove the specific role of biocompatibility because high-flux membranes are associated with the significant dialytic removal of β2-microglobulin. Furthermore, the authors found very high plasma levels of β2-microglobulin during less ‘biocompatible’ high-efficiency dialysis (we imagine 75 mg/l instead of the 75 mg/dl reported in the Figure and text).

Because there is no β2-microglobulin clearance when using cellulose acetate, and assuming steady-state plasma levels, for a whole-body clearance of 3.5 ml/min [2], the β2-microglobulin generation in the patients of Farrell and Bastani can be calculated as: generation = removal = 75/1000 × 3.5 = 0.26 mg/min (that is 15.6 mg/h) and, for a body weight of 70 kg, G = 0.22 mg/h/kg. This is a very high value because turnover studies with 125I-labelled β2-microglobulin in humans have shown that normal adults generation is 0.11–0.18 mg/h/kg, with a mean value of 0.13 mg/h/kg [3]. On the other hand, the authors found a decrease in plasma β2-microglobulin levels to 43 mg/l (−42.7%) during ‘biocompatible’ high-flux dialysis. On the basis of the results of previous kinetic studies [4,5], β2-microglobulin appears to be distributed in two compartments with volumes approximating those of plasma and interstitial fluid, and the capillary mass transfer coefficient is estimated to be 40–43.5 ml/min.

From a variable volume two-pool model, it can be estimated that a dialytic clearance of about 70 ml/min is necessary to obtain the reduction in plasma β2-microglobulin levels found in the patients of Farrell and Bastani. Unfortunately, the authors do not give any information concerning dialysis efficiency and treatment time, so that the effect of the generation and dialytic removal of plasma β2-microglobulin cannot be evaluated.

In a prospective trial involving 380 patients, we have also compared biocompatible and bioincompatible membranes [6]. The primary aim of the study was to evaluate whether, with bicarbonate dialysis, the polysulphone membrane offers any advantages in terms of pretreatment β2-microglobulin level over the cuprophane. A secondary aim was to assess whether the use of more sophisticated methods, consisting of biocompatible synthetic membranes with different hydraulic permeability (high-flux haemodialysis and haemodiafiltration), offers any further advantages. After a follow-up of 24 months, there was a significant decrease in predialysis plasma β2-microglobulin levels in patients treated with high-flux polysulphone membrane (both in high-flux dialysis and HDF) in comparison with the levels observed in the patients treated with cuprophane and low-flux polysulphone membranes, with no difference being found between the cuprophane and low-flux polysulphone membranes. During the 24-month follow-up, there was actually no change in the β2-microglobulin levels of the patients dialysed with cuprophane or low-flux polysulphone membranes. The results of our trial favour the effect of the removal of β2-microglobulin over the possibility of a lower rate of generation due to biocompatibility. Our data are therefore not in agreement with the results of Hakim et al. [7], quoted by Farrell and Bastani as supporting the effect of biocompatibility.

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Dialysis technique modulates alpha interferon pharmacokinetics in a patient with chronic hepatitis C

Sirs,

Alpha interferon (IFN), a glycoprotein of 165 amino acids, is effective in the treatment of hepatitis C virus infection. In blood, IFN does not bind to albumin and its breakdown