Brief Report

Removal of morphine with the new high-efficiency and high-flux membranes during haemofiltration and haemodiafiltration

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Abstract

We present three critically ill patients with severe renal failure who required haemofiltration or haemodiafiltration, with high-efficiency or high-flux membranes, while receiving an intravenous infusion of morphine. We show that despite the very high ultrafiltrability/diffusability of free morphine, only 1–3% of the total amount of infused morphine is removed in 24 h. This is in marked contrast to haemodialysis where, owing to much higher dialysate flow rate, a significant quantity of free morphine is removed.

Key words: Morphine; dialysis; haemofiltration; haemodiafiltration; toxicity

Introduction

Prolonged sedation and respiratory depression have been reported in uraemic patients receiving morphine [1–3]. Morphine has a molecular weight of 668.7 and is ~35% protein-bound in the plasma of healthy subjects. Protein binding is reduced to 25–30% in patients with renal failure [4]. Morphine is predominantly metabolized and eliminated by the liver, through conversion to morphine-3-glucuronide, morphine-6-glucuronide and normorphine. In patients with chronic renal failure there is a gradual accumulation of morphine and its metabolites in the central nervous system (CNS). Approximately 60–90% of the free morphine and its conjugated derivatives are excreted in the urine [1]. Earlier studies using radioimmunoassay (RIA) have suggested that morphine’s half-life is markedly increased with severe renal failure [5]. However, more recent studies indicate that RIA is a non-specific test for morphine since the antiserum also reacts, to some extent, with the glucuronide metabolites [6,7]. The morphine-6-glucuronide conjugate has been shown to be metabolically active, possibly even more potent than morphine itself [8]. More recent studies using specific high-performance liquid chromatography (HPLC) or gas-chromatography and mass-spectrometry, which accurately measure morphine and its metabolites separately, have shown no alteration in morphine pharmacokinetics and disposition in patients with severe renal failure [9,10]. However, concentrations of the glucuronide metabolites increase rapidly and remain elevated for a prolonged period (e.g. elimination half-life for the 3-glucuronide metabolite is 41 h in renal failure vs 4 h in normal controls) [9]. A very prolonged elimination half-life of the metabolites, some of which are shown to be more potent than morphine itself, would explain the prolonged respiratory/CNS depression observed in patients with severe renal failure. It also explains the high plasma morphine concentration and morphine half-life reported in earlier studies using less specific tests, i.e. RIA, that detected both morphine and its metabolites.

In a widely used reference book on drug prescribing in renal failure it is indicated that morphine is not haemodialysable, and that it is not known whether it is removed by haemofiltration [11]. However, in 12 critically ill patients, four of whom had severe oliguric renal failure requiring hemofiltration (Amicon Dialfilter 20; polysulfone membrane, hollow fiber, surface area 0.25 m²) and haemodialysis, who received an i.v. morphine infusion, morphine was detected in the ultrafiltrate with a mean percentage extraction of 47% [12]. Within 3–5 h of hemodialysis with Amicon Dialfilter 20, the mean fall in serum concentration of morphine during dialysis with ultrafiltration was 75% (range, 47–100%), and during dialysis without ultrafiltration was 48% (24–84%) [12]. Moreover, in our earlier observation [13] of two patients who were dialysed using F8 and CA210 dialysers, we found a percentage extraction of 23–51%, and plasma clearance rate of 64–122 ml/min, respectively, Table 1.

In this paper we report three new patients with severe acute renal failure requiring haemofiltration or haemodiafiltration with different high-efficiency and high-flux membranes, who received an i.v. morphine infusion while on mechanical ventilation. Free morphine levels in serum and ultrafiltrate were measured by gas-chromatography/mass-spectrometry (GC/MS) in a reference laboratory (ARIP Laboratories, Salt
Lake City, Utah, USA). The percentage extraction with hemofiltration was calculated as: (concentration in ultrafiltrate/concentration in pre-dialyser) × 100, as reported earlier [12]. The percentage extraction during hemodiafiltration was measured in two ways, one similar to the patients on haemofiltration, and the other similar to the patients on haemodialysis (concentrations in pre-dialyser – post-dialyser/pre-dialyser) × 100. Plasma clearance rate (ml/min) of morphine during haemodiafiltration was calculated as: (concentrations in pre-dialyser – post-dialyser/pre-dialyser) × blood flow rate in ml/min (1 – hematocrit).

**Case reports**

**Case I**

A 57-year-old white male with acute abdomen secondary to ruptured diverticulum, adult respiratory distress syndrome requiring intubation and mechanical ventilation, and severe acute renal failure requiring continuous veno-venous haemofiltration (CVVH), received an i.v. morphine infusion at the rate of 3 mg/h. The CVVH was performed using an F8 dialyser (Fresenius, Bad Hamburg, Germany; polysulfone, hollow fibre, surface area 1.8 m², Kuf 8.1, KoA 800), blood flow rate of 200 ml/min and ultrafiltration rate set at 900 ml/h (Ivac control of ultrafiltration line). The patient weighed 87 kg, and his haematocrit was 28.5%. Free morphine concentrations were as follows: pre-dialyser (arterial line) 35 mg/ml, post-dialyser (venous line) 31 ng/ml, ultrafiltrate 28 ng/ml. Percentage extraction was 80%, Table 1. However, the total amount of morphine removed in 24 h of CVVH was estimated to be ~0.6 mg which comprised only ~1% of the total amount infused.

On another occasion the patient’s CVVH was carried out using an F80 dialyser (Fresenius, Bad Hamburg, Germany; polysulfone, hollow fibre, surface area 1.8 m², Kuf 60, KoA 945), the concentrations of free morphine in the pre- and post-dialyser were equal at 73 ng/ml. This suggested that the ultrafiltrate (900 ml/h) also had the same morphine concentration, so that despite fluid removal the concentration in the venous and arterial lines were the same. Thus, we speculated that this represented a percentage extraction of 100% i.e. morphine was totally ultrafilterable with the F80 membrane. Assuming 100% ultrafiltrability of morphine (ultrafiltrate concentration of 73 ng/ml), total amount of morphine removed in 24 h of CVVH would be ~1.6 mg, which indicates that only ~2% of the infused morphine was removed by CVVH.

**Case II**

A 47-year-old white female developed severe pneumonia with *Legionella* and herpes simplex 2 weeks after her second kidney transplant. After withdrawal of immunosuppressive drugs she developed severe anuric renal failure necessitating continuous veno-venous haemodiafiltration (CVVHD). She required an i.v. morphine infusion at a rate of 2 mg/h while on mechanical ventilation. On CVVHD with an F8 dialyser,

| Table 1. Percentage extraction and plasma clearances of morphine during hemodialysis, hemofiltration and hemodiafiltration with different membranes |

<table>
<thead>
<tr>
<th>Reference</th>
<th>Dialyzer</th>
<th>Membrane</th>
<th>Surface area (m²)</th>
<th>Kuf</th>
<th>KoA</th>
<th>% Extraction</th>
<th>Plasma clearance (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>Amicon Dalfilter 20 (hemofiltration)</td>
<td>Polysulfone (hollow fiber)</td>
<td>0.25</td>
<td>—</td>
<td>—</td>
<td>47%*</td>
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<tr>
<td>12</td>
<td>Amicon Dalfilter 20 (hemodialysis)</td>
<td>Polysulfone (hollow fiber)</td>
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<td>—</td>
<td>—</td>
<td>48% (24–84)*</td>
<td>—</td>
</tr>
<tr>
<td>13</td>
<td>CA210 (hemodialysis)</td>
<td>Cellulose acetate (hollow fiber)</td>
<td>2.1</td>
<td>10.1</td>
<td>930</td>
<td>51%</td>
<td>122*</td>
</tr>
<tr>
<td>13</td>
<td>F8 (hemodialysis)</td>
<td>Polysulfone (hollow fiber)</td>
<td>1.8</td>
<td>8.1</td>
<td>800</td>
<td>23%*</td>
<td>64*</td>
</tr>
<tr>
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<td>F8 (hemofiltration)</td>
<td>Polysulfone (hollow fiber)</td>
<td>1.8</td>
<td>8.1</td>
<td>800</td>
<td>80%*</td>
<td>—</td>
</tr>
<tr>
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<td>Polysulfone (hollow fiber)</td>
<td>1.8</td>
<td>60</td>
<td>945</td>
<td>100%</td>
<td>—</td>
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<tr>
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<td>CA210 (hemodiafiltration)</td>
<td>Cellulose acetate (hollow fiber)</td>
<td>2.1</td>
<td>10.1</td>
<td>930</td>
<td>94%<em>, 6.5%</em></td>
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<td>Polysulfone (hollow fiber)</td>
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<td>8.1</td>
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<td>90%<em>, 5%</em></td>
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<td>8.1</td>
<td>800</td>
<td>91%<em>, 0%</em></td>
<td>0f</td>
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</table>

*%Extraction with hemofiltration calculated as: (concentration in ultrafiltrate/concentration in pre-dialyser) × 100; *without ultrafiltration; mean fall in blood level during 3–5 h of dialysis; *with ultrafiltration; *% extraction with hemodialysis calculated as: (concentration in pre-dialyser – post-dialyser/pre-dialyser) × blood flow rate (1–Hct); *% removal per 24 h calculated as: (dialysate concentration × dialysate volume in 24 h/total infused over 24 h) × 100; *ultrafiltration concentration not measured, but since pre- and post-dialyser concentration were equal it was assumed that ultrafiltrate concentration was also the same, thus 100% ultrafiltrable.
blood flow rate of 200 ml/min and dialysate (Dianeal, 1.5% dextrose solution) flow rate of ~900 ml/h, the patient had ~900 ml/h of dialysate outflow indicating no ultrafiltration at the time of study. The patient weighed 92 kg and her haematocrit was 23%. Measured free morphine concentrations were as follows: pre-dialyzer 40 ng/ml, post-dialyser 38 ng/ml, outflow dialysate solution 36 ng/ml. The percentage extraction and plasma clearance rate of morphine are shown in Table 1. Moreover, with an average dialysate outflow rate (combined dialysate solution and ultrafiltrate) of ~1500 ml/h, and dialysate morphine concentration of 36 ng/ml it was speculated that ~1.3 mg morphine was removed by CVVHD over a 24-h period. At a morphine infusion rate of 2 mg/h (48 mg/24 h) the estimated amount of morphine removed by CVVHD was ~2.7% of the administered dose, Table 1.

On another occasion, the patient received CVVHD with a CA-210 dialyser (Baxter Healthcare Corp., McGaw Park, IL, USA: cellulose acetate, hollow fibre, surface area 2.1 m², Kuf 10.1, KoA 930), blood flow rate of 150 ml/min, dialysate (Dianeal, 1.5% dextrose solution) flow rate of 900 ml/h, dialysate outflow rate (combined dialysate solution and ultrafiltrate) of ~1300 ml/h. At this time the patient weighed 94 kg and her haematocrit was 24.5%. Measured free morphine concentrations were as follows: pre-dialyzer 31 ng/ml, post-dialyzer 29 ng/ml, outflow dialysate solution 29 ng/ml. The percentage extraction and plasma clearance of morphine are shown in Table 1. Moreover, with an average dialysate outflow rate of 1700 ml/h, it was speculated that over a 24-h period ~1.2 mg morphine was removed by CVVHD, using a CA 210 dialyser. At the morphine infusion rate of 2 mg/h (48 mg/24 h) the estimated morphine removal by CVVHD with a CA210 membrane was ~2.5% of the administered dose, Table 1.

Case III

A 23-year-old black male with multiple bone fractures after a motor vehicle accident, aspiration pneumonia, bowel ischaemia and septicaemia, was mechanically ventilated. He received an i.v. morphine infusion at 5 mg/h. He subsequently developed severe acute renal failure requiring CVVHD using an F8 dialyser: blood flow rate 150 ml/min, dialysate (Dianeal, 1.5% dextrose solution) flow rate of 900 ml/h, with a dialysate outflow (combined ultrafiltrate and dialysate solution) at ~1600 ml/h. The patient weighed 95 kg and his haematocrit was 32%. Measured free morphine concentrations were as follows: pre-dialyzer 110 ng/ml, post-dialyser 110 ng/ml, outflow dialysate solution 100 ng/ml. The percentage extraction and plasma clearance of morphine are shown in Table 1. Moreover, it was estimated that ~3.8 mg morphine was removed per 24 h. This comprised ~3% of the cumulative dose the patient had received in 24 h, Table 1.

Discussion

Our results concur with two recent reports [12,13] and collectively indicate that morphine passes easily through the high-efficiency and high-flux membranes currently used for renal replacement therapy. However, with the current practice of ultrafiltration rates set maximally at ~1–2 l/h and dialysate flow rates of ~900 ml/h (haemodiafiltration, e.g. CVVHD), despite the very high ultrafiltrability/diffusability of morphine, the amount that will actually be removed accounts for only 1–3% of the total amount of morphine infused. This is in contrast to brief haemodialysis sessions where dialysate flow rate is routinely set at 500–800 ml/min (30–40 l/h, ~40 times the dialysate flow rate in CVVHD), and the highly ultrafiltrable/diffusible morphine will have a chance to equilibrate with a large volume of dialysis solution, as a result of which a significant quantity of morphine would be removed. Thus, we conclude that not much morphine is removed with either haemofiltration or haemodiafiltration (e.g. CVVH or CVVHD). Moreover, the rate of morphine removal with these modalities is primarily determined by the ultrafiltration and dialysate flow rates.

References


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