Pharmacokinetics of morphine and its glucuronides following intravenous administration of morphine in patients undergoing continuous ambulatory peritoneal dialysis

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Abstract

Background. Conjugation with glucuronic acid represents the major route of biotransformation of morphine. The glucuronides morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) are eliminated via the kidneys. Therefore, chronic renal failure should affect the disposition of M3G and M6G. Numerous patients undergoing long-term continuous ambulatory peritoneal dialysis (CAPD) require pain treatment with morphine. There are only limited data available about the disposition of morphine and its active metabolites M6G and M3G in patients on CAPD. We therefore investigated the pharmacokinetics of morphine and its metabolites in CAPD patients.

Methods. This was a single intravenous dose pharmacokinetic study in 10 CAPD patients (1 female, 9 male, age 31–69 years). Morphine-hydrochloride (Mo) (10 mg) was administered intravenously. Serum, urine, and dialysate samples were collected during 24 h. GC-MS-MS and HPLC-MS methods were used to quantify respectively morphine and morphine glucuronides.

Results. While systemic clearance of morphine (1246 ± 240 ml/min) was in the range observed in patients with normal kidney function, both M3G and M6G showed substantial accumulation. The area under the concentration–time curve (AUC) ratio of M3G:Mo (33.4 ± 7.1) and of M6G:Mo (12.2 ± 3.2) was 5.5 and 13.5 times higher than in patients with normal kidney function. Renal clearances of morphine, M3G, and M6G (morphine 3.0 ± 2.5 ml/min; M3G 3.9 ± 2.2 ml/min; M6G 3.6 ± 2.2 ml/min) and dialysate clearances (morphine 4.1 ± 1.3 ml/min; M3G 3.2 ± 0.7 ml/min; M6G 3.0 ± 0.8 ml/min) were extremely low. Therefore the accumulation of M6G and M3G is readily explained by kidney failure which is not compensated by CAPD.

Conclusion. Accumulation of M3G and M6G is due to the substantially lowered clearance by residual renal function and peritoneal dialysis. In view of the accumulation of potential active metabolites, subsequent investigations have to assess the frequency of side-effects in patients on CAPD.

Key words: morphine; morphine glucuronides; peritoneal dialysis; pharmacokinetics; renal failure

Introduction

Morphine remains the analgesic drug of choice for treatment of severe acute and chronic pain syndromes. In humans morphine is almost completely metabolized by the liver. The principal route of biotransformation is the glucuronidation of morphine by glucuronyl transferase. In healthy volunteers approximately 80–90% of an intravenously administered dose of morphine is recovered in urine, mainly as the glucuronide metabolites morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) respectively [1,2].

Thus, kidney failure is recognized to have profound effect on the behaviour of the glucuronide metabolites of morphine, because the elimination of these compounds is impaired in renal dysfunction. Several authors have confirmed the variability in the kinetics of morphine and its metabolites in the presence of renal impairment [1,3,4]. It has been reported that patients with renal impairment are at greater risk of developing opiate toxicity with prolonged narcotic effects and severe respiratory depression, probably caused by the accumulation of the active metabolite M6G [5]. Others reported a correlation between the severity of renal impairment and the occurrence of opiate side-effects like nausea and vomiting [6]. M6G is a potent μ-receptor agonist as well and therefore produces analgesia. The mechanism of action seems to be similar to that of morphine, but with a greater potency and a longer duration of action [7,8].
There are only limited data on the pharmacokinetics of morphine available in continuous ambulatory peritoneal dialysis patients. Osborne et al. [2] studied morphine disposition in CAPD patients immediately after placement of peritoneal catheter before a stable CAPD regime was established. Furthermore, urine and dialysis solution were not sampled in that study. The aim of our study was therefore to obtain more detailed data about disposition and excretion of morphine and morphine glucuronides in CAPD patients.

Subjects and methods

Patients

After obtaining Ethics Committee approval and written informed consent, 10 CAPD patients in the dialysis unit of the Robert-Bosch-Hospital Stuttgart (1 female, 9 male, age 31–69 years, mean 55.5 ± 10 years) were studied. The underlying renal disease were chronic glomerulonephritis in three, diabetic nephropathy in six, and nephrosclerosis in one case. Four of the patients were anuric and six had residual diuresis ranging from 400 to 2000 ml/24 h. Duration of peritoneal dialysis (PD) ranged from 3 to 60 months (mean 28.5 ± 18 months). Patients who had had peritonitis within the previous 2 months were excluded. The patients’ adequacy of CAPD treatment calculated as weekly Kt/V (weekly clearance of times the duration of CAPD treatment divided by the volume of distribution of urea in the body) and creatinine clearance were available with not more than 7 months (mean 4.7 ± 1.8 months) interval between Kt/V-test and study. No patient was receiving concurrent treatment with morphine or other narcotics. Details on patients are summarized in Table 1.

Experimental protocol

All patients received a single dose of morphine hydrochloride (10 mg, 26.6 μmol) in 100 ml NaCl0.9% infused over 10 min, starting at 8 a.m. after the fill following the drain of the overnight dialysis solution. Thereafter four exchanges of the PD solution were made at 5,10,15 and 24 h after the end of the infusion. The volumes were measured in conjunction with each exchange and aliquots of dialysis fluid (20 ml) were stored at −20°C for analysis. Venous blood samples (6 ml) were taken from a cannula in the opposite limb immediately before administration of morphine and 5, 30, 60, 120 min and 4, 8, 12, 23 and 24 h after the end of morphine infusion. After centrifugation serum samples were stored at −20°C until analysis. In patients with residual diuresis, urine was collected over 24 h after the infusion. After quantifying total urine volume aliquots (20 ml) were stored at −20°C.

Analytical methods

Analysis of morphine was performed by gas chromatography/tandem mass spectrometry (GC-MS-MS), analogous to an assay technique described for dihydrocodeine [9]. Morphine glucuronides were quantified simultaneously by high-pressure liquid chromatography with electrochemical detection (HPLC-MS) in accordance with an assay techniques described previously [10].

Pharmacokinetic parameters

Pharmacokinetic parameters of morphine and its glucuronides in serum were calculated using Topfit 2.0® Pharamaco-dynamic and Pharmacokinetic Data Analysis System for PC (Gustav Fischer Verlag, Stuttgart, Germany).

The area under the concentration—time curve (AUC) was calculated according to the linear trapezoidal rule. Concentrations of morphine, M3G or M6G were calculated using the amounts of morphine, M3G and M6G excreted in the urine (Eu) and dialysate (EcAPD). Renal clearance (CLR) and PD clearance (CLCAPD) were determined as Eu and EcAPD of morphine, M3G, and M6G divided by the AUC of the corresponding compound. Total serum concentration of morphine (CLspa) was determined using the formula dose/AUC. The results are given as mean ± SD.

Results

Generally the drug was well tolerated. One patient complained about nausea and vomiting 30 min after the infusion of morphine which resolved after intravenous injection of 10 mg metoclopramide hydrochloride. Two patients complained about temporary dizziness.

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Duration of dialysis (months)</th>
<th>CAPD regime (1/24 h)</th>
<th>Drug regimen*</th>
<th>Kt/V</th>
<th>CLRSPA (creatinine) (ml/min)</th>
<th>CLSPA (creatinine) (ml/min)</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>M</td>
<td>65</td>
<td>92.5</td>
<td>3</td>
<td>4 × 2000</td>
<td>1,2,3</td>
<td>2.1</td>
<td>5.3</td>
<td>6.2</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>31</td>
<td>75</td>
<td>12</td>
<td>4 × 2000</td>
<td>1,2,3,4,5,17</td>
<td>1.8</td>
<td>3.7</td>
<td>1.7</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>54</td>
<td>68.8</td>
<td>34</td>
<td>4 × 2000</td>
<td>4,5,7,11,14,17,18</td>
<td>1.4</td>
<td>2.8</td>
<td>2.7</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>54</td>
<td>116</td>
<td>40</td>
<td>4 × 2500</td>
<td>2,5,6,7,11</td>
<td>2.4</td>
<td>4.6</td>
<td>10.4</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>69</td>
<td>88.5</td>
<td>14</td>
<td>4 × 2000</td>
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<td>2.7</td>
<td>3.7</td>
<td>8.1</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>54</td>
<td>81.5</td>
<td>16</td>
<td>4 × 2000</td>
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<td>2.2</td>
<td>4.1</td>
<td>2.7</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>49</td>
<td>85</td>
<td>55</td>
<td>4 × 2500</td>
<td>4,6,8,11,17</td>
<td>1.5</td>
<td>5.4</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>64</td>
<td>66.4</td>
<td>60</td>
<td>4 × 2000</td>
<td>1,2,3,7,17</td>
<td>2.2</td>
<td>7.7</td>
<td>–</td>
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<tr>
<td>9</td>
<td>F</td>
<td>57</td>
<td>89.1</td>
<td>27</td>
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<td>1,2,3,5</td>
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<td>4.6</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>57</td>
<td>106</td>
<td>24</td>
<td>4 × 2500</td>
<td>5,10,15,17</td>
<td>2.2</td>
<td>4.4</td>
<td>10.1</td>
</tr>
</tbody>
</table>

*Drug regimen: 1, erythropoietin; 2, ferro(II)-glycin-sulfate-complex; 3, calcium-acetate; 4, aluminium chloride-hydroxide complex; 5, furosemide; 6, nifedipine; 7, enalapril; 8, doxazosin; 9, verapamil; 10, folicopril; 11, metoprolol; 12, gluquidone; 13, carvedilol; 14, isosorbid dihydrate; 15, doxepin; 16, ASS; 17, insulin; 18, calciotol.
None of the remaining seven patients had any adverse effect during or after the infusion. Whereas the serum concentration—time curves of morphine decline over 24 h, M3G and M6G accumulate over this time period, reaching a plateau only 40 min after the end of infusion (Figure 1). Dialysate concentration—time curves of morphine, M3G, and M6G show a similar behaviour, with a decline of morphine and accumulation of M3G and M6G (Figure 2). Only 11.9 ± 4.0% of the infused morphine was excreted in dialysate as morphine, M3G, or M6G during 24 h (Figure 3). In patients with residual renal function an additional amount of 12.0 ± 7.9% was excreted in the urine as morphine, M3G, and M6G (Figure 3).

The pharmacokinetic parameters of morphine, M3G, and M6G are summarized in Table 2. The terminal half-life of the parent drug (t_{1/2}) in serum was 309.6 ± 52.3 min. CL_{CAPD} and CL_R values are shown in Figure 4. CL_{CAPD} of morphine (4.1 ± 1.4 ml/min), M3G (3.2 ± 0.7 ml/min), and M6G (3.0 ± 0.8 ml/min) accounted for less than 1% of CL_{sys} of morphine (1246.2 ± 239.7 ml/min). In those patients with residual renal function, CL_R of morphine (3.0 ± 2.46 ml/min), M3G (3.9 ± 2.2 ml/min), and M6G (3.6 ± 2.2 ml/min) was also less than 1% of CL_{sys} of morphine. CL_R of M3G and M6G was correlated to creatinine clearance (M3G, r = 0.97, P < 0.005; M6G, r = 0.82, P < 0.05 (Figures 5 and 6). In all patients, most of the morphine serum clearance took place via routes other than PD or kidneys, i.e. by non-renal, non-CAPD clearance.

In view of the accumulation of morphine glucuronides, clearance of morphine is due to its metabolism to M3G and M6G, while the accumulation of M3G and M6G is readily explained by the substantially lowered clearance by residual renal function and peritoneal dialysis.

Based on these results, repeated i.v. administration of morphine in a clinical setting of an acute pain syndrome in PD patients is expected to result in an extreme accumulation of M3G and M6G. The data of morphine, M3G, and M6G after single i.v. application of 10 mg morphine-HCl were fitted to a three-compartment model (Topfit 2.0). Using these obtained parameters an extrapolation of serum concentration—time curves of morphine, M3G, and M6G for a 3-day treatment period with a dosing regime of 5 mg...
Fig. 3. Percentage of morphine, M3G, and M6G eliminated by CAPD (n=10) and residual renal function (n=6) in 10 CAPD patients.

Table 2. The pharmacokinetic parameters of morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) (mean±SD) in 10 continuous ambulatory dialysis (CAPD) patients, abbreviations see methods section

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Morphine</th>
<th>M3G</th>
<th>M6G</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC\text{CAPD} (µg)</td>
<td>33.0±10.6</td>
<td>854.7±277.5</td>
<td>310.2±117.3</td>
</tr>
<tr>
<td>EC\text{R} (µg) (n=6)</td>
<td>22.4±17.3</td>
<td>875.1±492.8</td>
<td>303.5±180.9</td>
</tr>
<tr>
<td>CL\text{CAPD} (ml/min)</td>
<td>4.1±1.4</td>
<td>3.2±0.7</td>
<td>3.0±0.8</td>
</tr>
<tr>
<td>CL\text{R} (ml/min) (n=6)</td>
<td>3.0±2.5</td>
<td>3.6±2.2</td>
<td>3.9±2.2</td>
</tr>
<tr>
<td>CL\text{tot} (ml/min)</td>
<td>1246.2±239.7</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>t\text{1/2} (min)</td>
<td>309.6±52.3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>AUC \text{m}–\text{24h} (nmol*h/l)</td>
<td>369.3±70.7</td>
<td>12493±2783</td>
<td>4302±1121</td>
</tr>
<tr>
<td>plasma concentration \text{30 min} (µmol/l)</td>
<td>–</td>
<td>449.9±148.8</td>
<td>161.0±60.9</td>
</tr>
<tr>
<td>plasma concentration \text{24 h} (µmol/l)</td>
<td>–</td>
<td>475.5±162.0</td>
<td>147.6±79.5</td>
</tr>
<tr>
<td>AUC M3G : AUC morphine</td>
<td>33.4±7.1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>AUC M6G : AUC morphine</td>
<td>12.2±3.2</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Fig. 4. Clearance of morphine, M3G, and M6G by CAPD (CL\text{CAPD}) (n=10) or residual renal function (CL\text{R}) (n=6) in 10 CAPD patients.

morphine HCl given i.v. four times a day was carried out; this is half the dose given in patients without renal impairment in the usual interval. While extrapolation data show no accumulation of morphine after a 3-day treatment period, M3G and M6G serum levels increase more than five times the level seen after single i.v. administration of morphine (Figure 7).

Discussion

In the present study GC-MS-MS and HPLC-MS methods were used to quantify serum and dialysate levels of morphine and morphine-glucuronides, respectively. Both assay techniques are well established and very sensitive. GC-MS-MS detecting limit of morphine is 50 fmol/ml, while HPLC-MS detecting limits for M3G and M6G are 2.5 pmol/ml and 0.5 pmol/ml, respectively.

Our data show that after single-dose i.v. administration of 10 mg morphine HCl, serum concentrations of morphine decrease over the following 24 h, while morphine metabolites show substantial accumulation. Compared with published data about disposition of morphine metabolites after i.v. administration, AUC ratios of M3G:Mo and M6G:Mo is 5.5 and 13.5 times higher than in patients with normal kidney function [11]. While accumulation of morphine
metabolites is due to its substantially lowered clearance by residual renal function and peritoneal dialysis, elimination of morphine mainly takes place by metabolism to morphine glucuronides.

In view of the accumulation of morphine metabolites it has been suggested that side-effects of morphine in patients with renal failure are related to accumulation of the active morphine metabolite M6G [5]. The analgesic properties of M6G were recognized in the early 1970s [7] and more recent studies in animals and humans suggest that M6G might have an analgesic potency many times that of morphine, depending on the route of administration [12,13].

Although our, and previously published pharmacokinetic data, indicate an extreme accumulation of M6G after single i.v. administration of morphine—which is expected to further increase under continuous treatment with morphine—none of the patients in the present study experienced respiratory depression or prolonged narcotic effect, and the number of published cases of serious adverse events in patients with renal impairment is small. In the latter case this may be due to cautious dosing of morphine in patients with end-stage renal disease, which is recommended to be 50% of the normal dose at the usual interval. On the other hand, as shown in our model, accumulation of morphine glucuronides is expected to occur even under repeated administration of a reduced morphine dose. We therefore have to consider possible additional factors affecting the occurrence of adverse events in patients with ESRD after repeated administration of morphine.

It can be suspected that although serum levels of M6G in patients with renal failure are very high, under normal conditions M6G cannot pass across the blood brain barrier (BBB) in amounts that produce analgesic effects or side-effects. Recent studies demonstrated that the transport of M6G across the BBB depends on an active transport mechanism, mediated by the 170-kD P-glycoprotein [14]. P-glycoprotein is an ATP-dependent P-glycoprotein [14]. P-glycoprotein is an ATP-dependent carrier system that acts as an active efflux pump to transport chemicals or metabolites from within the endothelial cell back to the blood compartment. Thus, P-glycoprotein poses a serious obstacle for the delivery of some drugs to CNS.
In patients with renal impairment, occurrence of adverse events might depend on co-medication as well. In a recent study of Lötsch et al. [18] M6G failed to demonstrate any analgesic effect after short-term i.v. administration in healthy volunteers. It can therefore be suspected that after single administration of morphine, brain concentrations of M6G are not high enough to produce an analgesic effect. Severe adverse events during morphine treatment in patients with renal impairment are almost always reported after repeated opiate administration.

In conclusion, our data show that CAPD patients accumulate morphine glucuronides after single i.v. administration of morphine, while systemic clearance of morphine is in the range observed in patients with normal kidney function. The accumulation of morphine glucuronides in serum is due to the substantially lowered clearance by CAPD or residual renal function. In view of the accumulation of an active metabolite, subsequent investigations have to assess the frequency of side-effects in patients on CAPD and the pharmacodynamic role of morphine metabolites in these patients. Better understanding of the transport mechanism of M6G on the BBB could help to identify patient at higher risk of developing opiate toxicity.

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References

1. Milne RW, Nation RL, Somogyi AA. The disposition of morphine and its 3- and 6-glucuronide metabolites in human and animals, and the importance of the metabolites to the pharmacological effects of morphine Drug Metab Rev 1996; 28: 345–472
2. Osborne RJ, Joel S, Trew D, Slevin M. Morphine and metabolite behavior after different routes of morphine administration. Demonstration of the importance of the active metabolite morphine-6-glucuronide. Clin Pharmacol Ther 1990; 47: 12–19

P-glycoprotein-function is known to be modulated by several other drugs. In vitro, inhibition of P-glycoprotein by verapamil results in an increase of M6G transport across the BBB [14]. In the case report published by Osborne et al. [5] patients with renal insufficiency received repeated doses of Omnopon® which, in addition to morphine, contains small quantities of papaverine. Calcium antagonists of the papaverine-type, like verapamil, are known to be very potent P-glycoprotein inhibitors [15]. It is therefore possible that adverse events in these patients were mediated by P-glycoprotein inhibition with subsequent greater amounts of M6G reaching the brain. In the study of Ashby et al. [6] chronically morphine-treated patients received concomitant drug treatment with corticosteroids, antidepressants, anticonvulsants, and sedatives. Some of these drugs, like corticosteroids (dexamethasone) or antidepressants (amitriptyline), are potent P-glycoprotein substrates or inhibitors [16,17].

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