STUDIES ON MORPHINE DISPOSITION: INFLUENCE OF RENAL FAILURE ON THE KINETICS OF MORPHINE AND ITS METABOLITES

J. W. SEAR, C. W. HAND, R. A. MOORE AND H. J. McQUAY

Prolonged and profound analgesia, sedation and ventilatory depression have been reported in patients suffering from renal failure and receiving parenteral doses of morphine [1-3]. Our previous studies suggested altered kinetics of morphine in anaesthetized patients receiving the opioid as part of a balanced anaesthetic technique for renal transplant surgery [4]. On the other hand, Aitkenhead and colleagues [5] and Woolner and colleagues [6] reported no alteration in parent drug disposition when i.v. morphine was administered to awake individuals with chronic renal failure. More recently, using a double radioimmunoassay technique, Chauvin and colleagues [7] reported unaltered morphine disposition in anaesthetized uraemic patients undergoing surgery for arterio-venous fistula formation. However, these authors did not assay the two glucuronides of morphine separately.

Criticisms and problems with many studies investigating the kinetics of morphine relate to assay methodology, and in particular to a lack of specificity of many radioimmunoassay antisera [8]. Recently, a differential radioimmunoassay technique has been reported that is specific for morphine, and also allows measurement of the two glucuronides of the opioid [9].

The present study has therefore re-investigated the pharmacokinetics of morphine both in healthy anaesthetized patients, and in patients with renal failure undergoing renal transplantation. The use of three separate antisera has allowed estimation of plasma concentrations of morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G).

SUMMARY

The influence of renal failure on the disposition of morphine and its metabolites was studied in nine patients with end-stage renal failure undergoing transplantation, and compared with five healthy anaesthetized patients. All patients received morphine sulphate pentahydrate 10 mg i.v. over 30 s, as part of a balanced anaesthetic technique. Venous blood samples were collected for up to 24 h, and plasma concentrations of morphine, morphine-3-glucuronide (M3G), and morphine-6-glucuronide (M6G) assayed by a differential radioimmunoassay method. There were no differences between the two groups for morphine elimination half-life (renal failure: 290 min; anaesthetized controls: 286 min), or clearance (renal failure: 533 ml min⁻¹; controls 741 ml min⁻¹). However, the volume of distribution at steady state was greater in the control group (241 litre v. 141 litre; P = 0.002). The peak concentrations of M3G and M6G were greater in the renal transplant patients (P = 0.001 and P = 0.01, respectively), as were the AUC (0-24 h) (P = 0.002 and P = 0.002). M6G has been shown to possess analgesic properties in both man and experimental animals, and therefore the increased AUC for M6G may contribute to the prolonged effect seen with morphine when given to patients with impaired renal function.
PATIENTS AND METHODS

The disposition of morphine was investigated in 14 patients, who gave their informed consent to the studies which were approved by the local research Ethics Committee.

Nine patients (four female; ages 19–48 yr, weights 46.8–70 kg) were studied while undergoing renal transplantation. Concurrent medication, including antihypertensive and anti-anginal drugs, was continued up to the morning of surgery, and additional drugs were given with premedication where appropriate. All the patients had undergone haemodialysis within the previous 6–20 h.

Patients were premedicated with oral diazepam 10 mg given 2 h before anaesthesia. Sleep was induced with thiopentone 3–4 mg kg$^{-1}$, and the trachea intubated after neuromuscular blockade was produced with vecuronium 0.1 mg kg$^{-1}$. Anaesthesia was maintained with nitrous oxide in oxygen supplemented with enflurane (up to 0.8% inspired concentration).

Following the onset of stable anaesthesia, morphine sulphate pentahydrate 10 mg in normal saline 10 ml (morphine 26.4 μmol) was injected into a flowing peripheral infusion over 30 s. Venous samples (from a central venous catheter) were collected before induction of anaesthesia, at 1, 2, 5, 10, 15, 30, 45, 60, 90, 120, 180 min and at appropriate times to 1440 min after i.v. injection of morphine. Blood samples were collected into tubes containing lithium heparin, plasma separated by centrifugation, and stored at −20 °C until analysis. Samples were assayed for morphine and its two glucuronides using three separate antisera under optimum conditions [9].

Data within the two groups were compared using the Mann–Whitney $U$ test. $P < 0.05$ was considered significant.

RESULTS

The conduct of anaesthesia was uneventful in all patients. Six of the transplant patients were receiving beta-adrenoceptor blocking drugs. The preoperative haemoglobin, plasma urea and creatinine concentrations in the transplant patients were in the ranges 5.8–10.9 g dl$^{-1}$, 9.0–33.9 mmol litre$^{-1}$ and 466–911 μmol litre$^{-1}$, respectively. Immediate postoperative creatinine clearances in the transplant patients were between 36 and 138 ml min$^{-1}$.

Plasma morphine concentrations declined in a curvilinear manner, with a terminal half-life between 204 and 350 min in the healthy patients (mean: 286 min), and 115 and 707 min (mean: 290 min) in the renal transplant patients (not significantly different). The derived kinetic parameters ($C/l_P$, MRT, $Vd^{ss}$) are shown for the two groups in table I.

However, there were differences in the peak concentration ($C_{max}$) and time to this peak ($T_{max}$) for the two glucuronide metabolites in the two patient groups (table II). Peak concentrations of $M3G$ ranged between 243 and 447 nmol litre$^{-1}$ in the healthy patients with $T_{max}$ between 30 and 90 min. In the recipients of renal transplants, $C_{max}$ was 720–1243 nmol litre$^{-1}$ and $T_{max}$ 60–240 min ($P = 0.001$ and 0.01, respectively). Similar differences existed for $M6G$, with peak concentrations of 21–112 nmol litre$^{-1}$ in the
TABLE I. Derived kinetic parameters for morphine in healthy anaesthetized patients (n = 5) and patients undergoing renal transplantation (n = 9). Data shown as mean (SD) [range]. **P = 0.002 (Mann-Whitney U test)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Anaesthetized patients</th>
<th>Transplant patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elimination half-life (min)</td>
<td>286.0 (53.1) [203.7-350.0]</td>
<td>290.4 (191.1) [114.9-707.1]</td>
</tr>
<tr>
<td>C/L (ml min⁻¹)</td>
<td>741.0 (169.0) [570.2-971.5]</td>
<td>533.0 (298.0) [225.4-925.5]</td>
</tr>
<tr>
<td>Vdss (litre)</td>
<td>240.8 (55.1) [195.4-334.9]</td>
<td>140.9 (37.8) [102.2-220.8]**</td>
</tr>
<tr>
<td>MRT (min)</td>
<td>326.6 (30.2) [326.6-351.4]</td>
<td>373.3 (264.5) [132.7-924.6]</td>
</tr>
<tr>
<td>AUC₀-24 (nmol litre⁻¹ min)</td>
<td>37044 (7940) [27158-46271]</td>
<td>65631 (34462) [28509-117605]</td>
</tr>
</tbody>
</table>

TABLE II. Concentration and time data for morphine-3-glucuronide and morphine-6-glucuronide in healthy anaesthetized patients and patients undergoing renal transplantation. Data shown as mean (SD) [range]. *P < 0.02; **P < 0.01; ***P < 0.001 (Mann-Whitney U test)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Anaesthetized patients</th>
<th>Transplant patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine-3-glucuronide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (nmol litre⁻¹)</td>
<td>320.3 (79.0) [242.5-447]</td>
<td>964.4 (191.1) [720-1243]</td>
</tr>
<tr>
<td>Tmax (min)</td>
<td>51.0 (25.1) [30-90]</td>
<td>137.8 (54.5) [60-240]</td>
</tr>
<tr>
<td>[AUC (nmol litre⁻¹ min)</td>
<td>123322 (22480) [90380-146712]</td>
<td>695542 (181813) [404182-1026364]</td>
</tr>
<tr>
<td>Morphine-6-glucuronide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (nmol litre⁻¹)</td>
<td>52.2 (40.6) [21.2-112.1]</td>
<td>126.5 (61.5) [50.3-252.4]</td>
</tr>
<tr>
<td>Tmax (min)</td>
<td>108.2 (45.5) [60-180]</td>
<td>162.2 (47.4) [120-270]</td>
</tr>
<tr>
<td>[AUC (nmol litre⁻¹ min)</td>
<td>15536 (7821) [8553-28296]</td>
<td>80206 (29867) [51773-117102]</td>
</tr>
<tr>
<td>Ratio Cmax M3G: Cmax M6G</td>
<td>10.2 (8.0)</td>
<td>8.7 (3.9)</td>
</tr>
<tr>
<td>AUC₀-24ₘₐₜ M6G: Morphine</td>
<td>0.43 (0.28)</td>
<td>1.78 (1.37)</td>
</tr>
</tbody>
</table>

healthy group, and 50–252 nmol litre⁻¹ in the transplant patients (P = 0.02). There were no differences in the Tₘₐₓ ranges for M₆G.

However, the AUC (0–1440 min) for M₃G and M₆G were significantly greater in those patients undergoing renal transplantation (P < 0.001) (table II, fig. 1). There was also a significantly greater value for the ratio AUC morphine-6-glucuronide/AUC morphine in the renal transplant patients (P < 0.02). In the nine patients with renal failure, there was no significant correlation (r = 0.264) between this ratio and immediate graft function expressed as the 24-h creatinine clearance.

The estimated half-lives in the transplant patients were 304–918 min for M₃G and 217–898 min for M₆G, compared with 173–324 min and 104–127 min in the healthy anaesthetized patients.

DISCUSSION

The disposition of morphine in renal failure patients undergoing transplantation was not significantly different from that in healthy anaesthetized patients, with the exception of a decrease in the volume of distribution at steady state (Vdss). This difference was observed also by Aitkenhead and colleagues in awake subjects [5], and by Chauvin and colleagues [7] in anaesthetized patients, in whom morphine concentrations were assayed by HPLC and RIA, respectively. A considerable variability in morphine kinetics in healthy anaesthetized patients has been reported [10–13]. This may relate to many factors such as study design, patient age and sex, anaesthetic technique, concurrent therapy, duration of sampling and assay methodology [14].

Comparing the mean data for healthy anaesthetized patients from the present study and those from Chauvin [7], the coefficients of variation for elimination half-life, clearance and apparent volume of distribution at steady state range between 20 and 30%, with no difference between the two studies. A similarly wide dispersion of data in both healthy and renal failure patients can be seen in the study of Aitkenhead and colleagues [5]. In the presence of renal failure, other factors may also interplay; these include a reduced total body water secondary to haemodialysis, and altered protein binding or plasma albumin concentrations.

Comparison of the data for healthy patients in
MORPHINE METABOLITES IN RENAL FAILURE

Fig. 1. Morphine clearance and area under concentration–time curves from 0–24 h for morphine, morphine-3-glucuronide and morphine-6-glucuronide following morphine 10 mg i.v. to healthy anaesthetized patients (black columns) (n = 5) and to patients undergoing renal transplantation (n = 9). Data shown as mean (SD). **P < 0.002 (Mann–Whitney U test).

this study and those for the anaesthetized group in the accompanying publication [15] show a longer elimination half-life and greater volume of distribution. This may be explained by the short sampling period in the previous study (180 min compared with 24 h), leading to an underestimation of the terminal half-life.

Why do these results differ from our earlier data [4]? Studies of the specificity of the RIA used in that paper reported a 1% molar cross reactivity of the antisera to morphine-3-glucuronide (the principal metabolite of morphine) and a 0.3% cross reactivity to normorphine [13]. Antisera produced by haptenization through 6-hemisuccinyl morphine also demonstrate significant cross reactivity to morphine-6-glucuronide. Boerner, Abbott and Roe [16] indicated a ratio of 100:1 for morphine-3-glucuronide to morphine-6-glucuronide in the urine of post-addict males. However, Svensson and colleagues have demonstrated greater concentrations of M6G—approximately 10% of M3G during chronic oral medication with morphine [17]. This is also in agreement with our own data following i.v. administration [9]. Hence our earlier morphine kinetics in patients with renal failure were inaccurate because of simultaneous measurement of both morphine and morphine-6-glucuronide [4].

Other data showing increased concentrations of M3G and M6G in patients with chronic renal failure have been reported [3, 18], in addition to altered kinetics of M6G when given i.v. to patients with renal failure compared with healthy volunteers [19]. Both of the studies reporting the disposition of morphine and its metabolites in renal failure [3, 18] indicated half-lives for M3G of 14.5–136 h, and M6G 38–103 h. Compared with these other reports, the shorter half-lives in our transplanted group may reflect restoration towards normal renal function that occurs following revascularization of the grafted kidney.

Morphine-6-glucuronide has been shown to be analgesically active when administered intracerebrally to rats, and to exhibit avid binding to opioid receptors in bovine brain [20–23]. In a preliminary study in man, Osborne [19] has reported that 1 mg of M6G provided analgesia lasting for 1–7 h. The increased peak concentrations and AUC for M6G in the patients with renal failure may be important in causing the enhanced clinical effects attributed to the parent opioid. Although the glucuronide metabolites are more polar and less lipid soluble than the parent compound, and hence show only slow diffusion into CSF, plasma accumulation of M6G may allow its more rapid diffusion into central nervous tissue, leading to the classical picture of respiratory depression [2, 3].

This present study has confirmed that renal dysfunction does not impair the clearance of morphine in the anaesthetized patient, but does alter clearance of the glucuronide metabolites. The clinical importance of this may relate to the net effect of a single dose of morphine being the sum of the effects of the parent compound and its active metabolite(s). If this is the case, increased M6G concentrations may predispose to a greater net effect for any given dose of morphine.

REFERENCES


