RELATIVE BIOAVAILABILITY OF CONTROLLED RELEASE MORPHINE TABLETS (MST CONTINUS) IN CANCER PATIENTS

P. POULAIN, P. J. HOSKIN, G. W. HANKS, O. A-OMAR, V. A. WALKER, A. JOHNSTON, P. TURNER AND G. W. AHERNE

Controlled release morphine tablets (MST Continus, MS Contin, MOS Contin) are used widely in the treatment of cancer pain. Controlled clinical trial data are limited [1, 2] but suggest that, for the majority of patients, twice daily administration of MST is equivalent to a 4-hourly regimen of aqueous morphine. This is supported by empirical clinical experience.

Investigations of the absolute bioavailability of MST in single dose studies have produced conflicting results. In one study in healthy volunteers, the mean systemic availability of MST in the first 7 h after administration was 18.3 % [3]. In contrast, in a study in patients, the bioavailability of MST was calculated to be 122 % [4].

An important difference in the methodology used in the two studies is that the first utilized a high performance liquid chromatography (HPLC) assay to measure plasma concentrations of unconjugated morphine [5, 6], whereas the second used a radioimmunoassay (RIA) utilizing antibodies raised to 6-succinylmorphine BSA [7]. The HPLC assay is a specific and sensitive method enabling the quantitative measurement of morphine and its main metabolites morphine-3-

SUMMARY

The bioavailability of oral controlled release morphine tablets (MST, Napp Laboratories) and oral morphine sulphate in aqueous solution (MSS) was compared in 10 patients with advanced cancer. Serum samples were analysed for morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) using a specific HPLC assay. The relative bioavailability of morphine with MST was significantly less than that with MSS (mean 80%, range 50–110%) although there was no difference between the formulations in the relative availability of M3G and M6G. There was no significant difference between the formulations in the serum concentration of morphine at 12 h. The mean ratios morphine:M6G:M3G (comparing areas under the serum concentration–time curves) were 1:9:56. There was a highly significant linear relationship between the dose administered and AUC for morphine, M3G and M6G after MSS; and for morphine after MST. Median t_{max} for morphine was 0.5 h with MSS and 2.5 h with MST; for M3G 1.5 h with MSS and 3.0 h with MST; and for M6G 1.5 h with MSS and 3.25 h with MST. A secondary peak of unconjugated morphine, which may represent enterohepatic circulation, was seen in several patients 2–4 h after administration of elixir and 4–6 h after administration of MST.

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assay) indicated a bioavailability of 86% relative to morphine sulphate in aqueous solution [10]. This figure is consistent with data from our earlier study in postoperative patients [11].

There is increasing evidence to suggest that the clinical effects of morphine, in particular its analgesic action, may result from not only the action of morphine itself, but also that of active metabolites, in particular morphine-6-glucuronide (M6G) [12, 13].

We have investigated the relative bioavailability of MST in patients with advanced cancer stabilized on oral morphine sulphate in aqueous solution (MSS), using an HPLC assay to measure both morphine and its principal metabolites.

PATIENTS AND METHODS

Patients with advanced cancer who were inpatients in the Continuing Care (palliative care) Unit at the Royal Marsden Hospital and who had pain requiring oral morphine were studied if their pain was controlled on a 4-hourly regimen of oral morphine sulphate (MSS) in the same dose for at least 5 consecutive days. The MSS was morphine sulphate in chloroform water with ethylene diamine tetracetic acid and benzoic acid as preservative. The concentration of MSS varied, according to the dose being administered, between the limits of 10–60 mg in 10 ml.

Patients whose clinical condition was poor or whose pain was not stable were excluded, as were patients receiving high daily doses of morphine (> 1 g) who would require a large number of tablets. Full explanation of the aims of the study and the procedures involved was given before consent to participate was obtained from patients. The study was approved by the Ethics Committee of the Royal Marsden Hospital.

A cannula was inserted into a convenient forearm vein and the study was extended over a period of 3 days. On the first study day, patients continued their usual 4-hourly doses of MSS and blood samples were taken over a 12-h period from the 8 a.m. dose. Sampling was performed at time zero and at 30-min intervals for 5 h, and at 7, 8, 11 and 12 h. On each occasion 10 ml of venous blood was taken, rolled in glass bottles without anticoagulant for at least 20 min, centrifuged at 3500 rev min⁻¹ and the serum separated and frozen immediately at −20 °C.

On the second day MSS was changed to MST, maintaining the same total daily dose in two equal parts. The final dose of MSS was given at 4 a.m. and the first dose of MST at 8 a.m. No blood samples were taken.

On the third day, blood samples were taken for a 12-h period following the 8 a.m. dose of MST, at the same times as on day 1.

On days 1 and 3, patients completed 10-cm visual analogue scales for pain intensity and pain relief at 8 a.m. and 8 p.m. and a four-point verbal rating scale for morphine-related side effects was completed each day.

Analytical method

Analysis of the samples was performed using an HPLC assay developed from the method of Svensson [5]. Extraction of serum samples was performed before analysis using multiple washings through two C18 SEP-PAK cartridges with a Vac-elute system. The chromatography used a 500-μl sample injected by autosampler. Detection of M3G was by u.v. fluorescence at 210 nm using an FS 970 LC Flurometer, and of morphine and M6G was by electrochemical detection using a two-channel detector and an additional guard cell. The intra-assay coefficient of variation using this assay was < 8% for morphine, < 6% for M3G and < 13% for M6G.

Statistical analysis

The area under the serum concentration–time curve (AUC) was calculated using STRIPE, an interactive curve stripping program [14]. Student's paired t test was used to compare assay techniques, AUC from the different preparations and visual analogue scale scores.

RESULTS

Ten patients were studied: six females (aged 60–79 yr, weights 35–90 kg) with cancer of the breast (three), lung (two) and colon (one); and four males (aged 44–72 yr, weights 65–102 kg) with cancer of the lung (two), kidney (one), and a soft-tissue sarcoma (one).

The dose range of morphine was 40–360 mg day⁻¹ (0.7–5.5 mg kg⁻¹). All patients had normal renal and hepatic function.

The blood samples were timed to give an accurate estimate of a 4-h period of administration for morphine elixir and of a 12-h-period of administration for MST. In calculating the AUC for MST, therefore, the 12-h data were used, but for morphine elixir the AUC for only the first 4 h
was calculated and multiplied by three for the purpose of comparison (table I).

There was a highly significant relationship between dose and AUC with both formulations: $r = 0.95$, $P < 0.001$ MSS; $r = 0.91$, $P < 0.001$ MST. However, the mean relative bioavailability of MST compared with MSS of 80% (range 50–110%) is significantly lower ($t = 2.5$, $P < 0.05$). There was no significant difference in serum concentrations of morphine produced by MSS and MST at 12 h.

The individual serum concentration–time curves for the 10 patients are shown in figure 1. A secondary peak in the concentration of unconjugated morphine is seen 2–4 h after administration of morphine elixir in patients Nos 1, 2, 3, 5, 6, 7 and 10. Similarly in the MST curves for patients Nos 3, 5, 8, 9 and 10 there appears to be a secondary peak 4–8 h after dosing.

Attenuation of the peak serum concentration ($C_{\text{max}}$) for morphine was seen after MST. The ratio of $C_{\text{max}}$ after MST to $C_{\text{max}}$ after MSS was 1.32 (SEM 0.13), while the dose ratio MST:MSS was 3. A similar effect was seen with the two metabolites, the mean ratio $C_{\text{max}}$ MST:$C_{\text{max}}$ MSS being 1.47 (0.26) for M3G and 1.25 (0.10) for M6G (table II).

Peak serum concentrations of morphine were achieved between 0.5 and 2 h after administration of morphine elixir (median 0.5 h) and at 0.5–4 h (median 2.5 h) after MST (table III).

For MSS there was a significant correlation between the AUC for both metabolites and dose of morphine (M3G: $r = 0.74$, $P < 0.01$; M6G: $r = 0.79$, $P < 0.001$) but this was not so for MST (M3G: $r = 0.32$; M6G: $r = 0.46$) (table IV). No significant difference between the formulations was seen in the relative bioavailability of either metabolite, although there was wide individual variation.
of pain intensity and pain relief should be shown previously in both open and controlled to provide equally good pain relief, as has been interpreted in this light. However, MST appeared
This study was primarily a pharmacokinetic

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>12-h dose (mg)</th>
<th>MSS M3G M6G</th>
<th>MST M3G M6G</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>19 477 72</td>
<td>26 855 114</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>19 426 59</td>
<td>15 1414 74</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>37 728 61</td>
<td>52 1139 77</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>20 1871 440</td>
<td>39 3395 527</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>26 827 145</td>
<td>28 782 189</td>
</tr>
<tr>
<td>6</td>
<td>90</td>
<td>50 2477 491</td>
<td>67 4481 718</td>
</tr>
<tr>
<td>7</td>
<td>120</td>
<td>51 2886 473</td>
<td>104 3300 539</td>
</tr>
<tr>
<td>8</td>
<td>120</td>
<td>97 3549 574</td>
<td>128 4498 907</td>
</tr>
<tr>
<td>9</td>
<td>180</td>
<td>122 3073 558</td>
<td>136 2080 649</td>
</tr>
<tr>
<td>10</td>
<td>180</td>
<td>115 3252 617</td>
<td>88 1409 336</td>
</tr>
</tbody>
</table>

The values for the AUC corrected to a standard dose of morphine 100 mg are shown in table V. The mean ratios morphine:M6G:M3G were 1:9:56.

Analysis of the VAS ratings for pain and pain relief (table VI) showed no difference between the two study days, and there was no difference in the incidence or severity of adverse effects.

**DISCUSSION**

This study was primarily a pharmacokinetic investigation and was not blinded, so the ratings of pain intensity and pain relief should be interpreted in this light. However, MST appeared to provide equally good pain relief, as has been shown previously in both open and controlled

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>AUC_{12h} (ng h ml^{-1})</th>
<th>Relative Bioavailability (MST/MSS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>4695 701</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>4041 456</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>6890 546</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>20784 4757</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>7503 1475</td>
</tr>
<tr>
<td>6</td>
<td>90</td>
<td>13589 3670</td>
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<tr>
<td>7</td>
<td>120</td>
<td>31963 4975</td>
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<td>120</td>
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<td>180</td>
<td>33181 5664</td>
</tr>
<tr>
<td>10</td>
<td>180</td>
<td>32791 6006</td>
</tr>
</tbody>
</table>

**TABLE VI. Visual analogue scales for pain (0 = no pain; 100 = worst possible pain) and pain relief (0 = no relief; 100 = complete pain relief). Mean (SEM) (mm)**

<table>
<thead>
<tr>
<th>Time</th>
<th>Pain</th>
<th>Pain relief</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 a.m.</td>
<td>12.3 (3.0)</td>
<td>10.3 (2.7)</td>
</tr>
<tr>
<td>8 p.m.</td>
<td>14.8 (3.7)</td>
<td>14.1 (4.1)</td>
</tr>
</tbody>
</table>

**BRITISH JOURNAL OF ANAESTHESIA**

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<table>
<thead>
<tr>
<th>Aqueous morphine</th>
<th>12.3 (3.0)</th>
<th>14.8 (3.7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MST</td>
<td>10.3 (2.7)</td>
<td>14.1 (4.1)</td>
</tr>
<tr>
<td>t</td>
<td>1.220</td>
<td>0.498</td>
</tr>
<tr>
<td>P</td>
<td>&gt;0.2</td>
<td>&gt;0.5</td>
</tr>
</tbody>
</table>

**TABLE IV. Twelve-hour cumulative area under the serum concentration-time curve (AUC_{12h}) and relative bioavailability for morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G)**

The values for the AUC corrected to a standard dose of morphine 100 mg are shown in table V. The mean ratios morphine:M6G:M3G were 1:9:56.

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RELATIVE BIOAVAILABILITY OF MST

studies [1, 2, 15, 16] in cancer patients. Similarly, there was no difference in side-effects.

The relative bioavailability of MST was measured 24 h after changing to this formulation. The time to achieve steady state is influenced by the absorption half-life, in addition to the elimination half-life, although the latter is the major determinant. We believe most patients will have achieved steady state by this time if they have already been stabilized on morphine elixir, as the elimination of morphine is not changed by this formulation.

Our pharmacokinetic data indicate that MST has a slightly lower systemic availability for morphine compared with MSS, although the relative amounts of the metabolites M6G and M3G produced by the two formulations was similar. These data, our clinical trial data [2] and those of others [1], refute the suggestion that MST may be more bioavailable [4, 17] and, therefore, relatively more potent than morphine in solution [18].

The results for M3G and M6G are of particular interest, since there are few comparable data in the literature. Sawe and her colleagues have demonstrated ratios of 1:24.4 for morphine:M3G and 1:2.5 for morphine:M6G after small single doses in cancer patients [19] and ratios of 1:34 and 1:3.9, respectively, in four patients after chronic use [20]. The corresponding ratios in this larger study were 1:56 and 1:9, which are considerably higher. We have suggested that M6G may contribute significantly to the analgesic activity of chronically administered oral morphine [12]. In our study similar amounts of M6G were produced by both MSS and MST. This may account for the equal efficacy of MST, although its bioavailability for unconjugated morphine appears to be slightly lower than that of MSS.

The median $t_{\text{max}}$ for MST in the present study (2.5 h) is similar to figures obtained in healthy volunteers after single (2.4 h–2.7 h) [3] and repeated doses (2.3 h) [10]. Similarly, the median $t_{\text{max}}$ for the solution of 0.5 h (range 0.5–2.0 h) is close to that found in healthy volunteers (0.8 h) [10] and in cancer patients (0.8 h) [19].

A recent investigation of the steady state pharmacokinetics of MST in healthy volunteers found a bioavailability of 86% relative to MSS [10]. The authors also found an “attenuation by 50% of the peak plasma morphine concentrations obtainable with controlled release morphine”.

We have shown a similar attenuation of peak serum concentrations following MST.

The secondary peak in the serum concentrations of unconjugated morphine in several patients is of considerable interest. It may represent enterohepatic circulation of morphine. This has been demonstrated clearly in rodents [21, 22] and we have recently shown high biliary concentrations of morphine, M3G and M6G in man [23]. A previous study (in healthy volunteers) showed a secondary peak in plasma concentrations of morphine 4–5 h after administration of MST [24]. In our data the secondary peak is seen most clearly in MSS curves between 2 and 4 h after dosing. We have suggested that enterohepatic circulation may be part of the explanation for the greater efficacy of repeated doses or oral morphine compared with single doses [12].

ACKNOWLEDGEMENTS

P. P. was supported by the Association pour la Recherche sur le Cancer, P. J. H. by the Cancer Research Campaign and V. A. W. by the Sir Halley Stewart Trust. This work was also supported by grants from the Royal Marsden Hospital Clinical Research Committee, and Napp Laboratories Ltd.

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