DISPOSITION OF MORPHINE-6-GLUCURONIDE AND MORPHINE IN HEALTHY VOLUNTEERS

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SUMMARY

The pharmacokinetics and subjective side effects of i.v. morphine sulphate 120 µg kg⁻¹ and morphine-6-glucuronide (M6G) 30 µg kg⁻¹ were determined in six healthy volunteers, using a placebo-controlled, single-blind randomized crossover design. Five of these volunteers underwent an additional (non-randomized) study of M6G 60 µg kg⁻¹. Subjective side effects were similar following both drugs, but of shorter duration following M6G. Morphine was not detected after administration of M6G. For M6G 30 µg kg⁻¹ the mean (SD) volume of distribution, elimination half-life and clearance were 29.38 (18.36) litre, 2.05 (1.2) h and 187.81 (37.41) litre h⁻¹, respectively. These values were not significantly different from those obtained for M6G 60 µg kg⁻¹. In all subjects the volumes of distribution and clearances were significantly smaller for M6G than for morphine, but the elimination half-lives were similar.

KEY WORDS

Analgesics: morphine, morphine-6-glucuronide Pharmacokinetics: morphine, morphine-6-glucuronide.

Pharmacologically active metabolites are of great interest to clinicians as they may augment or inhibit the effects of the parent drug, or enhance its toxicity [1]. Morphine-6-glucuronide (M6G) may make a significant contribution to the apparent analgesic efficacy of morphine [2–4], although previous authors have estimated that only 0.3–6.4% of administered morphine is recovered in urine as this metabolite [5, 6].

M6G has avid affinity for mu 1 and mu 2 receptors, to which it binds stereospecifically with an affinity similar to that of morphine [7, 8]. In rodents, M6G administered by the subcutaneous or intracerebral routes has a greater analgesic potency and a longer duration of action than morphine [9], and on direct injection into the peri-aqueductal grey matter it is 20 times as potent [8].

It is desirable to have a full understanding of the disposition and clinical effects of a pharmacologically active metabolite. In order to obtain this, it is necessary to administer the metabolite independently of the parent drug and thereby determine its volume of distribution, clearance and half-life. It may then be possible to calculate the percentage of the parent drug which is converted to the metabolite and enters the plasma compartment.

The object of this study was to obtain data on the disposition of M6G, together with its subjective effects in volunteers, and to compare them with those of morphine.

SUBJECTS AND METHODS

Six healthy subjects (three male, mean (SD) age 30.6 (2.5) yr, mean (SD) weight 68.3 (8.7) kg) gave informed consent to the study, which was approved by the hospital Ethics Committee. Each subject received morphine sulphate 120 µg kg⁻¹, M6G 30 µg kg⁻¹ and placebo (isotonic saline) on three non-consecutive mornings, in accordance with a randomized single-blind crossover design. Five of these subjects underwent an additional, single-blind, non-randomized study of M6G 60 µg kg⁻¹.

An i.v. cannula was inserted into each arm, and test drugs given over 4 min. Venous samples were obtained (from the contralateral arm) at 5, 10, 20,
40, 80, 160 and 320 min after injection of each test drug. Plasma was separated by immediate centrifugation and stored at −70 °C until analysed for morphine and M6G concentrations. Adverse reactions during or following the study were assessed by direct questioning, and the times to complete recovery were recorded.

Plasma concentrations of morphine and M6G were analysed simultaneously using high pressure liquid chromatography with recommended modifications [10, 11]. The standards used were morphine sulphate (McFarland Smith) and M6G (Ultrafine Chemicals). Calibration curves were constructed daily for both drugs, and were linear with correlation coefficients greater than 0.9970. The limit of detection for morphine and M6G was 1 ng ml⁻¹.

**Kinetic calculation**

Plasma morphine and M6G concentration-time data were analysed using an interactive curve-stripping program, using weighted non-linear least square regression analysis [12, 13]. For morphine (M) and directly injected M6G (M6G) the data were fitted to a two-compartment model in all subjects. For analysis of M6G concentrations occurring as a result of morphine metabolism (M6Gi), a one-compartment model was used. The areas under the concentration–time curves were calculated using the trapezoid rule and extrapolations to infinity estimated using the terminal elimination half-lives of the respective curves. The following kinetic parameters were obtained:

\[
\begin{align*}
Tm(h) & \quad \text{Terminal half-life for morphine} \\
AUCM_{0-320}(\text{ng h litre}^{-1}) & \quad \text{Area under the conc–time curve for morphine (0–320 min)} \\
AUCM_{0-\infty}(\text{ng h litre}^{-1}) & \quad \text{Area under the conc–time curve for morphine (0 to infinity)} \\
Vd^M(\text{litre}) & \quad \text{Volume of distribution for morphine} \\
Cl^M(\text{litre h}^{-1}) & \quad \text{Clearance for morphine} \\
Tm6G(h) & \quad \text{Terminal half-life for M6G} \\
AUCM6G_{0-320}(\text{ng h litre}^{-1}) & \quad \text{Area under the conc–time curve for M6G (0–320 min)} \\
AUCM6G_{0-\infty}(\text{ng h litre}^{-1}) & \quad \text{Area under the conc–time curve for M6G (0 to infinity)} \\
Vd^M6G(\text{litre}) & \quad \text{Volume of distribution for M6G} \\
Cl^M6G(\text{litre h}^{-1}) & \quad \text{Clearance for M6G} \\
AUCM6Gi_{0-320}(\text{ng h litre}^{-1}) & \quad \text{Area under the conc–time curve for M6Gi (0–320 min)} \\
AUCM6Gi_{0-\infty}(\text{ng h litre}^{-1}) & \quad \text{Area under the conc–time curve for M6Gi (0–infinity)}
\end{align*}
\]

The fraction (FM) of the i.v. dose of morphine metabolized to M6G and appearing in the plasma was calculated from equation (1), and the ratio of the elimination rate constants for M6G and morphine (kM6G : km) calculated from equation (2) [11]:

\[
FM = \frac{\text{AUCM6Gi}_{0-\infty}}{\text{AUCM}_{0-\infty}} \times \frac{Cl^M}{Cl^M6G}
\]

\[
kM6G : km = \frac{Cl^M6G}{Cl^M} \frac{Vd^M}{Vd^M6G}
\]

**Statistical methods**

The results, presented as mean (sd) and range, were analysed using the Mann–Whitney U test, with P < 0.05 being taken as the minimum level of significance.

**RESULTS**

**Kinetic data**

In all subjects M6Gi was detected in plasma within 10 min of administration of morphine. The concentrations reached were greater than those of morphine at, and at all times after, 80 min. Morphine was not detected after administration of M6G.

Mean plasma concentration–time curves for morphine, M6Gi and M6G at the two doses investigated are shown in figure 1. The elimination half-lives (Tm) for morphine and M6G were similar, but the apparent volumes of distribution and total body clearances were significantly smaller for M6G than for morphine (P < 0.05) (table I). The mean (sd) percentage of morphine metabolized to M6Gi (FM) was 11.5

![Fig. 1. Semi-logarithmic plots of morphine and morphine-6-glucuronide concentrations in normal volunteers. □ = Morphine sulphate 120 μg kg⁻¹ (n = 6); △ = morphine-6-glucuronide 30 μg kg⁻¹ (n = 6); ○ = morphine-6-glucuronide 60 μg kg⁻¹ (n = 5); ■ = morphine-6-glucuronide following morphine.](https://academic.oup.com/bja/article-abstract/66/1/103/244696)
MORPHINE-6-GLUCURONIDE DISPOSITION

Table I. Pharmacokinetic parameters for i.v. morphine and morphine-6-glucuronide (mean (SD) [range])

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Morphine (120 µg kg⁻¹)</th>
<th>M6G (30 µg kg⁻¹)</th>
<th>M6G (60 µg kg⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng litre⁻¹)</td>
<td>302.1 (163.9)</td>
<td>28.83 (16.08)</td>
<td>155.47 (49.26)</td>
</tr>
<tr>
<td></td>
<td>[105.4-531.8]</td>
<td>[16.0-60.4]</td>
<td>[101.4-236.6]</td>
</tr>
<tr>
<td></td>
<td>[105.4-531.8]</td>
<td>[16.0-60.4]</td>
<td>[101.4-236.6]</td>
</tr>
<tr>
<td>T½ (h)</td>
<td>2.03 (1.35)</td>
<td>1.88 (1.28)</td>
<td>2.05 (1.20)</td>
</tr>
<tr>
<td></td>
<td>[0.9-3.86]</td>
<td>[0.66-4.21]</td>
<td>[0.62-3.40]</td>
</tr>
<tr>
<td></td>
<td>[0.9-3.86]</td>
<td>[0.66-4.21]</td>
<td>[0.62-3.40]</td>
</tr>
<tr>
<td>AUC₁−∞ (ng h litre⁻¹)</td>
<td>139.3 (48.9)</td>
<td>96.7 (71.16)</td>
<td>208.8 (55.4)</td>
</tr>
<tr>
<td></td>
<td>[84.1-199.7]</td>
<td>[46.2-190.3]</td>
<td>[144.0-275.0]</td>
</tr>
<tr>
<td></td>
<td>[84.1-199.7]</td>
<td>[46.2-190.3]</td>
<td>[144.0-275.0]</td>
</tr>
<tr>
<td>AUC₀−t₅₀ (ng h litre⁻¹)</td>
<td>116.1 (44.16)</td>
<td>58.13 (50.75)</td>
<td>177.19 (47.37)</td>
</tr>
<tr>
<td></td>
<td>[73.4-188.5]</td>
<td>[21.0-137.4]</td>
<td>[117.9-246.8]</td>
</tr>
<tr>
<td></td>
<td>[73.4-188.5]</td>
<td>[21.0-137.4]</td>
<td>[117.9-246.8]</td>
</tr>
<tr>
<td>CI (litre h⁻¹)</td>
<td>1057.4 (498.8)</td>
<td>187.8 (37.4)</td>
<td>127.4 (37.1)</td>
</tr>
<tr>
<td></td>
<td>[667.6-2022.7]</td>
<td>[126.2-230.8]</td>
<td>[99.0-189.0]</td>
</tr>
<tr>
<td></td>
<td>[667.6-2022.7]</td>
<td>[126.2-230.8]</td>
<td>[99.0-189.0]</td>
</tr>
<tr>
<td>Vd∞ (litre)</td>
<td>180.6 (81.5)</td>
<td>29.4 (18.4)</td>
<td>19.3 (7.5)</td>
</tr>
<tr>
<td></td>
<td>[72.4-287]</td>
<td>[8.7-54.8]</td>
<td>[12.3-30.3]</td>
</tr>
</tbody>
</table>

Table II. Subjective side effects of morphine and morphine-6-glucuronide

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Placebo (n = 6)</th>
<th>Morphine (120 µg kg⁻¹) (n = 6)</th>
<th>M6G (30 µg kg⁻¹) (n = 6)</th>
<th>M6G (60 µg kg⁻¹) (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light headedness</td>
<td>1/6</td>
<td>6/6</td>
<td>6/6</td>
<td>5/5</td>
</tr>
<tr>
<td>Sedation</td>
<td>1/6</td>
<td>6/6</td>
<td>4/6</td>
<td>4/5</td>
</tr>
<tr>
<td>Nausea</td>
<td>0/6</td>
<td>5/6</td>
<td>0/6</td>
<td>2/5</td>
</tr>
<tr>
<td>Itching</td>
<td>0/6</td>
<td>2/6</td>
<td>0/6</td>
<td>0/5</td>
</tr>
<tr>
<td>Rash</td>
<td>0/6</td>
<td>2/6</td>
<td>0/6</td>
<td>0/5</td>
</tr>
<tr>
<td>Heavy/aching muscles</td>
<td>0/6</td>
<td>3/6</td>
<td>4/6</td>
<td>4/5</td>
</tr>
<tr>
<td>Mean (SD) time to complete recovery (h)</td>
<td>0 (5)</td>
<td>15 (5)</td>
<td>4 (1)</td>
<td>6 (2)</td>
</tr>
</tbody>
</table>

(9.1)% as calculated from concentration–time data extrapolated to infinity (molar ratios).

Subjective side effects

All volunteers reported some subjective side effects after both morphine and M6G, but the time taken for full recovery was shorter after M6G (table II).

DISCUSSION

The most striking aspect of M6G among the opioids is its small volume of distribution (< 0.5 litre kg⁻¹) and low clearance. This is apparent from the initial high plasma concentrations and gradual decay.

The results of the present study demonstrate that the terminal half-life of M6Gi is not significantly different from the terminal half-life of the parent drug or M6G administered directly. The only reported previous pharmacokinetic study of i.v. M6G in man with normal renal function (one patient following 1 mg/70 kg) [2] gave a terminal elimination half-life of about 2 h, which is in accordance with our findings.

As the concentration of M6Gi declines in parallel with morphine in the terminal phase, one may deduce that the elimination rate constant for M6Gi is greater than that of morphine, and that the decay of the concentration–time curve for M6Gi is limited by the rate of formation of M6Gi [1].

Previous studies have demonstrated the appearance of M6G in human CSF following oral and parenteral administration of morphine [3]. It is intriguing that an opioid, which is highly polar and less lipophilic than morphine, is able to penetrate the blood–brain barrier, as has been shown in animals and man [3, 14]. There is no identifiable system for active transport of M6G into CSF, nor any evidence for its metabolism in the CNS in vivo [15, 16], although human neural
tissue is capable of catalysing the conversion of morphine to M6G in vitro [17]. Diffusion of a drug across the blood–brain barrier is dependent on the plasma–brain concentration gradient of the unbound fraction, and the lipid solubility, degree of ionization and molecular conformation at physiological pH.

Our results show that the plasma volume is greater than 10% of the total volume of distribution of M6G, and the ratio of the plasma volume to the total volume of distribution ($V_p:Vd_{tot}$) for M6G is five times greater than the $V_p:Vd_{tot}$ ratio for morphine. The high concentrations of this metabolite present in the plasma compartment may facilitate penetration into the CNS. The terminal half-life of intrathecally administered M6G in CSF exceeds that of morphine [16], a further factor contributing to its therapeutic importance.

The half-lives of M6G and M6G are prolonged in patients with impaired renal function [2, 18] and an increase in AUC for M6G in anaesthetized patients (caused probably by decreased renal blood flow) has been reported [19]. The reduction in plasma proteins and alterations in their binding characteristics which occur in renal insufficiency [1] may contribute further to increased concentrations of free M6G. These considerations underline the relevance of M6G in producing toxicity in these patients, particularly in relation to respiratory function [21, 21].

M6G exerts an inhibitory action on C-fibre evoked potentials in the rat spinal cord after both direct application and systemic injection [22]. Its potency in this model was 13 times that of morphine, and in man intrathecal M6G has a greater potency than intrathecal morphine [16]. These findings, together with its interesting pharmacokinetic profile and low incidence of side effects, warrant further investigation to establish the relative analgesic potency of i.v. M6G in man.

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