PHARMACOKINETICS AND ANALGESIC EFFECT OF SLOW-RELEASE ORAL MORPHINE SULPHATE IN VOLUNTEERS

M. VATER, G. SMITH, G. W. AHERNE AND A. R. AITKENHEAD

SUMMARY
Sustained-release oral morphine sulphate (MST) 20 mg was administered to 11 healthy volunteers. Mean peak plasma morphine concentration was 14.8 ng ml⁻¹, and occurred at a mean time of 142.5 min after ingestion. Analgesia assessed by an ischaemic forearm pain test increased to a maximum approximately 40 min after the calculated peak plasma concentration of morphine had been achieved, and remained greater than control values as plasma morphine concentration decayed. However, there was not a significant correlation between analgesia and plasma morphine concentration. This may result from delay in brain penetration by morphine. The mean systemic availability of morphine in the first 7 h after administration of MST was 18.3%.

Sustained-release oral morphine sulphate (MST Continus: Napp Laboratories), has become popular as an analgesic for the relief of chronic pain. It has also been found to be effective in relieving acute pain after cholecystectomy or hysterectomy (Fell, Chmielewski and Smith, 1982).

Only two limited studies have been published of plasma morphine concentrations following the administration of MST. Leslie, Rhodes and Black (1980) found that peak concentrations occurred between 1 and 3 h after administration, and decayed over the subsequent 10 to 12 h. Hanks and colleagues (1981) attempted to relate plasma morphine concentrations to the intensity of pain following dental extraction. They found that peak concentrations were achieved 3.3 h following ingestion. It was also noted that there was a negative correlation between plasma morphine concentration and linear analogue pain score.

Estimates of the plasma morphine concentration required to provide adequate analgesia for post-operative or chronic pain vary from 23 ng ml⁻¹ (Nayman, 1979) to 50 ng ml⁻¹ (Berkowitz et al., 1975).

The purpose of the present study was to define more precisely the pharmacokinetic profile of MST, and the relationship between plasma morphine concentration and analgesia.

SUBJECTS AND METHODS
Eleven healthy volunteers (six female) aged between 24 and 40 yr, and with a weight of 59.6 ± 3.0 kg (mean ± SEM) were studied. Subjects were fasted for 6 h before the oral administration of two 10-mg MST-1 tablets. The study was passed by the District ethics committee and informed consent was obtained from each subject.

A cannula was inserted to an antecubital vein under local anaesthesia to facilitate the sampling of venous blood. Blood was obtained at 30-min intervals for 3 h following ingestion, and thereafter at 1-h intervals for a further 4 h.

Samples were centrifuged immediately, and the plasma stored at -70 °C before analysis for morphine concentration by both high pressure liquid chromatography (HPLC) and radioimmunoassay (RIA). The HPLC technique measured free morphine after extraction from plasma with chloroform (Aitkenhead et al., 1984). The RIA used goat antiserum, and cross-reacted with morphine-3-glucuronide by less than 5% (Aherne, 1982). For this reason, plasma morphine measured by RIA is referred to in this study as "cross-reacting morphine".

Analgesia was assessed using a method similar to that of Harrison and Bigelow (1943). A sphygmanometer cuff was placed around the elevated, dominant arm, and inflated to 200 mm Hg. A second, rolled cuff connected to an anaeroid gauge (fig. 1) was pre-inflated to a pressure of 100 mm Hg for male subjects and 200 mm Hg for females. Subjects squeezed the second cuff in the palm of the hand at 1 Hz until the needle reached the maximum value on the scale. When ischaemic pain in the forearm be-
came intolerable, the first cuff was deflated, and the time noted. This was termed "ischaemic tourniquet time" (ITT). Control ITT values were obtained 20 min, 10 min and immediately before the ingestion of MST. The test was repeated on each occasion blood was sampled.

Nine of the subjects received morphine 0.125 mg kg\(^{-1}\) i.v. on a separate occasion (Aitkenhead et al., 1984). Plasma morphine concentrations at sampling times up to 2 h after i.v. administration were measured using HPLC. Data from these subjects were used to assess the systemic availability of morphine after the administration of MST.

The analysis of the plasma morphine concentrations following i.v. administration is described elsewhere (Aitkenhead et al., 1984). Plasma morphine concentration–time data after ingestion of MST were analysed for each individual using non-weighted, non-linear least squares regression analysis. A one-compartment model with first-order input and output was assumed. Values for maximum concentration (\(C_{\text{max}}\)) and time to maximum concentration (\(t_{\text{max}}\)) were derived from standard formulae (Gibaldi and Perrier, 1975). The cumulative areas under the plasma concentration–time curve for 7 h (\(\text{AUC}^7\)) and, by extrapolation, 8 h (\(\text{AUC}^8\)), were calculated. Using data from the nine subjects given morphine by both routes, the fraction of MST available to the systemic circulation during the first 7 h (\(F\)) was calculated for each subject from the formula:

\[
F = \frac{\text{i.v. dose}}{\text{MST dose}} \times \frac{\text{AUC}^7}{\text{AUC}^7_{\text{irr}}}
\]

where \(\text{AUC}^7_{\text{irr}}\) = cumulative area under the plasma morphine concentration–time curve following i.v. administration, extrapolated to 7 h.

Statistical analysis of changes in ITT was performed using analysis of variance and a paired \(t\) test, with \(P<0.05\) being taken to represent statistical significance.

RESULTS

Mean plasma morphine concentrations and mean ITT for all 11 subjects at each time of sampling are shown in figure 2. The maximum mean prolongation of ITT occurred later than the mean peak measured plasma morphine concentration, and mean ITT remained relatively more increased than mean plasma morphine concentration until sampling was discontinued at 7 h. Changes in ITT with time were significant (\(F=2.18, P<0.05\)). The in-
crease in ITT compared with the control value was statistically significant at all times except 30 min. There was no significant correlation ($r = 0.171$, $P > 0.05$) between ITT and plasma morphine concentration (fig. 3).

Mean plasma morphine concentrations and mean plasma “cross-reacting morphine” concentrations at each sampling point are shown in figure 4. Mean $C_{\text{max}}$, calculated from the best fitting curve for the plasma concentration–time data for each individual (fig. 5), was significantly greater for “cross-reacting morphine” (table I). There was no significant difference between mean $t_{\text{max}}$ for morphine and “cross-reacting morphine”.

The calculated mean fractional systemic availability ($F$) of MST at 7 h was $0.183 \pm 0.017$ (mean $\pm$ SEM).

Eight subjects given MST experienced dysphoria, and six drowsiness, during the period of observation.

**DISCUSSION**

Plasma concentrations of morphine measured with HPLC were significantly lower at all sampling times after 30 min than those of “cross-reacting morphine” measured using RIA. The goat antiserum used in the RIA technique utilized in this study cross-reacted by up to 5% with the morphine-3-glucuronide present in plasma, in addition to detecting free morphine. Morphine-3-glucuronide is the principal hepatic metabolite of morphine. Plasma concentrations of glucuronide exceed those of free morphine within 10 min of i.v. administration of the drug, and by 90 min, the concentration of free morphine is less than 10% of the total detectable morphine (Murphy and Hug, 1981). After oral administration, metabolism to glucuronide occurs in the wall of the small intestine as well as in the liver.

**TABLE I. Mean (SEM) values derived from analysis of plasma concentration–time curves after morphine assay with high pressure liquid chromatography (HPLC) or radio-immunoassay (RIA)**

<table>
<thead>
<tr>
<th></th>
<th>HPLC</th>
<th>RIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng ml$^{-1}$)</td>
<td>14.83 (1.44)</td>
<td>31.43 (2.11)</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (min)</td>
<td>142.5 (27.0)</td>
<td>163.2 (23.1)</td>
</tr>
<tr>
<td>AUC$^1$ (ng h ml$^{-1}$)</td>
<td>79.3 (7.4)</td>
<td>161.2 (11.5)</td>
</tr>
<tr>
<td>AUC$^2$ (ng h ml$^{-1}$)</td>
<td>86.9 (26.9)</td>
<td>175.4 (44.1)</td>
</tr>
<tr>
<td>Elimination half-life (min)</td>
<td>246.0 (35.0)</td>
<td>226.8 (59.8)</td>
</tr>
</tbody>
</table>
Fig. 3. The relationship between plasma morphine concentration and ITT in 11 subjects.

Fig. 4. Comparison between mean plasma morphine concentration measured using HPLC (---) and mean plasma "cross-reacting morphine" concentration measured using RIA (-----). Bars represent SEM. Data from 11 subjects.
Using HPLC to measure free morphine, we found that, from 60 to 420 min after administration of MST, mean plasma morphine concentration was between 40 and 50% of mean "cross-reacting morphine" concentration. As our RIA method detected up to 5% of morphine-3-glucuronide, it can be estimated that glucuronide concentrations were up to 20 times those of free morphine during this period. Hanks and colleagues (1981), using the same RIA antiserum as ourselves, found that $C_{\text{max}}$ was 55.0± 14.8 ng ml$^{-1}$ (mean ± SEM), $t_{\text{max}}$ was 3.3± 0.5 h, and AUC at 8 h was 250.9± 25.7 ng h ml$^{-1}$ in a group of young adult patients who had undergone dental extraction during general anaesthesia. These values are all of slightly greater magnitude than the corresponding figures from the present study (table I). This may be accounted for by differences in absorption, distribution and metabolism between normal subjects and patients in the period immediately after operation.

The tourniquet test used was a modification of an objective method of measuring ischaemic forearm pain (Harrison and Bigelow, 1943). A similar technique used by Clements and Nimmo (1981) to quantify the analgesic effect of ketamine produced a mean control value (75 s) which was in close agreement with that in the present study. The mean maximum increase in ITT in our study (45 s) was greater than that produced by ketamine 250 μg kg$^{-1}$ (30 s).

Changes in ITT in the present study lagged behind plasma morphine concentrations. This may reflect the delay in equilibration of morphine between plasma and opiate receptors. Penetration of the blood–brain barrier by opiates depends on molecular size, $pK_a$, drug binding on each side of the membrane and, in particular, on lipid solubility. Morphine is relatively insoluble in lipids, and is known to penetrate the brain much more slowly than most other opiates (Oldendorf et al., 1972). In animals, brain concentrations of morphine reach their maximum later than plasma concentrations after bolus administration, and analgesia is maximum later, and decays more slowly, than brain morphine concentration (Dahlstrom and Paalzow, 1978).

Berkowitz and colleagues (1975) have suggested that a plasma morphine concentration of 50 ng ml$^{-1}$ is necessary for the production of moderate analgesia. However, the methods used to reach this
conclusion are dubious. Plasma morphine concentrations were measured in anaesthetized patients given i.m. morphine, and assayed using an RIA technique which cross-reacted with morphine-3-glucuronide. Analgesia was assessed in a totally different group of patients suffering from chronic pain and receiving regular narcotic analgesic therapy. The only similarity between the two groups was the dose of morphine administered.

In a study of analgesia in patients receiving morphine by i.v. infusion after cholecystectomy, Nayman (1979) estimated that a plasma morphine concentration of 23–25 ng ml⁻¹ was associated with adequate pain relief.

In the present study, a significant analgesic effect was evident when the mean plasma morphine concentration had reached 14.8 ng ml⁻¹; it reached a peak approximately 40 min after the calculated mean plasma concentration of 14.8 ng ml⁻¹ had been attained and was sustained as the plasma morphine concentration decreased. A significant effect was still present at 420 min when mean plasma morphine concentration was 7.7 ng ml⁻¹. These differences in time relationship between mean plasma concentration and analgesia, together with the lack of a direct correlation between ITT and plasma morphine concentration, probably reflect delays in, and protraction of, opiate receptor binding. However, in considering the analgesic effect with relation to plasma concentrations of morphine, it must be borne in mind that the pain stimulus used in this study cannot be equated with postoperative pain.

Morphine administered by the oral route undergoes extensive first-pass hepatic metabolism, principally to morphine-3-glucuronide. It has been suggested that the ratio of oral to parenteral potency is between 1:6 and 1:8 after a single dose (Beecher et al., 1953), although in chronic use, the ratio appears to be nearer 1:3 (Twycross, 1980). Such ratios appear to have been estimated from clinical observation. In the present study, the fraction of morphine available to the systemic circulation, calculated from comparison of the plasma concentration decay curves following i.v. administration and oral MST in the same subjects, was 18.3% (range 8.5–23.9%), corresponding fairly closely with these clinical estimates.

A number of potential errors exist in such a calculation. The method assumes that the volume of distribution of the drug was the same in each individual on two occasions, and remained unchanged irrespective of the route of administration. A single function exponential was used to describe the decay of plasma morphine concentration after administration of MST, and a tri-exponential function after i.v. morphine. However, in each case, the function used was that which provided the best mathematical fit to the data.

Because enterohepatic recirculation of unconjugated morphine is believed to occur, and is thought to be responsible for increases in plasma morphine concentration 8 h after MST ingestion (Leslie, Rhodes and Black, 1980), it was decided to restrict the comparison to the area under the plasma concentration–time curve up to 7 h, at which time none of our subjects showed evidence of an increase in plasma morphine concentration. The validity of extrapolation of the i.v. concentration–time curve to 7 h is tenable only if the terminal elimination phase is constant over this period, and if its half-life is close to that after MST. Stanski, Greenblatt and Lowenstein (1978) found that the rate of decay in plasma morphine concentration was constant until 8 h after i.v. administration, although a decrease was present in some subjects after that time. They felt, however, that the later change might have been an artefact resulting from their assay technique at low plasma concentrations. The mean terminal elimination half-lives in our subjects were not significantly different after i.v. (210 min ± 32) and MST (246 min ± 35) administration. Systemic availability calculated in this way reflects losses resulting from incomplete absorption and first-pass metabolism both in bowel wall and liver.

During the first 7 h after administration of MST, approximately one-fifth of the total dose of morphine becomes available to the systemic circulation. Despite relatively low plasma morphine concentrations, analgesia, as assessed by an artificial pain stimulus, was apparent 1 h after ingestion, and was sustained for at least 7 h.

ACKNOWLEDGEMENT

This work was supported by a grant from Trent Regional Health Authority.

REFERENCES


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