CONTROLLED-RELEASE MORPHINE TABLETS

A double-blind trial in dental surgery patients

G. W. HANKS, N. M. ROSE, G. W. AHERNE, E. M. PIALL, S. FAIRFIELD AND T. TRUEMAN

SUMMARY

We report a randomized double-blind comparison of controlled-release morphine tablets (MST-1; 2 x 10 mg) and oral morphine sulphate in solution (20 mg) in 28 patients (20 females) who had undergone removal of impacted lower third molars or a dental clearance under general anaesthetic. The response in both groups was very poor; eight of 15 patients in MST-1 group and six of 13 patients in the standard group required "rescue" analgesics and were withdrawn from the study within the first 2 h. No threshold plasma concentration of morphine corresponding to a particular analgesic effect was apparent. MST-1 produced significantly greater plasma concentrations at 8 h compared with the standard preparation. Controlled-release morphine, or any oral formulation of morphine, may not be suitable for the treatment of acute pain after operation.

MST-1 (Napp Laboratories) is a controlled-release tablet formulation of morphine sulphate 10 mg which, it is suggested, has a 12-h duration of action (Leslie, Rhodes and Black, 1980). However, there are as yet no clinical data on the duration of its analgesic effect. The pharmaceutical formulation (the "Continus" tablet) has been used for other drugs. It is known to be an effective sustained-release vehicle and to maintain blood concentrations over a prolonged period of time (Boroda et al., 1973).

Since MST-1 is very likely to be used in the period after operation, we have investigated its duration of analgesia and the plasma morphine concentrations after its use in patients who have undergone dental surgery. This is a model which has been increasingly used for the evaluation of oral analgesics (Cooper and Beaver, 1976; von Graffenried et al., 1980) since it has been shown to be reliable and has the advantage of being applicable to outpatients. We have completed a randomized double-blind evaluation of MST-1 in comparison with oral morphine sulphate in aqueous solution. This has been reported previously in outline (Hanks et al., 1981).

PATIENTS AND METHODS

Twenty-nine consecutive patients (21 female) admitted for removal of impacted lower third molars or dental clearance under general anaesthesia entered this study. They were aged between 18 and 65 yr. On admission they were given a detailed explanation of the purpose of the study and the procedures involved before consent was obtained.

On the morning of operation all patients received diazepam 7.5-20 mg orally (according to weight and build) 2 h before surgery. Anaesthesia was induced with thiopentone (maximum 500 mg i.v.); gallamine 20 mg i.v. and suxamethonium (maximum) 100 mg i.v. were also given. After nasotracheal intubation and insertion of a throat pack, anaesthesia was maintained with nitrous oxide in oxygen and halothane with spontaneous breathing. A venous cannula was inserted to a convenient forearm vein during the operation and was kept patent with heparinized saline 10 u. ml⁻¹.

Patients were seen in the recovery room by a nurse observer. When conscious they were asked if they had pain and if they complained of moderate or severe pain they were admitted to the study. Baseline assessments were carried out and a 10-ml venous blood sample was obtained. Patients were randomly allocated to treatment with either MST-1 (2 x 10 mg tablets) or a standard solution of morphine sulphate 20 mg in chloroform water.
made up to 4 ml. A double-dummy technique was used so that all patients received two tablets (either active or placebo) and 4 ml of solution (either active or placebo). Patients were subsequently interviewed by the same nurse observer at 30 min, 1, 2, 4 and 8 h following administration of the analgesic. Pain intensity at baseline and at each subsequent interview was based on the patient’s own assessment and scored on a four-point scale: 0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain. Pain intensity difference (PID) scores were derived by calculating the arithmetical difference between a patient’s pre-treatment pain intensity score and each post-treatment score. An SPID (Sum of Pain Intensity Difference) score was then calculated for each patient. Patients were also asked to complete a 10-cm line visual analogue scale marked at one end with the words “No pain” (0 mm) and at the other end “Worst Possible Pain” (100 mm).

At each interview after treatment patients were asked to give an estimate of pain relief on a scale from 0 to 4: 0 = none; 1 = slight; 2 = moderate; 3 = extensive; 4 = complete. A visual analogue scale marked at one end “Complete Pain Relief” (0 mm) and at the other “No Pain Relief” (100 mm) was completed at the same time. Any ill-effects experienced by the patient were noted and a venous blood sample was taken. If patients experienced no pain relief and asked for additional analgesics they were given two Distalgesic (dextropropoxyphene plus paracetamol) tablets. Patients who received the “rescue” analgesic were withdrawn from further assessment and for the purpose of analysis their baseline pain intensity score was substituted for any interview not completed.

Plasma morphine concentrations were measured by radioimmunoassay (Aherne et al., 1976). The antiserum used was raised in a goat to 6-succinyl morphine-BSA and cross-reacted with morphine 3-glucuronide by less than 10%. For this reason plasma morphine was measured as cross-reacting morphine or “morphine equivalents”.

**RESULTS**

Of the 29 patients who entered the study one was excluded because her initial pain severity was “mild”. There were no important differences between the two groups in terms of age and sex distribution (MST-1: 10 females of mean age 27.6 yr, five males of mean age 25.6 yr; standard morphine sulphate: 10 females of mean age 22.9 yr, three males of mean age 28 yr) and the type of operation (removal of impacted lower third molars in almost all cases).

The study was discontinued earlier than planned because response was extremely poor. Eight of 15 of the MST-1 patients and six of 13 of the standard morphine sulphate patients required rescue analgesics because they had failed to experience any change in pain intensity within the first 2 h after administration of morphine.

Table I shows the ordinal pain intensity difference (PID) and the sum of pain intensity difference (SPID) scores and pain relief scores. The corresponding visual analogue scale (VAS) scores followed very similar patterns. Statistical analysis (using the Mann-Whitney U-test for the ordinal scale and Student’s t test for the VAS) revealed a significant difference in favour of the standard solution at 1 h (PID ordinal) and at 2 h (pain relief VAS), although the scores favoured the standard morphine group throughout.

Only four patients experienced unequivocally good pain-relief: one in the MST-1 group and three in the standard morphine group.

**Plasma morphine concentrations**

The results of the plasma morphine analyses and the plasma concentration–time curves for the two preparations are shown in table II and figure 1.

<table>
<thead>
<tr>
<th></th>
<th>0.5 h</th>
<th>1 h</th>
<th>2 h</th>
<th>4 h</th>
<th>8 h</th>
<th>SPID</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MST-1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PID</td>
<td>0.25 ± 0.11</td>
<td>0.43 ± 0.13*</td>
<td>0.43 ± 0.2</td>
<td>0.67 ± 0.21</td>
<td>0.67 ± 0.25</td>
<td>2.40 ± 0.7</td>
</tr>
<tr>
<td>Pain relief</td>
<td>1.04 ± 0.17</td>
<td>1.27 ± 0.21</td>
<td>1.29 ± 0.3</td>
<td>1.80 ± 0.31</td>
<td>1.87 ± 0.34</td>
<td></td>
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<tr>
<td><strong>Standard morphine sulphate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PID</td>
<td>0.58 ± 0.15</td>
<td>0.88 ± 0.11*</td>
<td>1.12 ± 0.18</td>
<td>0.67 ± 0.23</td>
<td>1.00 ± 0.32</td>
<td>3.96 ± 0.7</td>
</tr>
<tr>
<td>Pain relief</td>
<td>1.46 ± 0.27</td>
<td>1.88 ± 0.25</td>
<td>2.12 ± 0.3</td>
<td>1.96 ± 0.33</td>
<td>2.50 ± 0.39</td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05 (Mann-Whitney U test)
The only statistically significant difference was at 8 h.

Figure 2 shows the distribution of morphine plasma concentrations at each point on the ordinal pain intensity scale, and figure 3 the plasma concentrations plotted against visual analogue scale pain intensity scores. When examined separately there was a good negative correlation between the MST-1 plasma concentrations and pain intensity \( r = -0.62, P < 0.001 \) on the ordinal scale; \( r = -0.4, P < 0.05 \) on the visual analogue scale), but no such relationship between the standard morphine sulphate plasma concentrations and pain intensity \( r = 0.03 \) and \( r = 0.15 \) respectively). These results were supported by an examination of the ordinal pain relief scale for MST-1, where there was a positive correlation with plasma morphine concentration \( r = 0.57, P < 0.001 \), but again no correlation for the standard morphine solution. It is noteworthy that
FIG. 3. Individual plasma concentrations of "morphine equivalents" corresponding to visual analogue scale pain intensity scores.

the two patients with the highest peak concentrations (122 ng ml\(^{-1}\) and 131 ng ml\(^{-1}\), both in the standard morphine sulphate group and both at 2 h) required rescue analgesics because of unremitting severe pain.

**Adverse effects**

Both preparations were generally well tolerated. Drowsiness, transient nausea and dizziness were reported equally in both groups. In only one patient (who had received MST-1) were symptoms of nausea severe, but this patient had a history of nausea and vomiting following any general anaesthetic.

**DISCUSSION**

From our results it is clear that oral morphine in either formulation is not suitable for the treatment of pain after dental surgery. The poor analgesic effect of single doses of orally administered morphine was demonstrated a long time ago (Beecher et al., 1953) and has been the basis for suggesting that the oral to parenteral potency of morphine is in the region of 1 : 6 or 1 : 8 (Houde, Wallenstein and Beaver, 1965). Our results are in accord with this view, although we were surprised at how ineffective both preparations were. We had selected a dose (20 mg) which we felt would be effective, but it was clearly inadequate.

It has been widely taught that morphine is ineffective when given by mouth, but there is extensive clinical experience with oral morphine in the treatment of terminal cancer pain where it has become the strong narcotic of choice (Editorial, 1980). In this situation the potency ratio of oral to parenteral morphine is approximately 1 : 3 (Twycross, 1980). The difference in apparent potency in acute and chronic use has its basis in differences in the pharmacokinetics of single and repeated doses of oral morphine. Morphine undergoes extensive "first pass" metabolism to (inactive) morphine-3-glucuronide both in the intestinal mucosa and in the liver. There is some evidence that this glucuronidation of morphine is dose-dependent; total morphine clearance has been shown to be dose related (Garrett and Jackson, 1979). The enterohepatic recirculation of morphine which has been demonstrated in animals (Walsh and Levine, 1975; Dahlstrom and Paalzow, 1978) probably also occurs in man and might produce a secondary peak of unconjugated morphine which, on chronic dosing, might be expected to contribute significantly to circulating concentrations.

Some authors have suggested that there is a relationship between plasma concentrations of unconjugated morphine and analgesic effects (Berkowitz et al., 1975; Dahlstrom et al., 1979) with a threshold concentration of 50 ng ml\(^{-1}\) being necessary for relief of moderate to severe pain. However no relationship between the plasma concentration of morphine and morphine-induced changes in ventilatory function was found by Rigg (1978).

We have shown a difference between the standard morphine solution and the controlled-release preparation. The latter produced plasma concentrations which showed an apparently good correlation with pain intensity (on both scales) and pain relief. However, the analgesic response was so poor that it is difficult to interpret this result and it may be that the correlation is spurious. Plasma concentrations following the standard solution did not appear to bear any relationship to pain...
intensity measures and in neither case was there any suggestion of a threshold analgesic plasma concentration of unconjugated morphine.

Our results indicate that MST-1 administration does produce sustained plasma concentrations of morphine which may be adequate after chronic administration only, but further clinical and pharmacokinetic data after repeated dosage are required.

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REFERENCES


COMPRIMES DE MORPHINE A DISPERSION CONTROLEE

Essais à double inconnue effectués sur des patients subissant une opération de chirurgie dentaire

RESUME

Notre rapport couvre une comparaison à double inconnue, faite au hasard, sur des cachets de morphine à dispersion contrôlée (MST-1; 2 x 10 mg) et sur le sulfate de morphine en solution (20 mg) administrée par voie buccale à 28 patients (dont 20 femmes) ayant subi une extraction de la troisième molaire inférieure (barrée) ou une extraction dentaire totale sous anesthésie générale. La réaction a été médicérale dans les deux groupes: huit patients sur les 15 du groupe MST-1 et six patients sur les 13 du groupe standard ont dû recevoir des analgésiques de "secours" et être retirés de l'étude au cours des deux premières heures. On n'a constaté aucune concentration de seuil de morphine dans le plasma, correspondant à effet analgésique particulier. MST-1 a produit après 8 h des concentrations dans le plasma sensiblement plus fortes qu'avec la préparation standard. La morphine à dispersion contrôlée ou toute autre formulation de morphine pour administration par voie buccale peut ne pas convenir pour le traitement des douleurs aiguës survenant après les interventions chirurgicales.

MORPHIUMTABLETTEN MIT GESTEUERTER FREISETZUNG:

Doppelblind-Versuch bei Patienten einer zahnärztlichen Klinik

ZUSAMMENFASSUNG

Wir berichten über einen wahllosen Doppelblind-Vergleich zwischen Morphiumtabletten mit gesteuerter Freisetzungs- (MST-1; 2 x 10 mg) und oral verabreichtem Morphinum sulfat in einer Lösung (20 mg) bei 28 Patienten (20 davon weiblichen Geschlechts), die sich der Extraktion eines retinierten dritten Molars oder einer vollständigen Räumung unter Allgemeinnarkose unterzogen hatten. Bei beiden Gruppen war die Reaktion sehr schlecht; 8 von den 15 Patienten der MST-1 Gruppe und 6 von den 13 Patienten bei der Standardgruppe mussten mit Schmerzlinderungsmitteln "gerettet" werden und sind schon innerhalb der ersten 2 Stunden aus dem Versuch ausgeschieden. Dabei wurde keine Grenzplasmakonzentration von Morphium festgestellt, die einer spezifischen analgesischen Wirkung entsprach. MST-1 führte zu bedeutend größerer Plasmakonzentrationen nach 8 Stunden, verglichen mit dem Standardpräparat. Morphium mit gesteuerter Freisetzungs, oder irgend eine orale Formulierung von Morphium, könnte sich als ungeeignet für die Behandlung von akuten Schmerzen nach der Operation erweisen.
Se efectuó una comparación aleatoria de doble anonimato de tabletas de morfina de descarga controlada (MST-1; 2 × 10 mg) y sulfato de morfina por vía bucal (20 mg) en 28 pacientes (20 mujeres) quienes habían sido sometidos a extracción de molares terceros inferiores chocados, o a una eliminación dental bajo anestesia general. La respuesta en ambos grupos fue muy pobre: 8 de los 15 pacientes del grupo de MST-1 y 6 de los 13 pacientes en el grupo normal, necesitaron analgésicos de "urgencia" y fueron retirados del estudio a las 2 h. No fueron aparentes las concentraciones umbrales de morfina en el plasma, correspondientes a un efecto analgésico particular. El MST-1 produjo concentraciones en el plasma que fueron significativamente superiores al cambio de las 8 h, en comparación con la preparación normal. La morfina de descarga controlada, o cualquier otra formulación de morfina, puede no ser adecuada para el tratamiento del dolor agudo posoperatorio.