

ORAL MODIFIED RELEASE MORPHINE FOR THE MANAGEMENT OF SEVERE PAIN: A UK PERSPECTIVE

PJ Wiffen, RA Moore, and HJ McQuay

Pain Research, Nuffield Department of Anaesthetics, University of Oxford, The Churchill, Headington, Oxford OX3 7LJ, UK

Corresponding author: PJ Wiffen (pwiffen@pru.ox.ac.uk)

ABSTRACT

Objective: To describe the oral modified release morphine products available in the UK and to identify all the randomised controlled trials associated with these products to determine effectiveness and adverse effects

Data sources: A comprehensive search of the Cochrane Library, MEDLINE and Embase was undertaken. Some information was obtained from manufacturers of modified morphine products

Results: Products from four pharmaceutical companies are described together with a review of the literature covering 54 RCTs (3749 participants). These demonstrate the effectiveness of modified release morphine products when compared to instant release morphine and also demonstrate that modified release products are equivalent to one another. Daily doses in studies ranged from 25mg to 2000mg with an average of between 10 mg and 250 mg. Dose titration can be undertaken with both instant release or modified release products. Approximately 4% of patients are unable to tolerate the adverse effects of morphine.

Conclusions: Oral modified release morphine products are effective analgesics for both malignant and non-malignant pain for the majority of patients.

Background

Morphine in one form or another has been available for centuries, and appeared in Pliny's *Historia Naturalis* (AD 77) as opium, the resin derived from poppy sap. Morphine was extracted from opium in 1803 and named as such by Sertürner a German pharmacist from Einbeck in 1817 [1]. Oral morphine was first recommended in England in the 1950s for the treatment of cancer pain. This was often in the form of the so called 'Brompton cocktail' containing cocaine and alcohol in addition to morphine or diamorphine. Treatment moved towards oral morphine alone as this demonstrated effective pain relief without the side effects linked to the 'cocktail'.

Following the publication of World Health Organisation guidelines in the mid 1980s, the oral administration of aqueous morphine solution every four hours by the clock rather than waiting for the return of pain became commonplace

for moderate or severe cancer pain [2]. European guidelines for the use of opioids in cancer pain are also available [3]. Morphine in a modified release tablet was first marketed around the mid 1980s, allowing the dosage interval to be extended to 12 hours. There are now 24 hour release products available.

Morphine, usually as the sulphate or hydrochloride salts, is available in four oral formulations: an elixir or solution of morphine in various concentrations; an immediate release tablet; a number of different preparations of modified release tablets or capsules; and a modified release suspension. Oral modified release products are routinely used for the management of moderate to severe cancer pain. This review will use the convention of using the term *modified release* as used by the British National Formulary in preference to sustained release, extended or prolonged release.

The wide range of formulations and dosages allows great flexibility in the management of severe pain [4], whether of malignant or non-malignant origin. Potent opioid analgesics are particularly indicated for the relief of pain in malignant disease, and often have the additional very useful actions of relieving anxiety, producing drowsiness and allowing sleep [4]. However, all opioid analgesics have the potential to produce adverse effects including respiratory depression, nausea and vomiting, constipation, and itching. During chronic opioid therapy larger doses may be required to sustain the analgesic effect (tolerance), and patients become at risk of an opioid withdrawal syndrome upon sudden cessation or administration of an antagonist (physiological dependence).

This descriptive review will describe release mechanisms for modified release products, cover the range of products available in the UK and provide evidence for effectiveness from a current update of a Cochrane review [5].

Sources

A comprehensive search of the Cochrane Controlled trials database (CENTRAL) for Issue 2006.4, MEDLINE 1966 to Dec 2006 and Embase 1984 to Dec 2006. Data on release mechanisms was requested from Pharmaceutical companies.

Pharmacokinetics

This review is not going to examine in detail the pharmacokinetics of morphine, other than to remind the reader that a systematic review of 69 studies with information on 2146 subjects (454 patients and 1692 healthy volunteers) examined the maximum plasma concentration (C_{max}) and the time taken to reach maximum concentration (T_{max}) for different oral morphine formulations [6]. Data from healthy volunteers reflected that seen for patients but was less variable. For immediate-release morphine there was no difference in either dose-corrected C_{max} or T_{max} between solution and tablets, or between different salts. For controlled-release formulations, little difference was observed between brands; time to maximum morphine concentration in plasma increased from about one hour for immediate release formulations, about three hours for controlled release, and eight hours for once a day formulations.

Morphine is extensively to both morphine-3-glucuronide and morphine-6-glucuronide, and the extent of metabolism is influenced by route of administration amongst other factors [7,8]. Major problems can be encountered when the active metabolite, morphine-6-glucuronide, accumulates, especially in renal insufficiency in the older patient.

Release mechanisms

A list of the sustained release morphine products available in the UK in 2007 is in Table 1, arranged in order of the annual number of prescriptions and tablets, capsules, or sachets consumed. Over 96% of all prescriptions and 97% of all tablets, capsules, or sachets consumed were for MST Continus and Zomorph. All of these products are bioequivalent (see [9] for comparison of Continus and Zomorph) and

are interchangeable, other considerations aside.

Release mechanism of Morphine Continus® tablets [10]

The controlled-release characteristics of the *Continus* [10] tablet system result from the incorporation of the active principle in a mixture of hydrated hydroxyalkyl cellulose and a higher aliphatic alcohol. The control of this system depends on two factors: dissolution of the higher aliphatic alcohol, and diffusion of the active principle through *in vivo* hydration of the hydroxyalkyl cellulose.

There is a high degree of flexibility in the extent to which the ultimate release of the drug can be controlled. This is possible because of the ability to vary:

- the type of hydroxyalkyl celluloses used
- the type of higher aliphatic alcohols used
- the degree of hydration of the hydroxyalkyl celluloses
- the relative amounts of hydroxyalkyl celluloses and higher aliphatic alcohols

Release of active principle from a *Continus* tablet is independent of pH. This ensures a smooth release of drug throughout the gastrointestinal tract without the need for enteric coating or the inclusion of shellacs or acrylic materials

Release mechanism of MXL® capsules [10]

The 24-hour release profile of *MXL* capsules is dependent on a simple multiparticulate technology. In the manufacture of *MXL* capsules, powdered morphine is mixed with a strongly hydrophobic wax and then cooled. The resulting blend consists of multiparticulates of evenly distributed morphine and wax, each measuring 0.25 mm - 1.8 mm in diameter. These multiparticulates are then encapsulated.

The capsules disintegrate within 15 minutes of being swallowed. Water enters the multiparticulates and dissolves with morphine which then diffuses out of each particle. However, water entry into the multiparticulates is retarded because of the hydrophobic nature of the wax. The release rate of *MXL* capsules is determined by the rate of water entry into the particles and the rate of drug diffusion out of them. The release rate is unaffected by the differing pH values present in the gastrointestinal tract.

Release mechanism of MST Continus suspensions [10]

MST Continus suspension consists of morphine bound to an ion exchange resin. When the suspension is swallowed the morphine is displaced by sodium and potassium ions present throughout the gastrointestinal tract. Morphine bound on the surface ionic sites is displaced first. As the sodium and potassium ions travel further into the resin bead, this process continues. Morphine is therefore released over time with the morphine at the centre of each bead being released last. The morphine-free resin is then excreted.

Table 1: Products available in the UK and prescribing by GPs in England

Name of Product	Strengths available and colour of dose	Release mechanism	Cost of 120 mg/day for 28 days (BNF [13])	Annual UK prescriptions [14]	Annual UK tablets or capsules consumption [14]
MST Continus®	5 mg (white) 10 mg (brown) 15 mg (green) 30 mg (purple) 60 mg (orange) 100 mg (grey) 200 mg (green)	Prolonged release, film-coated, biconvex tablets	£23.97	541,000	37,300,000
Zomorph®	10 mg (yellow/clear) 30 mg (pink/clear) 60 mg (orange/clear) 100 mg (white/clear) 200 mg (clear)	Microgranules, with number of granules in a capsul shell determining dose of morphine sulphate. Should not be crushed or chewed, but may be sprinkled on food	£17.78	127,000	8,600,000
MXL®	30 mg (light blue) 60 mg (brown) 90 mg (pink) 120 mg (green) 150 mg (blue) 200 mg (red-brown)	Capsules, prolonged release Hard gelatine capsules containing white to off white multi-particulates	£29.15	17,000	661,000
Morphgesic® SR	10 mg (buff), 30 mg (violet) 60 mg (orange) 100 mg (grey)	Prolonged release film coated tablets	£17.87	7,000	470000
MST Continus® Suspension granules	Sachet sizes: 20mg, 30mg, 60mg, 100mg, 200mg	Single dose sachets – mixed with water to generate suspension	£102.41	6,000	354000

Release mechanism for Morphgesic SR [11]

Morphgesic SR has a similar release profile to MST Continus

Release mechanism for Zomorph capsules [12]

Zomorph capsules contain a number of individual pellets each having a similar sustained release profile. The nature of the pellets is the same for each capsule strength in the Zomorph range. The number of pellets contained in a capsule shell determines the dose of morphine sulphate.

Morphine sulphate in combination with a binding agent is applied to an inert sucrose and starch sphere. The sustained release mechanism is then applied in a coating suspension which, once dry, forms a continuous layer enveloping the pellet. The thickness of the coat is carefully controlled to ensure the desired release characteristics. The coat is ethyl-

cellulose and controls the release of morphine sulphate by diffusion of the active material across this layer. The permeability of the ethylcellulose coat is not affected by pH, offering consistent diffusion properties along the length of the gastro-intestinal tract.

The sustained release mechanism is dependent on the integrity of this outer coat. Crushing or chewing of the pellets will destroy this coat and therefore alter the products release profile.

Discontinued products

Morcap 24 hour modified release product has been discontinued by Mayne in the UK during 2006. Rhotard tablets have also been discontinued

Switching between brands of modified release morphine

In 2004, 'Building a Safer NHS for Patients [15], a government document was issued and highlighted medication errors with opioid analgesics stating 'Oral sustained-release opiates are a particular source of error and care should be taken to avoid any possible ambiguity when prescribing these drugs. Including the brand name on the prescription and dispensing label will aid in the identification of the correct formulation to be dispensed or administered.'

Since then the position has changed and the British National Formulary staff are quoted in a statement on palliativedrugs.com:

'The BNF accepts that generic prescribing of any medicine can lead to switching of brands and confusion for the patient. However, before recommending brand-name prescribing of opioids, the BNF require evidence that there is a particular safety issue over and above that already associated with the generic prescribing of drugs. They stated that they have yet to see convincing pharmacokinetic or safety data to justify recommending brand-name prescribing of opioids. They had also sought evidence from the Department of Health to support the view that omission of brand names was responsible for errors, but were not supplied with any supporting evidence'

The website also quotes the response of the National Patient Safety Agency who state 'based on the numbers of reports it had received, that there is little evidence to suggest that unintentional switching between different brands of m/r morphine (or fentanyl patches) poses a safety risk to patients and thus agrees that these products do not need to be routinely prescribed by brand name. However, they also confirmed the importance of pharmacists ensuring that patients receive the intended formulation of a drug.'

'However, the National Patient Safety Agency has received several reports of significant harm arising from confusion between normal-release and m/r formulations of morphine and other opioids, e.g. when a normal-release formulation of the same strength has been supplied or used instead of the intended m/r formulation.'

That being said, given the difference in appearance of the different preparations, patients should not regularly be switching between different brands simply to satisfy the diverse stock holding preferences of pharmacists.

Overview of the randomised controlled trial (RCT) literature

The 54 studies that met the inclusion criteria for the Cochrane review contain 3749 enrolled participants. There was no language restriction and as far as we know this is the total of the world's published RCTs. Trial size varied from 11 to 699 subjects. This review describes the studies that examine the use of modified release products (18 studies 1522 participants).

1. Morphine modified release (Mm/r) compared to Morphine immediate release (MIR)

This comparison is arguably the most important as it seeks to establish the efficacy of modified release morphine products, currently the mainstay of pain relief in cancer care. In spite of this importance the literature is small: 15 studies of 460 subjects. None of the trials was large, with a median size of 27 subjects (range 16-73). Eleven of the trials were of crossover design. The results of these trials show that Mm/r and MIR are both effective in similar doses for pain relief.

The crossover studies show a wide variation in treatment periods from 2 by 2 days to 2 by 15 days; 10 of the studies were for 2 by 7 days. None of the studies addressed the issue of carry-over of analgesic effect from those who receive the Mm/r product. Examples of studies included are:

Walsh [16] 1992 took patients who were stable on morphine or on other opioids which were converted to morphine. The mean daily dose at trial entry was 109 mg per day. Patients were randomised either to Mm/r or MIR using a double-dummy technique. Crossover occurred at two days. There was no significant difference detected in mean daily morphine dose, visual analogue score (VAS) pain data, breakthrough pain or use of rescue analgesia. Equally, scores for adverse effects, including nausea, confusion, constipation and anxiety, were similar. A preference for Mm/r was stated by 22 of the 33 patients who entered the study. Only 27 patients were evaluated.

Hanks [17] 1987a et al conducted a similar study although one third of the 27 patients dropped out early. Both intervention groups experienced adequate pain control but those on Mm/r experienced better quality sleep at night. Another study by Walsh [18] 1985a used crossovers at day 3 and again at days 5 and 8. This study also reported no differences in either pain relief or side effects. The authors stated that they did not detect any carry-over effects.

While 29 patients entered a study by Arkininstall [19] 1989, only 17 completed. Again, patients were as well controlled on Mm/r twice a day as on MIR six times a day, with no reported difference in adverse effects. A small number of non-cancer pain patients were included in this sample.

2. Morphine modified release (Mm/r) comparisons - different strengths and dose intervals

Twelve studies (1010 participants) compare Mm/r at different strengths or release profiles. These can be sub-divided as follows:

- different dose strength combinations of 12 hour release
- studies of 24 hour release

(2a) Five studies (243 participants) examined different dose strength or interval combinations of 12 hour release Mm/r.

Using a double blind design, Mignault [20] in a Canadian study showed that 12-hourly dosage was as effective as 8-

hourly administration. This was a small study of 19 patients; there were no differences in adverse effects and the majority of patients felt that the 12-hour regime had advantages in terms of convenience. The need for high dose tablets of Mm/r led to three studies. Portenoy [21] compared three tablets of Mm/r 30 mg (MS Contin) with one tablet of 100 mg Mm/r. Patients were stabilised on MIR over a one- or two-day period then randomised to either Mm/r 100 mg or Mm/r 90 mg (3 x 30 mg) every 12 hours. Comparison of the pain intensity and rescue analgesic consumption (MIR) showed no significant differences. The reported side effect profiles were also similar.

Two studies compared Mm/r 100 mg with Mm/r 200 mg (MS Contin). Smith [22] studied 20 patients who received either dose for three or four days. Doses ranged from 400 mg to 1800 mg per day. Pain assessment and pharmacokinetic monitoring confirmed similar analgesic efficacy and plasma profiles. In another three day crossover study of the same formulations, Hanks [23] also showed comparable efficacy in a study of 25 patients. Patients in this study used doses of 400 mg to 2000 mg per day. Several products are now available with a once-a-day dosing option.

A different brand of modified release capsule was used in a Chinese study by Guo-Zhu [24]. M-Eslon® (Zormorph capsules) was compared to MS Contin® in 120 patients. Both were designed for 12 hourly dose intervals. The study was conducted at two dose levels: 20 mg every 12 hours and 30 mg every 12 hours. No titration was permitted. Using a range of analgesic assessments there was no significant difference between the two products, and adverse effects were also similar.

(2b) Studies of 24 hour release

Seven studies (767 participants) of once-daily morphine tablet or capsule (marketed under a number of trade names including Kadian®, Kapanol® and Morcap® or MXL® capsules).

MXL capsules were shown to be comparable to an equivalent dose of MS Contin in a study of 85 patients by O'Brien [25]. The comparators were MXL 60 mg versus Mm/r 30 mg twice a day. The dose could be multiplied for patients requiring higher doses. While the majority of participants needed 60 mg a day, doses up to 300 mg per day were used. There were no significant differences in pain relief between patients.

The study by Flöter [26] included patients with non-cancer pain such as post-trauma and neuropathic pains. The authors claim a significant difference in favour of the once-daily product for pain intensity (VAS) when measured immediately prior to the evening dose. Data were not available for a separate analysis of the patients with cancer pain.

Broomhead [27] conducted a study of 150 patients with cancer pain in two separate phases. Phase one contained a placebo arm to demonstrate that the study could differentiate between active and placebo. Rescue medication was available in the form of MIR. Phase two consisted of three arms: Kapanol every 24 hours, Kapanol every 12 hours and Mm/r every 12 hours. There was no significant difference

between the groups in terms of rescue medication requirement. Patients' global assessments of 'good' or 'very good' pain control were 89% for the Kapanol 24-hour group, 76% in the Kapanol 12-hour group and 68% in the Mm/r group. Adverse events were similar between groups and there was no increase in adverse effects associated with the larger unit dose of the once-daily product.

Gourlay [28] showed that there were no significant differences between Kapanol once a day and Mm/r twice a day for either analgesic effect or adverse effect. The pharmacokinetic profile was much flatter for Kapanol 24 hour, reflecting the designed release profile.

Twenty nine patients were enrolled in a study comparing MS Contin XL with MS Contin [29]. All patients experienced good pain relief though it was observed that pain scores were more stable through the day on the once daily formulation. One hundred and thirty four patients [30] were titrated to pain relief of cancer pain with MIR then randomised to either Mm/r 24 hour (Kadian) or Mm/r 12 hour (MC Contin) formulations. Only 104 patients entered the efficacy trial which was a crossover design. No dose adjustments were allowed but rescue MIR was provided. 57/104 preferred Kadian, 34/104 MS Contin and 13/104 expressed no preference.

One hundred and fifty three participants entered a study by Vielvoye-Kerkmeer [31] but only 110 were enrolled after a 14-day run-in period. It was not stated why the 43 participants dropped out. No significant differences were detected between groups in terms of pain intensity, rescue analgesia or sleep quality.

3. Morphine modified release (Mm/r) tablet compared to Morphine modified release (Mm/r) oral suspension

Only one study [32] was found comparing morphine modified release suspension with modified release tablets in a double blind double-dummy crossover study of 52 patients. Using visual analogue scores and categorical scales, there were no significant differences between the groups regarding pain relief or other measured indicators such as activity, mood or sleep. There was no clear patient preference for any product.

Key messages

Oral morphine is effective at treating severe pain in the majority of patients.

- **Dose titration:** The general rule of thumb is to titrate the dose until either pain relief or intolerable adverse effects are experienced. Doses used in the included studies ranged from 25mg/day to 300mg/day for opioid naïve patients. The maximum dose recorded was 2000mg/day. Mean daily doses were in the range 100mg/day to 250mg/day.
- **Product:** There is good evidence that products are interchangeable but it is wise to allow for some dose manipulation to ensure that patients get good pain relief

while minimising adverse events. When patients are getting breakthrough pain at the end of the time span of their modified release product, it is usually a sign of under-dosing. Some practitioners do use the 12 hour formulation on an eight hourly schedule (maintaining a similar total daily dose). Here is evidence to show that doses can be titrated to effect using the modified release formulation.

The goal then is cost-effective prescribing, where cost minimisation is the main aim. Most oral sustained release morphine prescribing in the UK uses lower cost alternatives.

- **Patients who have difficulty swallowing:** Either sachets are available for reconstitution (expensive) or capsules can be opened and taken on jam or a similar substance for those with difficulty in swallowing. Care needs to be taken to ensure that the microcapsules are not destroyed by chewing.

Adverse effects

Approximately 4% of patients in the studies withdrew due to intolerable adverse effects. Constipation, dry mouth, nausea, and sedation were commonly reported adverse events with confusion, dizziness or hallucinations occur much less frequently. There were no reports of respiratory depression or dependence in the randomised trials.

Equi-analgesic dosing

There are a number of points to consider when converting patients from one opioid to another:

- ratios for acute pain may not be the same as for chronic pain
- ratio tables are available but can only give a rough guide, doses need to be initiated cautiously and titrated to effect
- regular monitoring of pain and of pain relief should be undertaken until a stable situation is reached
- monitor adverse effects
- tolerance to one opioid may not be carried over to another leading to greater than anticipated potency
- additional caution needed in patients with liver or renal failure

Charts for conversion from one opioid to another are available [33]. A conversion programme is also available from the John Hopkins Center for Cancer Pain Research [34].

Conclusion

The over-riding aim when prescribing for severe pain is effective pain relief. While oral morphine will provide effective pain relief for a large proportion of patients with severe pain, in some it will not. For these patients other routes of administration, or other therapies, will have to be tried. For those in whom oral morphine works well, there is no great difference between the various sustained release preparations, though the ability to have morphine as a drink or to have microgranules sprinkled on food will benefit those with difficulty swallowing.

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