Clinical efficacy, safety and pharmacokinetics of a newly developed controlled release morphine sulphate suppository in patients with cancer pain

Abstract  
Objective: To compare the efficacy, safety and pharmacokinetics of a newly developed controlled-release suppository (MSR) with MS Contin tablets (MSC) in cancer patients with pain.

Methods: In a double-blind, randomised, two-way crossover trial, 25 patients with cancer pain were selected with a morphine (M) demand of 30 mg every 12 h. Patients were divided into two groups. Group 1 received active MSC (30 mg) and placebo MSR, followed by placebo MSC and active MSR (30 mg) each for a period of 5 days. Group 2 started with active MSR and placebo MSC, followed by active MSC and placebo MSR, each for a period of 5 days. Blood for determination of plasma concentration of morphine (M) and its 3- and 6-glucuronides (M3G, M6G) was collected, and area under the plasma concentration–time curve (AUC)0–12 h, peak plasma concentration (Cmax), time to reach Cmax (tmax), and C0 and C12 of M, M6G and M3G were determined on day 5 and day 10. Intensity of pain experienced by each patient was assessed every 2 h on a 0–10 scale, while side effects and rescue medication were recorded.

Results: Twenty patients (ten patients in each group) completed the study. A pronounced inter-patient variability in plasma concentrations of M, M3G and M6G was observed after administration of both forms. Apart from the C0 and C12, no significant differences in AUC0–12 h, tmax and Cmax of morphine between the rectal and oral route of administration were found. In the case of the metabolites, it was found that AUC0–12 h and Cmax of M6G, and AUC0–12 h, Cmax, C0 and C12 of M3G after rectal administration were significantly lower than after oral administration. However, apart from the tmax of M6G, none of the pharmacokinetic parameters of M, M6G or M3G met the criteria for bioequivalence. There were no significant \( P \geq 0.44 \) differences in pain intensity score between the oral and rectal forms within the two groups, regardless of the treatment sequence. No treatment differences in nausea, sedation or the demand on escape medication (acetaminophen tablets) between the rectal and oral forms were observed.

Conclusion: The newly developed controlled-release M suppository is safe and effective and may be a useful alternative for oral morphine administration in patients with cancer pain.

Key words  
MS Contin · Rectal absorption · Morphine sulphate

Introduction  

Controlled-release oral morphine represents an innovation over conventional immediate-release morphine dosage forms because of its convenient 12-h dosing schedule and ease of administration. When the oral route is no longer satisfactory, rectal dosing with morphine may be a useful alternative for pain control in terminally ill patients [1]. A sustained-release rectal dosage form can be used to avoid the cumbersome 4-hourly rectal dosing schedule, which is usually required because of the fast rectal absorption and elimination of morphine [2]. 

Recently, we described the absorption profiles and bioavailability of morphine in human volunteers \( n = 13 \) after oral administration of MS Contin tablets.
(MSC) and rectal administration of a newly developed controlled-release suppository (MSR). By manipulating the viscosity of the fatty suppository base and introducing hydrophilic gel-forming excipients, a matrix system containing morphine sulphate (30 mg) was prepared with an identical cumulative morphine input to oral dosing [3]. No discomfort following application of the rectal dosage form was reported by the volunteers. Furthermore, apart from a temporary sedation, fatigue and some nausea, none of the volunteers suffered from any side effect. We, therefore, concluded that the newly developed suppository was safe and suitable for further clinical testing. Until now, there are few data available regarding plasma steady-state pharmacokinetics of morphine and its metabolites after rectal dosing in patients with cancer pain [4, 5]. However, the composition of the rectal dosage form is mostly not disclosed and relevant pharmacokinetic data including that of the active 6-glucuronide metabolite of morphine have not been determined. Moreover, the individual daily morphine dose requirement varies substantially (60–1000 mg/day) among the patients included. We studied the clinical efficacy, safety and pharmacokinetics of the developed MSR compared with MSC in 25 patients with cancer pain using a double-blind, randomised, two-way crossover design. Patients were selected with a demand of 30 mg morphine every 12 h, and plasma concentrations of morphine and its 3- and 6-glucuronides (M3G and M6G) were determined. Pain intensity and rescue medication were recorded.

Materials and methods

Subjects

The study protocol was approved by the ethics committee of the Groningen Academic Hospital and informed consent was obtained. Twenty-five patients already receiving chronic oral morphine (MSC, 30 mg every 12 h) for cancer pain were included in this study. The patients characteristics are described in Table 1. Criteria for exclusion included severe obstructive lung disease, diarrhoea, concurrent use of higher doses of morphine or other opioid analgesics, and abnormal liver/kidney/thyroid gland blood values. All patients were also treated with several other drugs, mainly laxatives, hypnotics and anti-emetics. Acetaminophen (tablet, 500 mg) was permitted as a rescue analgesic during the course of the study.

Procedure

Dosage forms

Fatty suppositories were prepared by mixing morphine sulphate pentahydrate (USP) carefully with aerosil R972 (Hüls-Degussa) and hydroxypropylmethylcellulose 4000 (K4M, Collorcon), then mixing with a molten base of Witepsol W25 (Hüls-Degussa). The suppositories were poured into plastic moulds (3 ml) and stored at 4°C. Each suppository contained 30.0 mg morphine sulphate, 108 mg aerosil R972, 300 mg HPMC 4000 and 2390 mg Witepsol W25. The oral dosage form used in this study was the commercially available MS Contin tablets (Dagra-Pharma BV, the Netherlands) containing 30 mg morphine sulphate.

Table 1: Demographic characteristics for patients completing the study

<table>
<thead>
<tr>
<th>Number</th>
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<tr>
<td>Male/female</td>
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<tr>
<td>Age (median)</td>
<td>59 (41–80)</td>
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<tr>
<td>Primary tumour (number)</td>
<td>Lung (13)</td>
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<td></td>
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<td>Prostate (1)</td>
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</tbody>
</table>

Study design

Double-blind conditions were maintained using matching placebos. Patients were divided into two groups. Group 1 received active MSC (30 mg every 12 h) and placebo MSR, followed by placebo MSC and active MSR (30 mg every 12 h), each for a period of 5 days. Group 2 started with active MSR and placebo MSC every 12 h, followed by active MSC and placebo MSR every 12 h, each for a period of 5 days.

Venous blood samples were obtained at 0, 1, 2, 4, 6 and 12 h after drug administration on day 5 and day 10. Plasma was immediately separated and stored frozen until analysed. Pain intensity was assessed by the patient every 2 h on a 0–10 scale, while side effects and rescue medication were also recorded.

Data analysis

The plasma concentrations of morphine and its glucuronides M6G and M3G were determined. Pain intensity and rescue medication were analyzed by calculating the average number of acetaminophen tablets taken daily by each patient over a period of 5 days. Group 1 started with active MSR and placebo MSC every 12 h, followed by placebo MSC and active MSR every 12 h, each for a period of 5 days.

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Statistical analysis of the pharmacokinetic parameters AUC0–12 h, Cmax, CO and C12 of morphine, M6G and M3G was performed according to the procedure by Hauschke et al. [7]. This method is a modification of the Wilcoxon/Tukey signed-rank test, taking into account any period effect. According to the usual regulatory guidelines, bioequivalence with respect to a particular parameter was inferred if the 90% confidence interval of the ratio rectal/oral was included within the interval of 0.80–1.25. In addition, the 95% confidence interval of the ratio rectal/oral was calculated using the same method. Differences between rectal and oral dosage forms were considered statistically significant if the 95% confidence interval of the ratio rectal/oral did not include the value 1. Two-way analysis of variance (ANOVA) of logarithmically transformed data was used to test for period and treatment sequence effects.

Demographic data of the patients in groups 1 and 2 were compared using the Wilcoxon/Mann-Whitney test. The pain intensity score of each patient was averaged over the 5 days of each phase and was statistically tested using the non-parametric method described by Koch [8]. In addition, the pain score was analysed using the aforementioned non-parametric bioequivalence test.

Use of analgesics was analysed by calculating the average number of acetaminophen tablets taken daily by each patient over