Cancer Chemother Pharmacol (1992) 31: 251–254

Cancer Chemotherapy and Pharmacology

Pharmacokinetics and efficacy of rectal versus oral sustained-release morphine in cancer patients

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Received 7 March 1992/Accepted 11 August 1992

Summary. Sustained-release morphine (MST) given by the rectal route was compared with oral MST in an open randomised cross-over trial in ten patients with cancer who received stable doses of MST. No significant difference was found in the areas under the curve of the concentration-time profiles (AUC) following oral or rectal administration for parent morphine. The AUCs determined for morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G) after oral administration were approximately twice those obtained following rectal administration. The maximal concentration achieved was lower and the time to maximal concentration was longer following rectal administration for morphine, M6G and M3G. The relative mean arrival times following rectal administration were significantly longer for morphine and M3G but not for M6G. These findings suggest slower absorption but less first-pass metabolism of MST after rectal administration. No significant difference was noted between the oral and the rectal route in measurements on visual-analogue scales for pain or side effects. We recommend the rectal route as being suitable for MST administration when the oral route is no longer available. In changing from oral to rectal administration, the same dose and dose interval may be used, but dose adjustment may be needed.

Introduction

The administration of morphine in a sustained-release oral preparation (MST) q 12 h eliminates excessive fluctuations in morphine concentrations and has resulted in better pain control and fewer side effects [9]. MST has been used rectally in New Zealand in patients with cancer who are unable to take medication orally. Pumps for subcutaneous administration of morphine are not widely available. Anecdotal experience and a retrospective study [8] have suggested that similar analgesia can be achieved after MST administration has been changed from the oral to the rectal route without major dose adjustment. However, few data are available on the comparative pharmacokinetics of MST given by the oral and rectal routes to cancer patients on stable 12-h doses. The only study known to us used normal male volunteers and compared single doses of 30 mg MST given rectally and orally [6]. The areas under the curves of the plasma concentration-time profiles (AUC) of morphine were similar, but the peak was delayed and attenuated after rectal administration.

The activity of morphine may be partly related to the metabolite morphine-6-glucuronide (M6G) [2, 3], with some observers attributing most of the analgesic effect to this metabolite [11]. The other major metabolite, morphine-3-glucuronide (M3G), has been regarded as being inactive in humans [3] but is an antagonist of both morphine and M6G in rats [15]. The exact role of these major metabolites is unclear. Differences in metabolite concentration profiles could be important for efficacy. We examined the pharmacokinetics of morphine, M6G and M3G as well as the efficacy and the adverse-effect profile following the administration of MST by the oral and rectal routes in patients with cancer receiving stable twice-daily doses.

Patients and methods

Hospital inpatients with cancer aged between 20 and 85 years who had received stable 12-h doses of oral MST (MST Continus, Douglas Pharmaceuticals Ltd.) for the previous 5 days were eligible for this study. Patients were excluded if they showed a plasma albumin level of less than 30 g/l, a prothrombin ratio of greater than 1.5 times normal or a calculated creatinine clearance of less than 60 ml/min (Cockcroft and Gault [1]) or had colorectal cancer or proctitis.

All patients were randomised to receive their stabilised doses of MST q 12 h by either the oral or the rectal route. The fourth dose of MST was given at 9 a. m. and blood was taken at 30-min intervals from 9 a. m. until 1 p. m., hourly until 3 p. m. and every 2 h thereafter until 9 p. m. Drug

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Table 1. AUCs of concentration-time profiles following oral and rectal administration of MST[a]

Patient	MST dose	Morphine			Morphine-3-glucuronide			Morphine-6-glucuronide		
		Oral	Rectal	Ratio	Oral	Rectal	Ratio	Oral	Rectal	Ratio
1	150 mg	0.706	0.516	1.37	47.2	25.0	1.89	6.58	3.77	1.75
2	220 mg	1.210	1.800	0.67	24.0	19.6	1.22	4.11	3.03	1.36
3	20 mg	0.267	0.221	1.21	6.6	3.3	2.00	1.14	0.57	2.00
4	80 mg	0.344	0.263	1.31	17.6	10.8	1.63	1.95	1.18	1.65
5	160 mg	1.174	1.198	0.98	34.7	16.0	2.17	5.24	2.69	1.95
6	30 mg	0.115	0.052	2.21	18.8	6.2	3.03	2.90	0.91	3.18
7	40 mg	0.423	0.263	1.61	23.6	5.4	4.37	4.94	1.03	4.79
8	40 mg	0.171	0.241	0.71	12.2	8.8	1.39	1.95	1.53	1.27
9	140 mg	0.653	0.297	2.20	31.0	12.7	2.44	4.42	1.96	2.26
10	160 mg	1.437	0.846	1.70	27.4	14.2	1.93	5.04	2.04	2.47
Mean[b]				1.30			2.07			2.10
95% CI[b]				0.96–1.75			1.58–2.69			1.58–2.79

[a] Expressed in mg h l^{-1}

[b] Calculated on log-transformed data

administration was then changed to the alternative route, and after the fourth dose the patient was studied in the same manner; all patients thus served as their own controls. Exact times were recorded when they differed from those specified.

At the end of each study period (at 9 p. m.), the patient was required to indicate on a 10-cm visual-analogue scale (VAS) [13] the appropriate position that best represented the degree of pain experienced over the preceding 12-h period. A similar scale was used for side effects, with severity ranging from none to extreme. All patients determined which side effects they regarded as being significant or important. On completion of the entire study, each patient was asked to state the preferred route of MST administration.

Patients were questioned about pain every 3–4 h by the nursing staff. Breakthrough pain was managed with paracetamol or oral pethidine; use of this additional analgesia was recorded. Patients could ask for extra pain relief or discontinue the study at any time. Prior to rectal administration of MST, patients were encouraged to empty their bowels. Regular laxatives (lactulose or coloxyl only) were continued unchanged throughout the study period. Bowel stimulants were not used.

The blood samples obtained were immediately centrifuged and the plasma was stored at −20° C until analysis. Plasma morphine, M6G and M3G concentrations were measured using a modification of a previously published method [4]. Instead of one high-performance liquid chromatography (HPLC) system equipped with two detectors (an electrochemical detector and a fluorescence detector) in series, we used two HPLC systems, one of which was equipped with a model GM970 fluorescence detector (Schoeffel Instruments, Westwood, USA) for the analysis of M3G and the other, with a model 410 electrochemical detector (Waters Associates, Milford, USA) for the analysis of M6G and morphine. The applied voltage on the electrochemical detector was +0.7 V. The mobile phase for the M3G HPLC system was the same as that previously described elsewhere [4] and was pumped through a μBondapak C18 column (30 cm × 10 μm Waters Associates) at a rate of 1.5 ml/min. The mobile phase for the M6G/morphine HPLC system was the same as that used in the M3G system except that 1% isopropyl alcohol was added, and it was pumped through a phenyl radial-compression module cartridge (4 μm; Waters Associates) at a rate of 1.5 ml/min.

Plasma samples were extracted using a previously described method [16] that was modified as follows: an internal standard (nalorphine hydrobromide) was added to each sample and the eluting solvent was changed from 3 ml 10% acetonitrile in 0.01 M sodium dihydrogen orthophosphate buffer (pH 2.1) to 1.5 ml 26% acetonitrile in 0.01 M sodium dihydrogen orthophosphate buffer (pH 2.1). A 100- to 200-μl aliquot of the eluent was injected into each HPLC system. The minimal quantifiable concentrations of M3G, M6G and morphine were 40, 10 and 5 μg/l, respectively. The between- and within-day coefficients of variation at these concentrations as calculated using analysis of variance were less than 10%.

The AUCs over a single dose interval (0–12 h) were calculated using the linear trapezoidal rule. The relative mean arrival time (MAT) was calculated as the difference between the mean residence time (MRT) after rectal administration and the MRT after oral administration.

Oral: rectal ratios of AUC and maximal concentrations achieved (C_{max}) were used to correct for dose. These data were then log-transformed to ensure normality and 95% confidence intervals (CI) were calculated. The differences in the morphine: metabolite and M3G : M6G ratios between the routes were compared using the Wilcoxon signed-rank test for paired samples. Student's two-tailed *t*-test for paired samples was used to analyse differences in the time to maximal concentration (T_{max}), MRT and the visual-analogue scale measurements for pain and side effects for each route of administration. The study was approved by the Canterbury Area Health Board Ethics Committee and all patients gave written informed consent.

Results

A total of 11 patients entered the study, but 1 patient died before completing the second phase. The 10 patients who completed the study (6 men and 4 women) were aged a median of 70 years (range, 40–83 years). The diagnoses were lung cancer (n = 3), prostate cancer (n = 3), breast cancer (n = 2), myeloma (n = 1) and adenocarcinoma of unknown primary (n = 1).

The MST dose and the AUCs calculated for morphine, M3G and M6G following oral and rectal administration are shown in Table 1. No significant difference was found in the AUCs of parent morphine between the oral and the rectal route. Rectal administration resulted in less production of the metabolites. The mean AUC ratio for M3G calculated following oral administration of MST was 2.07 times that observed after rectal dosing, and the mean AUC ratio for M6G following MST oral administration was 2.10 times that after rectal dosing. In addition, the metabolite:parent morphine ratios were lower following rectal administration. The median AUC ratio of M6G: morphine was 4.2 : 1 (range, 1.7–18) following rectal administration of MST as compared with 6.2 : 1 (range, 3.4–25) after oral

Table 2. Pharmacokinetic comparison of oral versus rectal administration of MST

Parameter	Morphine	Morphine-3-glucuronide	Morphine-6-glucuronide
C_{max} oral: rectal ratio:			
Mean[a]	1.69	2.36	2.28
95% CI[a]	1.33–2.14	1.81–3.08	1.82–2.85
T_{max} rectal – oral difference (h):			
Mean	3.4	2.0	2.8
95% CI	2.1–4.6	0–4.1	0.1–5.4
P	<0.001	0.053	0.046
MAT (h):			
Mean	0.57	0.37	0.25
95% CI	0.02–1.11	0.02–0.71	–0.24–0.74
P	0.04	0.04	0.27

[a] Calculated on log-transformed data

C_{max}, Maximal concentration achieved; T_{max}, time to maximal concentration; MAT, relative mean arrival time

dosing ($P < 0.01$), and the median AUC ratio of M3G: morphine was 29:1 (range, 11–119) following MST rectal administration as compared with 49:1 (range, 19–163) after oral dosing ($P < 0.01$). The mean AUC ratio of M3G:M6G did not significantly differ between the routes, being 6.5:1 (range, 5.2–9) following rectal administration of MST as compared with 6.4:1 (range, 4.8–9) after oral dosing.

The C_{max} was lower and the T_{max} and MRTs were longer following rectal administration (Table 2). Peak morphine concentrations were reached on average at 6.7 h (95% CI, 5.3–8.0 h) after rectal administration as compared with 3.3 h (95% CI, 2.2–4.3 h) after oral dosing. The AUC for parent morphine was linearly correlated with the dose, whether given orally ($r^2 = 0.79$) or rectally ($r^2 = 0.72$), suggesting dose proportionality.

No significant difference was found between the oral and the rectal route in measurements on the VAS for pain (mean differnce, –0.19 cm; 95% CI, –1.0–0.63 cm; $P = 0.61$). When MST was given by the oral route, four patients required additional analgesia (two received paracetamol; one, oral pethidine; and one, both oral pethidine and paracetamol), whereas following rectal administration, six patients required extra analgesia (all received oral pethidine). No significant difference was observed between the oral and the rectal route in measurements on the VAS for side effects (mean difference, 0.22 cm; 95% CI, –0.26–0.70 cm; $P = 0.33$). The overall preference was for the oral route (eight patients), with one patient preferring the rectal route (because of nausea) and one having no preference.

Discussion

Using a wide range of MST doses in cancer patients, this study demonstrated no difference in the extent of availability of parent morphine following rectal administration of MST as compared with that following oral administration. The extent of availability of M6G and M3G was approximately 2 times greater after oral administration. The ratio of the metabolites to parent morphine was significantly lower when MST was given rectally, consistent with less first-pass metabolism after rectal administration.

Multiple or delayed peak concentrations made the assessment of T_{max} and C_{max} less meaningful [18]. It is therefore useful to compare the relative MAT between the two routes of administration for the assessment of differing rates of drug availability. This assumes that the distribution and clearance of morphine and its metabolites remain constant in a given patient. The longer relative MAT found for both parent morphine and M3G following rectal administration of MST is consistent with slower absorption and less first-pass metabolism. This finding together with the lower C_{max} and the longer T_{max} indicates that there are fewer fluctuations in concentrations over the 12-h dose interval following rectal administration.

The data we obtained following oral administration of MST are similar to the findings of other investigators. The mean T_{max} of 3.3 h (95% CI, 2.2–4.3 h) found for parent morphine in the present study is comparable with the 2.5 h (95% CI, 1.9–3.1 h) previously reported, and the median AUC ratios of 1:6.2:49 determined for morphine:M6G:M3G are comparable with the 1:7.8:57 ratios previously reported for other cancer patients taking oral MST (calculated from raw data [12]). A longer T_{max} and a lower C_{max} for parent morphine has also been observed following the administration of a single rectal dose of 30 mg MST to young healthy men [6].

M6G may have analgesic activity in humans [11]. M3G has not been regarded as being active in humans [3] but antagonises morphine and M6G in rats [15]. The relative contributions of M6G, M3G and parent morphine to the analgesic effect are unknown [2, 3]. If only parent morphine is active, our data suggest that equivalent analgesia would result from MST administration by either route. If M6G is also active, greater analgesia would be expected after oral administration. If M3G is antagonising M6G, no overall analgesic difference would be expected, as the M3G:M6G ratio was the same by either route. Our data on efficacy do not clarify this issue. A retrospective subjective review of analgesic requirements after a change from oral to rectal MST administration showed that no patient required an increased dose, whereas 11 of 39 patients required a decreased dose [8].

Reports on the relative dose requirements for non-sustained-release preparations given via the two routes have been inconsistent. The bioavailability of parent morphine following rectal administration as a suppository was similar to that following oral administration of a morphine solution [10]. Other investigators have suggested giving 2–2.5 times the oral dose to achieve equivalent analgesia by the rectal route [7]. Morphine suppositories may vary in formulation, as they are not made commercially. The absolute bioavailability of morphine following oral administration in cancer patients is known to be variable (15%–64%) and to be related to variations in liver function, in liver blood flow and in the status of the gut mucosa [14]. The absolute bioavailability of morphine following rectal administration in healthy patients is also known to be variable (41%–88%) and may be related to adsorption to faeces, to

poor absorption from rectal mucosa [5] and to the state of hydration [17].

In cancer patients, the oral route may become unsuitable for MST administration as a result of vomiting, dysphagia or decreased level of consciousness or following an anaesthetic. The rectal route of administration offers a simple alternative to subcutaneous or intravenous infusion, and MST provides a consistency in formulation that morphine suppositories may lack.

The rectal use of MST is not recommended routinely. The results of this study support the use of the rectal route of administration of MST when the oral route is no longer available and the parenteral route is undesirable or impractical. We recommend that in changing from oral to rectal administration, the same dose and dose interval be used, but dose adjustment may be needed.

Acknowledgements. We are grateful to the patients who participated in this study and to Charge Nurse Ms. D. Gunn and the nurses of Ward 30, Christchurch Hospital, who helped in their care. We thank Drs. A. Abdelaal and C. Atkinson and Assoc. Prof. B. Colls for allowing their patients to be studied, Dr. C. Frampton for statistical advice and Douglas Pharmaceuticals Ltd. for funding the morphine assays.

References

1. Cockcroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. Nephron 16: 31–41
2. Hanks GW, Hoskin PJ, Aherne GW, Turner P, Poulain P (1987) Explanation for potency of repeated oral doses of morphine? Lancet II: 723–725
3. Hoskin PJ, Hanks GW (1990) Morphine: pharmacokinetics and clinical practice. Br J Cancer 62: 705–707
4. Joel SP, Osborne RJ, Slevin ML (1988) An improved method for the simultaneous determination of morphine and its principal glucuronide metabolites. J Chromatogr 430: 394–399
5. Jonsson T, Christensen CB, Jordening H, Frølund C (1988) The bioavailability of rectally administered morphine. Pharmacol Toxicol 62: 203–205
6. Kaiko RF, Healy N, Pav J, Thomas GB, Goldenheim PD (1989) The comparative bioavailability of MS Contin tablets (controlled release oral morphine) following rectal and oral administration. RSM Int Congr Symp Ser 149: 235–241
7. Lipman AG, Anderson BD (1984) Bioavailability of morphine from rectal suppositories. Am J Hosp Pharm 41: 636–638
8. Maloney CM, Kesner RK, Klein G, Bockenstette J (1989) The rectal administration of MS Contin: clinical implications of use in end stage cancer. Am J Hospice Care July/August: 34–35
9. Meed SD, Kleinman PM, Kantor TG, Blum RH, Savarese JJ (1987) Management of cancer pain with oral controlled-release morphine sulfate. J Clin Pharmacol 27: 155–161
10. Moolenaar F, Visser J, Leuverman A, Schoonen BJM (1988) Bioavailability of morphine from suppositories. Int J Pharm 45: 161–164
11. Osborne R, Joel S, Trew D, Slevin M (1988) Analgesic activity of morphine-6-glucuronide. Lancet I: 828
12. Poulain P, Hoskin PJ, Hanks GW, et al. (1988) Relative bioavailability of controlled release morphine tablets (MST Continus) in cancer patients. Br J Anaesth 61: 569–574
13. Revill SI, Robinson JO, Rosen M, Hogg MIJ (1976) The reliability of a linear analogue for evaluating pain. Anaesthesia 31: 1191–1198
14. Säwe J, Dahlström B, Paalzow L, Rane A (1981) Morphine kinetics in cancer patients. Clin Pharmacol Ther 30: 629–635
15. Smith MT, Watt JA, Cramond T (1990) Morphine-3-glucuronide – a potent antagonist of morphine analgesia. Life Sci 47: 579–585
16. Svensson JO, Rane A, Säwe J, Sjoqvist F (1982) Determination of morphine, morphine-3-glucuronide and (tentatively) morphine-6-glucuronide in plasma and urine using ion-pair high-performance liquid chromatography. J Chromatogr 230: 427–432
17. Van Hoogdalem EJ, Boer AG de, Breimer DD (1991) Pharmacokinetics of rectal drug administration. Clin Pharmacokinet 21: 11–26
18. Veng-Pedersen P (1989) Mean time parameters in pharmacokinetics; definition, computation and clinical implications. Clin Pharmacokinet 17: 424–440