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The bioavailability and pharmacokinetics of morphine after intravenous, oral and buccal administration in healthy volunteers

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1 The absolute bioavailability of morphine from oral aqueous solution, a controlled release oral tablet (MST-Continus) and a controlled release buccal tablet has been investigated in six healthy volunteers.
2 Analysis of plasma samples for morphine and its active metabolite morphine-6-glucuronide (M6G) was by means of a differential radioimmunoassay technique. Absolute bioavailability for morphine was estimated to be 23.9% after oral solution, 22.4% after MST-Continus and 18.7% after the buccal tablet. Maximum plasma morphine concentrations were seen at 45 min (oral solution), 2.5 h (MST) and 6 h (buccal).
3 There was no difference in the amount of M6G appearing in plasma after intravenous, oral or buccal administration but the mean ratio of AUCs for M6G : morphine in plasma after intravenous morphine was 2 : 1 compared with 11 : 1 after oral and buccal morphine.

Keywords morphine pharmacokinetics bioavailability buccal controlled-release

Introduction

In the treatment of chronic pain associated with advanced cancer, morphine given by regular oral administration is a highly effective drug when a strong analgesic is required (Hanks & Hoskin, 1986). Despite extensive clinical experience, however, there is little reliable information on its bioavailability and pharmacokinetics. In particular there has been no prospective investigation of the absolute bioavailability of oral formulations of morphine in healthy subjects. The main reason for this has been the difficulty in developing assay techniques to measure morphine and its main metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). M6G may contribute to the pharmacodynamic effect of repeated oral doses of morphine (Hanks *et al.*, 1987).

The first choice route of administration in chronic pain is by mouth and two formulations of morphine are available in the UK: aqueous morphine sulphate solution (MSS) and a controlled release tablet based on the Continus system (MST Continus, Napp Laboratories). Recently there has been interest in buccal administration of morphine which may be of particular value in patients who are unable to swallow. However, there are few data on the bioavailability or efficacy of morphine given by this route.

We have completed an investigation of the absolute bioavailability of oral aqueous morphine sulphate solution, oral controlled release morphine sulphate tablets, and buccal controlled release morphine sulphate tablets in healthy volunteers.

Method

Six healthy volunteers (four female, two male) with a mean age of 31 years (range 26–40) were included in the study. One of the volunteers (male) was a regular smoker. All underwent a general medical examination, chest X-ray,

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routine haematology, biochemistry, and urinalysis. All subjects had normal hepatic and renal function. A urine specimen was also examined in a screen for psychotropic or other drugs with CNS activity. The study had the approval of the Ethics Committee of the Royal Marsden Hospital and written informed consent was obtained from each subject.

Subjects were fasted from midnight on the study day and at 08.00 h an intravenous cannula was inserted into a forearm vein. All subjects received an intravenous morphine sulphate injection (5 mg), oral aqueous morphine sulphate solution (10 mg in 10 ml), a controlled-release oral morphine sulphate tablet (MST Continus) (10 mg), and a controlled-release buccal morphine sulphate tablet (10 mg). The doses used were constrained by the availability of 10 mg controlled-release tablets and the limitation of not using higher doses in normal volunteers. The oral solution was freshly prepared in distilled water no more than 24 h before administration. The subjects received each formulation at intervals of at least 1 week in the same order: oral solution, buccal tablet, MST tablet, i.v. injection. The intravenous injection was administered over 2 min. The aqueous solution and oral controlled-release tablet were taken with 100 ml tap water. After administration of the doses the subjects remained supine and fasting for 2 h. Venous blood samples were obtained at 15, 30, 45, and 60 min, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10 and 12 h after the oral and buccal form; and at 2, 5, 10, 15, 30, 45, and 60 min, 1.5, 2, 2.5, 3, 4, 6, 8, and 12 h after the start of the intravenous injection. Venous blood was collected into plastic heparinised tubes and spun immediately at 3,500 rev min^{-1} for 10 min. Plasma was separated and stored at −20°C prior to analysis.

Assay method

Morphine was measured by a specific radioimmunoassay using an antiserum raised in sheep to an *N*-succinyl normorphine-BSA conjugate which cross-reacts with M6G and M3G at 50% of zero binding to the extent of 0.013% and 0.011%, respectively (Aherne & Littleton, 1985).

The assay was carried out in plastic tubes (LP3 Luckhams Ltd), and 0.05 M phosphate-buffered saline pH 7.4, containing 0.1 g% gelatin was used as the buffer. One hundred μl of diluted morphine alkaloid standard (0.2–4.0 ng ml^{-1}) or suitably diluted plasma sample, 100 μl of diluted antiserum (1 : 100), and 100 μl of diluted [^{3}H]-dihydromorphine (Amersham International plc) equivalent to 0.3 pmol were incubated with 300 μl assay buffer for 1 h at 4°C. Phase separation was achieved using 100 μl of dextran-coated charcoal (2.5% w/v) and following centrifugation (10 min, 2500 rev min^{-1}) an aliquot of each supernatant was taken for liquid scintillation counting. The limit of assay for plasma samples was approximately 0.1 ng ml^{-1} and recovery of morphine added to normal drug-free plasma was 100, 105 and 101.2% at morphine concentrations of 1, 10 and 100 ng ml^{-1}. Quantitative recovery of morphine was also obtained in plasma spiked with both morphine and either M6G or M3G at morphine to metabolite ratios of 1 : 1 to 1 : 100 (101.3% recovery, CV 9.03% for M6G and 90.7% recovery, CV 8.3% for M3G, $n = 6$). Aliquots of a control serum sample were assayed twice in each assay and a mean value of 123 ng ml^{-1} ($n = 40$, CV = 8.8%) was obtained. This radioimmunoassay has been validated against a specific high performance liquid chromatography assay (Svensson, 1986), the correlation coefficient for 41 samples containing morphine concentrations from 1 to 75 ng ml^{-1} being 0.9787 ($y = -0.83 + 1.24\ x$). These results have also been analysed using the method described by Bland & Altmann (1986), and the mean difference between the methods was 1.5 ng ml^{-1} (s.d. = 4).

Concentrations of M6G were measured using a differential radioimmunoassay technique similar to that described by Hand *et al.* (1987). Samples were analysed using the methodology described above except that an antiserum which was raised in a goat to a 6-succinyl morphine-BSA conjugate was used. This antiserum cross-reacts completely with M6G but by less than 3% with M3G. In samples spiked with morphine and increasing amounts of M6G, complete recovery (98.5%, CV 8.1%, $n = 6$) of both morphine and metabolite was obtained. The concentration of M6G was calculated by subtracting the amount of morphine measured with the specific antiserum, from the result obtained with the goat antiserum. M6G concentrations obtained in this way correlated with results obtained by h.p.l.c. (Svensson, 1986), $r = 0.9601$, but were consistently higher ($y = 0.147 + 1.6\ x$). Using the method of Bland & Altmann (1986) the mean difference between the methods across a range of concentrations from 4 ng ml^{-1} to 100 ng ml^{-1} was 9.4 ng ml^{-1} (s.d. = 9.4).

Statistical analysis

The area under the curve from time zero to infinity (AUC) and elimination half-life were calculated using STRIPE (Johnston & Woollard, 1983), an interactive curve stripping program. The AUC was calculated from time zero for each set of data. The extrapolation to infinity resulted

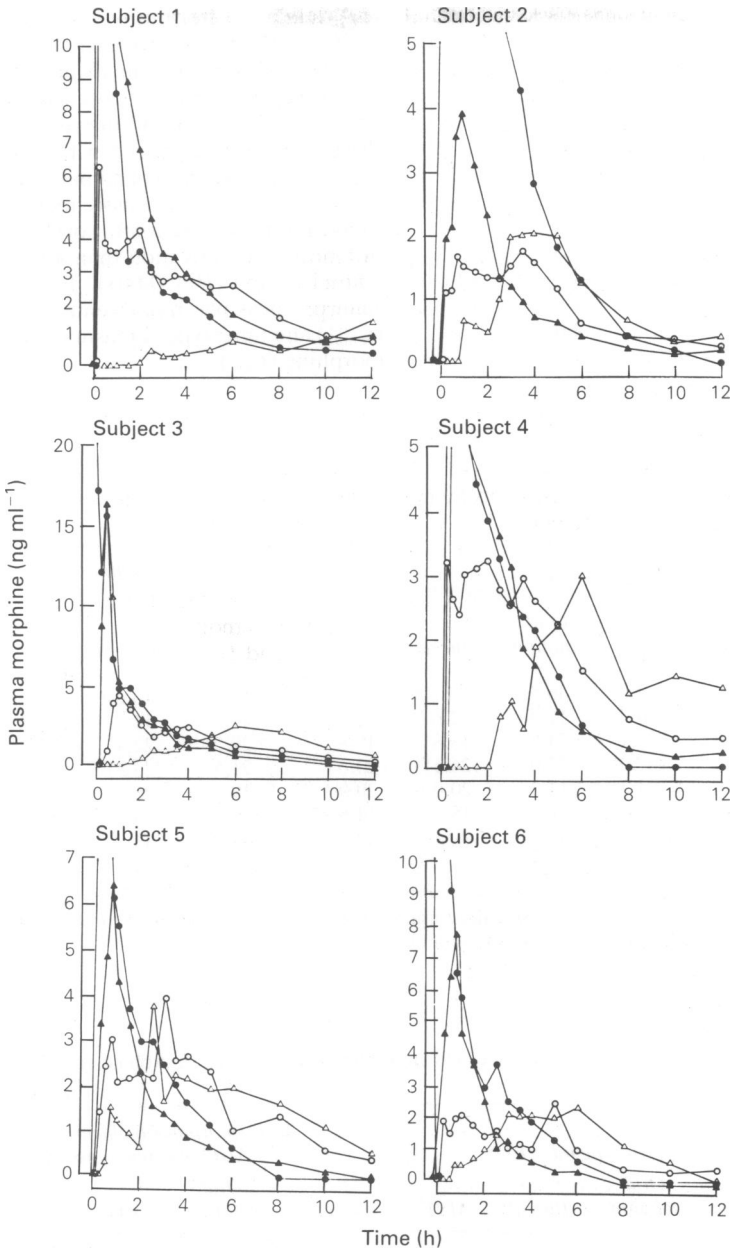

Figure 1 Individual plasma concentration-time profiles for morphine after intravenous injection (●), oral solution (▲), MST-Continus (○) and controlled release buccal tablet (△).

in an increase compared with the AUC_{0-12} of less than 10% for morphine and up to 30% for M6G reflecting the difference in elimination phases for morphine and M6G. Clearance was determined by the ratio of dose over AUC. Data were compared using Student's paired *t*-test.

Results

The individual concentration *vs* time profiles for the four formulations studied in each of the six subjects are shown in Figure 1.

Table 1 gives details of elimination half-life

Table 1 Pharmacokinetic parameters for morphine after i.v. administration

Subject	$t_{½}$ *(h)*	*Clearance (ml min^{-1} kg^{-1})*
1	2.2	13.9
2	1.5	16.1
3	2.5	21.0
4	1.5	40.4
5	1.7	29.3
6	1.8	22.2
Mean	1.9	23.8
s.e. mean	0.2	4.0

and clearance after intravenous morphine. The AUC for morphine after each of the four routes together with absolute bioavailability for each of the oral and buccal routes is shown in Table 2. The AUC for M6G and the relative amount of this metabolite compared with morphine after each of the four routes of administration is shown in Table 3. Significantly more metabolite relative to morphine is present after oral administration or buccal administration than after intravenous administration ($P < 0.001$). Table 4 shows the values for peak plasma concentration of morphine (C_{max}) and time to peak plasma concentration of morphine (t_{max}).

Table 2 AUC and bioavailability for morphine after oral and buccal administration (i.v. corrected to 10 mg dose)

	AUC (ng ml^{-1} h)				*% absolute bioavailability*		
Subject	*i.v.*	*Oral solution*	*Buccal*	*MST*	*Oral solution*	*Buccal*	*MST*
1	102.6	46.5	(18.1)*	31.9	45.3	(10.6)*	31.0
2	106.7	11.9	12.6	11.5	11.2	11.8	10.7
3	85.1	24.9	18.8	19.8	29.2	22.1	23.2
4	107.0	23.0	(26.1)*	23.6	21.5	(20.5)*	22.0
5	74.7	14.3	20.0	20.9	19.2	26.7	28.1
6	75.2	12.5	15.1	14.6	16.7	20.1	19.4
Mean	91.9	22.2	16.6	20.4	23.8	20.2	22.4
s.e. mean	6.3	5.3	1.7	2.9	4.9	3.1	2.9

* These figures are derived using the elimination rate after *i.v.* administration and are not included in the calculation of the means.

Table 3 AUC for morphine-6-glucuronide and morphine-6-glucuronide : morphine ratio (i.v. data corrected to 10 mg dose)

	AUC (ng ml^{-1} h)				*AUC (morphine-6-glucuronide) : AUC (morphine) ratio*			
Subject	*i.v.*	*Oral solution*	*Buccal*	*MST*	*i.v.*	*Oral solution*	*Buccal*	*MST*
1	210.4	310.7	*(227.9)	206.5	2.0 : 1	6.7 : 1	*(12.6 : 1)	6.5 : 1
2	189.8	185.2	138.0	199.5	1.8 : 1	15.6 : 1	10.9 : 1	17.3 : 1
3	170.9	149.6	144.3	151.7	2.0 : 1	6.0 : 1	7.7 : 1	7.7 : 1
4	247.1	257.8	*(301.0)	191.7	2.3 : 1	11.2 : 1	*(11.5 : 1)	8.1 : 1
5	140.6	218.9	268.1	254.0	1.9 : 1	15.3 : 1	13.4 : 1	12.1 : 1
6	143.7	131.6	145.0	221.5	1.9 : 1	10.5 : 1	9.9 : 1	15.1 : 1
Mean	183.7	209.0	173.8	204.2	#2.0	10.9 : 1	10.5 : 1	11.1 : 1
s.e. mean	20.2	27.6	31.4	13.8	0.1	1.6	1.2	1.8

Difference is significant compared with oral, MST and buccal routes, $P < 0.001$

* These figures are derived using the elimination rate after i.v. administration and are not included in the calculation of the means.

Table 4 Values for maximum peak concentration (C_{max}) and time to peak concentration (t_{max}) for morphine

	C_{max} ($ng\ ml^{-1}$)				t_{max} (h)			
Subject	*i.v.*	*Oral solution*	*Buccal*	*MST*	*i.v.*	*Oral solution*	*Buccal*	*MST*
1	315.0	16.2	1.4	6.2	0.03	0.25	12.0	0.25
2	276.0	3.9	2.0	1.8	0.03	1.00	4.0	3.5
3	314.0	16.4	2.5	4.5	0.03	0.50	6.0	1.0
4	574.0	12.7	3.0	3.2	0.03	0.75	6.0	2.0
5	274.0	6.5	3.7	3.9	0.03	0.75	2.5	3.0
6	288.0	7.8	2.3	2.4	0.03	0.75	6.0	5.0
Mean	340.2	10.6	2.5	3.7	Median 0.03	0.75	6.0	2.5
s.e. mean	47.3	2.15	0.33	0.64				

(i.v. data corrected to 10 mg administered dose)

Discussion

The pharmacokinetic parameters after intravenous administration of morphine in these healthy volunteers are in keeping with those reported from other recent studies in which specific morphine assays have been used (Owen *et al.*, 1983; Sawe *et al.*, 1985; Persson *et al.*, 1986). No evidence of dose-dependence with increases of up to 23 times an initial oral dose has been seen in the plasma kinetics of morphine in cancer patients (Sawe *et al.*, 1983). There are no reliable data for the absolute bioavailability of an oral elixir in healthy volunteers but studies in cancer patients have reported mean values between 26 and 47% (Sawe *et al.*, 1981, 1985; Gourlay *et al.*, 1986). The findings in this study show a lower absolute bioavailability in healthy volunteers. One study has reported a bioavailability of 100% for oral solution in patients (McQuay *et al.*, 1983) but the assay method employed is now recognised to cross-react extensively with metabolites giving a falsely elevated result (Aherne & Littleton, 1985).

The absolute bioavailability for morphine of controlled release morphine sulphate (MST Continus) was not significantly different from that after oral aqueous solution, in keeping with a number of studies (Hanks *et al.*, 1981; Savarese *et al.*, 1986; Homesley *et al.*, 1986; Sloan *et al.*, 1987; Khojasteh *et al.*, 1987; Poulain *et al.*, 1988) which have shown the relative bioavailability of MST compared with aqueous solution to be between 85 and 94%. The figure (for absolute bioavailability) of 22% is similar to that reported by Vater and his colleagues (1984), who investigated the intravenous pharmacokinetics of morphine in a group of healthy volunteers, and in a subsequent study compared these data with plasma concentrations after MST administered to the same subjects.

The buccal tablet appeared to yield similar amounts of morphine but with greater inter-subject variation, not only in bioavailability but also in C_{max} and t_{max}. The reasons for this are unclear since buccal absorption of morphine in aqueous solution occurs readily (AlSayed *et al.*, 1987). Differing rates of dissolution of the buccal formulation used in this study may account for the variability in the results and similar problems have been reported with another buccal formulation (Fisher *et al.*, 1987). Two subjects failed to reach an elimination phase at 12 h, and the AUC in these has been estimated using the elimination half-life determined after intravenous injection. These data are therefore less reliable than those obtained from the intravenous and oral routes, and have been excluded from the calculated mean values.

The appearance of M6G in the plasma after each of the oral and buccal preparations was remarkably similar. Relatively more metabolite was produced after oral administration than intravenous administration. It is perhaps a little surprising that a similar amount was also produced after buccal administration which should avoid the first pass effect. This may reflect swallowing of morphine released from the buccal preparation since no measures were taken to prevent this.

The ratio of AUCs for M6G to morphine of around 11 : 1 after oral administration is higher than has been reported previously after single doses of morphine and is the same as that found in cancer patients after chronic oral administration (Poulain *et al.*, 1988). This may be due in part to some overestimation of M6G using the differential RIA technique due to cross-reactivity of the antiserum with M3G. Such cross-reactivity has been seen in recovery experiments when the ratio of morphine to M3G is greater than 1 : 50, resulting in overestimation by up to 40%. It is

however difficult to estimate the effect of this *in vivo* when not only morphine and M3G, but also M6G and possibly other morphine metabolites, are present and competing for the antiserum binding sites.

M6G is highly polar and is therefore likely to cross the blood brain barrier with difficulty. We believe that on chronic administration of oral morphine the distribution of M6G within the CNS contributes significantly to the overall analgesic effect, and that the poor effect of single doses is explained by extensive first pass metabolism of morphine to inactive metabolites and slow passage of M6G across the blood brain barrier (Hanks *et al.*, 1988).

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