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Serum morphine concentrations after buccal and intramuscular morphine administration

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1 This study compared serum concentrations of morphine after administration of a buccal tablet (25mg) with those after intramuscular injection (10mg).

2 Buccal morphine was administered to eleven healthy volunteers and intramuscular morphine was given to five preoperative surgical patients. Serum morphine concentrations were assayed by high performance liquid chromatography (h.p.l.c.) in samples taken up to 8 h after drug administration.

3 Mean maximum morphine concentrations were eight times lower after buccal administration than after intramuscular injection and occurred at a mean of 4 h later. Individual morphine concentration–time profiles showed marked interindividual variability after administration of the buccal tablet, consistent with considerable variation in tablet persistence time on the buccal mucosa.

Keywords morphine buccal serum concentrations

Introduction

Buccal morphine tablets have recently been developed which are claimed to produce a plasma concentration–time profile similar to that of intramuscular morphine. The mean plasma morphine concentration was found to rise more quickly after intramuscular than after buccal administration to a slightly earlier and slightly higher peak value, but buccal morphine exhibited a greater AUC(0, 8 h) (Bardgett *et al.*, 1984; Bell *et al.*, 1985). A 10 mg tablet was used in these studies. We have now measured serum morphine concentrations after administration of 25mg tablets of the same formulation to healthy subjects and compared them with those found after the intramuscular injection of 10mg morphine to surgical patients.

Methods

Five preoperative, elective surgical patients, without hepatic or renal disease and not receiving concurrent drug therapy were given intramuscular morphine (10 mg) as premedication 90 min before general anaesthesia for minor surgical procedures not involving further morphine administration, significant blood loss or intravenous infusions. Eleven healthy volunteers, who were not taking other drugs, were given a buccal morphine tablet (25mg). All subjects had nil-by-mouth during the studies.

Blood samples were drawn from the subjects immediately prior to and at intervals of 15*, 30, 60, 90*, 120, 180**, 240, 360 and 480 min after morphine administration (*i.m. subjects only, **buccal subjects only). Blood was collected into siliconised glass tubes through an indwelling peripheral venous cannula (Wallace 16g 2Y-Can). The samples were allowed to clot and serum was obtained after centrifugation. The serum samples were deep-frozen pending subsequent analysis for morphine by high performance liquid chromatography.

A note was made of the length of time the buccal tablet or its residue persisted on the buccal mucosa.

The investigation was performed with the informed consent of the subjects and after approval from the Hospital Ethics Committee.

Table 1 Demographic and tablet persistence data

	Age (years) mean (s.d.)	*Height (m) mean (s.d.)*	*Weight (kg) mean (s.d.)*	*Tablet (h) persistence mean (range)*	n
Intramuscular	50.8 (12.9)	1.71 (0.08)	79.3 (10.7)	N/A	5
Buccal	22.8 (1.3)	1.69 (0.07)	63.1 (6.3)	4.9 (3.3–7.1)	11

N/A = not applicable

Morphine assay

The following reagents and materials were used: morphine sulphate (King's College Hospital Pharmacy); nalorphine hydrobromide (Wellcome Foundation Ltd, Kent); h.p.l.c. grade water, methanol, acetonitrile, and analytical grade chloroform and propan-2-ol (Rathburn Chemicals Ltd, Scotland). Other chemicals were of analytical grade (BDH, Essex). ChemElut extraction columns (CE1003) were obtained from Analytichem International (CA, USA) via Jones Chromatography, Wales.

The h.p.l.c system comprised a Kratos Spectroflow 400 solvent delivery pump (ABI Analytical, Kratos Division, Cheshire), and a Rheodyne 7125 sample injector (Rheodyne, USA) fitted with a 100 μl loop and an analytical column (250 × 4.6 mm i.d.) packed with Spherisorb ODS-2 (5 μm) (HPLC Technology, Cheshire), preceded by an 'uptight precolumn' (C130-B, Upchurch Scientific, Inc., USA) packed with the same material. Both columns were housed in a Perkin Elmer LC 100 column oven (Perkin Elmer, Connecticut, USA) operating at 40°C. Electrochemical detection was carried out using a 5100A coulochem detector fitted with a 5100 detector cell (Environmental Sciences Associates, USA). The potential of detector 1 was maintained at 0.25V and that of detector 2 at 0.40V. Peak heights were measured with a Shimadzu C-R1A Chromatopac integrator (Shimadzu, Japan).

Morphine analysis was carried out using the extraction (method II) and chromatographic procedure described by Todd *et al.* (1982), with minor adjustments to volumes and concentrations of buffers and solvents used.

Calibration curves were linear over the concentration range studied and the lower limit of detection was 0.8 ng ml^{-1} morphine base. Recoveries of morphine base from spiked serum samples were 94.7% ± 4.6% at 8.2 ng ml^{-1} and 98.3% ± 3.4% at 81.8 ng ml^{-1} (± coefficient of variation, $n = 4$).

The inter-assay coefficient of variation was 7.4% ($n = 9$) at 4.1 ng ml^{-1} and 6.0% ($n = 6$) at 81.8 ng ml^{-1}. Intra-assay coefficients of variation ($n = 8$) at these concentrations were 3.9% and 3.4%, respectively.

Results

Demographic data and buccal tablet persistence times are shown in Table 1. Mean serum morphine concentration–time profiles obtained in the two groups of subjects are shown in Figure 1, indicating peak values of 70–75 ng ml^{-1} 30 min after intramuscular injection, but only 6–7 ng ml^{-1} achieved 3 h after buccal administration. Interindividual variability in drug concentration–time profiles was associated with mean C_{max} values of 84 and 11 ng ml^{-1}, and t_{max} values of 30 and 284 min, respectively. Mean values of AUC(0, 8 h) after intramuscular and buccal administration were 11337 and 2156 ng ml^{-1} min, respectively (Table 2).

Discussion

The two groups of patients and volunteers were not matched, so that age and weight related pharmacokinetic differences may have contributed to the results. Nevertheless we feel that the considerable difference in magnitudes and profiles of serum morphine concentration in the two groups more probably reflects the different modes of drug administration.

Table 2 Values (mean ± s.d.) of C_{max}, t_{max} and AUC(0, 8 h) after administration of intramuscular morphine 10 mg to surgical patients ($n = 5$) and buccal morphine 25 mg to healthy subjects ($n = 11$).

	C_{max} *(ng ml^{-1})*	t_{max} *(min)*	*AUC(0, 8 h) (ng ml^{-1} min)*
Intramuscular	84.4 (17.1)	30 (18)	11337 (2857)
Buccal	10.8 (6.6)	284 (132)	2156 (1313)

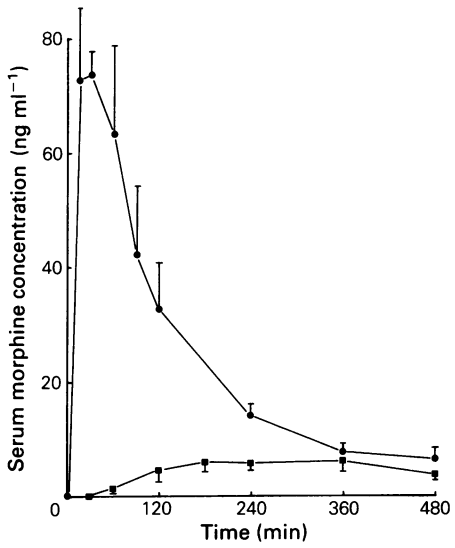

Figure 1 Change in serum morphine concentration (mean ± s.e. mean) with time after administration of intramuscular morphine 10 mg to surgical patients (●, $n = 5$) and buccal morphine 25 mg to healthy subjects (■, $n = 11$).

The serum drug concentration–time profiles observed after intramuscular administration of morphine (Figure 1) were similar to those found by Bell *et al.* (1985) using the same dose. However, whereas the latter found similar changes in morphine concentration with time after the administration of 10 mg morphine either buccally or intramuscularly, we found that the buccal administration of 25mg morphine resulted in a more slowly rising serum concentration (Figure 1). Thus, the mean C_{max} value was eightfold less than that following intramuscular injection, whilst mean t_{max} was almost tenfold greater. AUC (0, 8 h) was greater after intramuscular than after buccal administration (Table 2).

A feature of the serum morphine concentration data after administration of the buccal tablet was the large interindividual variation, particularly in t_{max}. This was suspected from clinical responses observed in our earlier investigation (Fisher *et al.*, 1986) and may reflect the wide range of tablet persistence times (Table 1). Individual serum morphine concentration–time profiles showed peak concentrations between 2 and 8 h post-dose. In two subjects the serum concentration was still rising at 8 h when blood sampling ceased. Further studies would require longer sampling times to characterise adequately the profile after buccal morphine.

In conclusion, buccal administration of the formulation of morphine which we have studied was an unpredictable mode of delivery. In contrast to the findings of others using a 10 mg tablet it did not produce serum morphine concentrations similar to those following intramuscular administration. To what extent such unpredictability is a function of the formulation or the route of administration is not clear.

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