An investigation of premedication with morphine given by the buccal or intramuscular route

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- 1 Premedication with 30 mg buccal morphine or 10 mg intramuscular morphine was evaluated in 40 healthy women undergoing major gynaecological surgery.
- 2 Buccal administration of morphine produced lower plasma morphine concentrations than intramuscular injection of morphine ($P < 0.01$).
- 3 The mean systemic availability of the buccal tablet, during the first 5 h after administration, was approximately 3% relative to that of the intramuscular preparation.
- 4 Poor absorption of buccal morphine resulted in inadequate sedation prior to surgery and poor post-operative analgesia.
- 5 Patients experienced difficulty with the buccal formulation of morphine; tablet bitterness and failure to dissolve were particular problems.

Keywords premedication analgesics narcotic morphine

Introduction

Morphine premedication was first used by Lorenzo Bruno in 1850, to reduce the 'trauma of anaesthesia and surgery' (Cohen & Beecher, 1951). Opioids are still widely used prior to surgery to smooth induction of anaesthesia, contribute to balanced anaesthesia and provide postoperative pain relief. Morphine premedication is usually administered intramuscularly, although alternatives, such as orally administered controlled release morphine (Kay & Healy, 1984; Pinnock *et al.*, 1985) or morphine suppositories (Hanning *et al.*, 1984), have been evaluated. Intramuscular injections are uncomfortable for the patient and demanding of nurses' time and skill. High plasma morphine concentrations occurring after intramuscular injection may lead to nausea and excessive sedation prior to surgery, and the relatively short duration of action of intramuscular morphine may result in poor pain relief in the early postoperative period. A simple

method of administering morphine, designed to produce a flatter plasma morphine concentration-time profile and a longer duration of action, would be desirable. Controlled release trans-buccal formulations of morphine have been developed, to allow morphine to be absorbed from the buccal mucosa, directly into the systemic circulation, at a constant rate (Bell *et al.*, 1985). The present study compared buccal with intramuscular morphine for premedication in women undergoing major gynaecological surgery.

Methods

Ethics Committee approval was granted for the study which involved 40 women undergoing major gynaecological surgery. All patients were healthy, and none was taking analgesic or psychotropic medication. Patients were ran-

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domly assigned to receive one of two pre-medication regimens, in a double-blind manner, either 30 mg buccal morphine 2 h before surgery and placebo intramuscularly 1 h before surgery, or buccal placebo 2 h before surgery and 10 mg morphine intramuscularly 1 h before surgery.

Patients were assessed by the anaesthetist before premedication, 1 h after premedication and prior to induction of anaesthesia using rating scales for sedation (1 alert and awake, 2 awake but drowsy, 3 asleep but easily roused and 4 asleep not easily roused) and emesis (1 none, 2 nausea, 3 nausea and vomiting and 4 repeated vomiting).

A standard anaesthetic was administered, which included thiopentone, paralysis with a competitive muscle relaxant, intubation and ventilation using 33% oxygen and 67% nitrous oxide with 0.5% halothane. All patients received fentanyl preoperatively on a weight basis (< 59 kg 0.1 mg, 60–80 kg 0.15 mg and > 81 kg 0.2 mg). The type and duration of surgery were noted. The same anaesthetist assessed sedation and emesis immediately after recovery from anaesthesia and at 1, 2 and 3 h postoperatively. Pain was also assessed at these times using a 10 cm visual analogue score and a rating scale (1 none, 2 mild, 3 moderate and 4 severe). Post-operative analgesia was given on request as papaveretum intramuscularly and emesis was treated with prochlorperazine. The time of administration of the first dose of papaveretum was noted. Patients were visited by the anaesthetist on the day after surgery and overall post-operative sedation and pain were assessed. Patients were asked to rate satisfaction with premedication and to give a preference for the buccal or intramuscular route of administration. Any problems experienced with the buccal tablets, by the patients or anaesthetists, were recorded.

Venous blood was sampled, prior to induction of anaesthesia, immediately after recovery from anaesthesia and 2 h postoperatively, for measurement of plasma morphine concentrations. Blood samples were collected on ice into heparinised, siliconised, glass tubes and plasma was stored at -20°C . Morphine was measured using a radioimmunoassay, with prior liquid-solid extraction, to reduce cross reactivity with glucuronides. All results were expressed as morphine base, the lowest limit of detection was 0.6 ng ml^{-1} and the mean deviation of measured from standard values was 6.5%.

Parametric data were analyzed using the Student's *t*-test or one way analysis of variance

for independent groups. The areas under the plasma morphine concentration-time curves (AUCs) were approximated, using the combined regular and logarithmic trapezoidal method (Chiou, 1978), in patients who had produced three blood samples prior to administration of supplementary intramuscular opioid. The mean systemic availability of the buccal tablet relative to the intramuscular injection, during the first 5 h after administration, was approximated from the ratio of the mean dose corrected AUCs. Non-parametric data, including pain scores, were analyzed using Chi square, Kruskal Wallis analysis of variance, Mann Whitney U test, Wilcoxon test and the binomial test.

Results

The ages, weights and duration of surgery were not significantly different in the two groups (Table 1). Two hours after surgery, prior to taking the third blood sample for morphine assay, 15 of the buccal group and 11 of the intramuscular group had already received supplementary intramuscular opioid. Morphine concentrations measured after administration of papaveretum were not included in the analysis. During the 5 h after administration of premedication, plasma morphine concentrations were lower after 30 mg buccal morphine than after 10 mg intramuscular morphine ($p < 0.01$, Figure 1). The mean (s.d.) AUCs, in patients who did not receive papaveretum, were $6.24 (2.5)\text{ ng ml}^{-1}\text{ h}$ after buccal morphine ($n = 5$) and $68.9 (13.4)\text{ ng ml}^{-1}\text{ h}$ after intramuscular morphine ($n = 9$) ($P < 0.01$). The mean systemic availability of buccal morphine, during the first 5 h after administration, was approximately 3% relative to that of intramuscular morphine.

No patient was sedated before premedication. Prior to induction of anaesthesia, more patients were sedated after intramuscular morphine (65%) than after buccal morphine (25%) ($P < 0.05$). There was no significant difference between the groups in sedation after surgery. There was no significant difference between the

Table 1 Mean (s.d.) age, weight and duration of surgery

	Intramuscular (n=20)	Buccal (n=20)
Age (years)	49.1 (9.5)	49.6 (11.0)
Weight (kg)	66.9 (9.6)	66.1 (10.2)
Duration (min)	49.3 (17.1)	48.4 (19.5)

Figure 1 Plasma morphine base concentrations at each time (mean $\pm$ s.e. mean); the data points at 5 h represent the five buccal and nine intramuscular patients who had not received papaveretum.

groups in postoperative emesis; in the buccal group, 42% patients were nauseated and 26% vomited and in the intramuscular group, 30% were nauseated and 40% vomited.

Pain was significantly worse in the buccal morphine group compared with the intramuscular morphine group at 3 h after surgery ($P < 0.05$). Patients rated pain as worse, during the 24 h after surgery, after buccal morphine than after intramuscular morphine premedication ($P < 0.05$). The mean (s.d.) time to the first dose of postoperative papaveretum was not significantly different between the two groups; 150.7 (224.7) min in the buccal group and 189.4 (239.2) min in the intramuscular group.

There was no significant difference between the groups in patients' satisfaction; 75% of the buccal group and 70% of the intramuscular group were satisfied with premedication. There was no significant difference in preference for buccal or intramuscular premedication; 70% of the buccal group and 55% of the intramuscular group stated that they would prefer an injection on a future occasion. Many patients experienced problems with the active buccal morphine tablet; of the 20 patients who received buccal morphine, six complained of bitter taste, eight stated that it was irritating because it did not dissolve and four swallowed it or had it removed prior to anaesthesia because it was loose. Examination of the 40 patients prior to anaesthesia

revealed that the tablet had migrated from the buccal sulcus in six cases.

Discussion

Initial assessment of a transbuccal formulation of morphine suggested that the preparation may be useful perioperatively. In 1984, a preliminary study by Bardgett *et al.* based on data from two volunteers, showed that small doses of buccal morphine (6 or 10 mg) produced detectable plasma morphine concentrations within 1–2 h and maintained concentrations for 4–6 h. Evaluation of 10 mg buccal morphine and 10 mg intramuscular morphine, in two patients following minor surgery, showed that morphine absorption was similar after both routes of administration (Bardgett *et al.*, 1984). In 1985, a larger study (Bell *et al.*) compared postoperative analgesia and morphine absorption, after administration of 10 mg buccal morphine or 10 mg intramuscular morphine to 40 patients who had undergone orthopaedic surgery. There was no significant difference in postoperative analgesia following buccal or intramuscular administration, however a 46% increase in bioavailability and a reduction in adverse effects was reported after buccal morphine.

In view of the favourable outcome of studies of the use of buccal morphine as a post-operative analgesic, its role as premedication was assessed. In 1986, Fisher and colleagues evaluated premedication with 10 mg buccal morphine or 10 mg intramuscular morphine in 50 surgical patients. They recorded sedation and anxiety, but did not study postoperative pain or measure plasma morphine concentrations. Intramuscular morphine was shown to be a better sedative than buccal morphine, and problems with acceptability of the buccal tablets were reported for the first time. The bitter taste of the buccal preparation was sufficient for a significant number of patients to prefer injectable morphine over the buccal tablet.

In a later study, plasma morphine concentrations were measured after 25 mg buccal morphine was given to 11 volunteers, and 10 mg intramuscular morphine was given to five patients prior to surgery. It was shown that absorption of morphine from the buccal mucosa was significantly less than after intramuscular administration; the mean systemic availability of buccal morphine was only approximately 7.6% relative to that of intramuscular morphine (Fisher *et al.*, 1987). In the present study the mean systemic availability of buccal morphine during the first 5 h after administration was 3%

relative to that of intramuscular morphine. Consequently, inadequate absorption of morphine from the buccal mucosa led to poor pre-operative sedation and inadequate post-operative analgesia.

The present study also highlighted the lack of acceptability of buccal morphine in the peri-operative period; 30% patients complained about tablet bitterness and 40% were irritated by the persistence of the tablet. There was concern about migration of buccal tablets at a time when patients' protective reflexes may be depressed; 15% buccal tablets were removed prematurely because the anaesthetist, or the patient, was fearful about the possibility of inhalation of the tablet. A recent study of absorption of 20 mg buccal morphine in five healthy

volunteers showed that the mean time to achieve maximum plasma morphine concentrations was 6.8 h after administration (Fisher *et al.*, 1988). In the present study, the lack of acceptability of the buccal preparation, leading to premature removal of the tablet within the first 5 h after administration, may have been partly responsible for the poor absorption of morphine from the buccal mucosa.

In conclusion, morphine absorption was severely limited after administration of a buccal formulation of morphine to patients awaiting surgery. Furthermore, the bitterness, lack of dissolution and mobility of the buccal morphine tablets made administration of the preparation unacceptable in the perioperative period.

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