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SUBLINGUAL BUPRENORPHINE USED POSTOPERATIVELY: CLINICAL OBSERVATIONS AND PRELIMINARY PHARMACOKINETIC ANALYSIS

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1 Buprenorphine is a long-acting opiate analgesic. This study was designed to investigate the pharmacokinetics of this drug when given by the sublingual route to ten postoperative patients. Plasma levels of buprenorphine were measured by a specific radioimmunoassay.

2 Plasma levels of the drug following sublingual administration of 0.4 mg showed an apparent delay in absorption and then rose slowly to reach low but significant levels by 3 h. There was considerable variation in the time at which peak levels were achieved. The average systemic availability of the drug by this route was estimated to be 30% by 3 h.

3 Analgesic efficacy and duration of sublingual buprenorphine were assessed using demand analgesia. The analgesia was of about 9 h duration, similar to that achieved by parenteral administration of 0.3 mg of the drug to an equivalent group of patients. The sublingual dose caused a significant fall in the postoperatively elevated plasma glucose, and prevented any further rise in plasma cortisol.

4 Reasons for the efficacy of the sublingual route are discussed and it is suggested that this route may be particularly appropriate for highly lipophilic drugs like buprenorphine.

Introduction

Potent opiate analgesics all show a considerable first pass effect, with large interindividual variation in its extent. The oral route for these drugs is consequently unpredictable; the route is therefore unsatisfactory in the management of postoperative pain. Sublingual doses of potent analgesics avoid initial hepatic passage and are as convenient as the oral route for the patients and nursing staff. In addition, the high first pass effect then acts as a safety factor should the drug be swallowed.

Buprenorphine is a synthetic opiate analgesic with mixed agonist-antagonist properties. It has been shown to be effective by the sublingual route in postoperative pain (Edge, Cooper & Morgan, 1979), and the suitability of the drug for this route is suggested by its high lipophilicity, high first pass effect, long duration of action and low addiction potential.

This study was designed primarily to measure plasma levels of buprenorphine given sublingually. In addition the resulting analgesic effect together with the effects of the drug on ventilation and metabolism were studied.

The design and method was the same as that used to establish the kinetics and effects of the drug when given by the intravenous and intramuscular routes (McQuay *et al.*, 1980), to permit comparison of drug kinetics and effects when given by the three routes.

Methods

Ethical committee approval was obtained to perform this study and signed consent to research forms were obtained from each patient.

Ten patients undergoing elective total hip replacement at the Nuffield Orthopaedic Centre, Oxford, were selected sequentially from operation lists provided that their age was between 45 and 75 years and their weight was less than 80 kg. Those with serious medical disorders or taking cardiovascular drugs other than thiazides were excluded. Preoperative full blood count and biochemical profile were normal in all patients.

Patients underwent an anaesthetic technique which was identical to that reported in detail in a similar study utilizing parenteral buprenorphine (Bullingham *et al.*, 1980). Patients were premedicated with 10 mg diazepam orally 2 h preoperatively. Thiopentone 4 mg/kg and pancuronium 0.1 mg/kg

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were followed by intubation and mechanical ventilation on the Bain circuit; the tidal volume was 10 ml/kg and fresh gas flow 70 ml/kg using nitrous oxide and oxygen (2:1) and halothane 0.5%. Fluid administration was with 5 ml kg^{-1} h^{-1} of Hartmann's solution for the first 2 h, and then with blood transfusion to a specific schedule depending on the preoperative haemoglobin and the blood loss. At the end of surgery the anaesthetic gases were discontinued and residual neuromuscular blockade was reversed by atropine 1.2 mg and neostigmine 2.5 mg given intravenously.

Buprenorphine (0.3 mg) diluted to 10 ml with normal saline was injected intravenously over 1 min following induction of anaesthesia. Blood samples for plasma buprenorphine levels following the intravenous dose were taken at 0, 30, 150 and 180 min, and for blood gases and hormones at 30 and 150 min.

Postoperatively, and 3 h after the first dose of buprenorphine, a further 0.4 mg (two 0.2 mg tablets) was given sublingually, provided that patients were able to open their eyes to command. Patients were instructed to keep the tablets under the tongue, and neither to chew nor swallow them. Blood samples for plasma buprenorphine levels were taken at 0, 5, 10, 15, 20, 40, 60, 80, 120, 150 and 180 min. Samples for blood gas and hormone assays were taken at 10, 60, 120 and 180 min.

Blood samples were taken through a radial artery cannula (0.53 mm i.d., Longdwell), which was used for intraoperative direct arterial pressure monitoring. The samples were collected into lithium heparin and potassium fluoride tubes; after centrifugation the plasma was separated and stored at −20°C until analysed. Buprenorphine was measured by radioimmunoassay, using the method of Bartlett *et al.* (1980), cortisol by the method of Beardwell, Burke & Cope (1968) and glucose by a standard glucose oxidase procedure. Blood gases were measured using a Radiometer ABL2 blood gas analysis system.

Pharmacokinetic analysis

1 The intraoperative plasma buprenorphine values of the ten patients were compared individually against the mean intravenous kinetics established previously in an equivalent study (Bullingham *et al.*, 1980). All values were within two standard deviations from this mean curve. The mean decay curve for the present patient group was therefore assumed to be as previously established.

2 The contribution of the initial (i.v.) buprenorphine dose to the measured plasma levels after the sublingual dose was computed from the known mean terminal exponential decay rate (Bullingham *et al.*, 1980) of the first dose, applied to the values obtained in that individual. By subtracting these computed values from the measured plasma levels after the sublingual dose, plasma levels were obtained which represent the contribution of the sublingual dose alone. This procedure assumes linear behaviour of the pharmacokinetic system. The excellent fit to a triexponential model for parenteral doses provides justification for this (Bullingham *et al.*, 1980).

3 The individual stripped plasma buprenorphine values obtained in (**2**) were averaged. Area under the curve for the first 3 h after the sublingual dose (AUC_{3sl}) was estimated from these by numerical integration (Greville, 1969). The sublingual AUC_{3sl} was then compared with an intravenous postoperative total AUC_{iv} (zero to infinity). This was computed as the mean of the total AUC_{iv}s obtained from a different but strictly comparable ten patients who had received 0.3 mg intravenously as their postoperative dose (Bullingham *et al.*, 1980); the AUC_{iv} was multiplied by 4/3 to obtain dose equivalence. Systemic availability of the sublingual dose to 3 h was then calculated as $AUC_{3sl}/1.33AUC_{iv}$.

Demand analgesia

Six hours after the first dose of buprenorphine the patients were connected to a demand analgesia system via a separate 0.6 mm i.d. intravenous cannula (21 g Butterfly). The system had been explained to them the previous day. The apparatus used a modified Mill Hill infusion pump (Muirhead Ltd, 34 Croydon Rd, Beckenham, Kent), which delivered 0.25 mg diamorphine each time that the patient pressed a button. This was the only analgesia received by the patients until they left the recovery room the following morning. The analgesic demands were recorded automatically over this period.

i) Duration of analgesia The automatic recordings of each patient's postoperative analgesic demands were analysed to provide quantification of the duration of action of buprenorphine. Time to the fifth demand made by each patient was used. The choice of the fifth demand was made because of the potentially exploratory nature of the initial presses, though a number of other criteria (time to 2, 3 or 4 demands and regression to zero demand axis at the time when demands became frequent) gave similar results.

ii) Sex difference The difference in drug analgesic effect between men and women was shown by a comparison of regression slopes obtained from plots of the averaged cumulative demands for each 15 min period against time. The demands made between 60 and 600 min were used for the analysis and values between 0 and 60 min were excluded because, in this initial period, the slopes were markedly different from the succeeding 9 h.

Results

The age, weight, sex distribution, duration of surgery and intraoperative Pa_{CO_2} values are shown in Table 1. The patient group showed no significant differences for these variables from the previously described parenteral groups (McQuay *et al.*, 1980). The intraoperative course was uneventful with no unexpected changes in pulse and blood pressure.

Table 1 Patient data ($n = 10$)

Age (years)	59.8 ± 3.7
Weight (kg)	68.8 ± 3.0
Duration of surgery (min)	99.9 ± 3.8
Intraoperative Pa_{CO_2} (kPa)	4.90 ± 0.18
Blood loss (ml)	510 ± 91.0
Sex distribution	6M:4F

Results are mean ± s.e.mean

Following the sublingual dose, the onset of analgesia, estimated by the observer, occurred between 15 and 45 min. There was less drowsiness after the sublingual dose than had been noted for parenteral administration. One patient vomited 10 min after the sublingual dose was given, and one of the tablets was returned in the vomitus. This patient showed typical absorption of the sublingual buprenorphine, and his results are included for all analyses.

Plasma buprenorphine concentrations

The mean measured values after the sublingual dose are shown in Figure 1, together with the mean values obtained from the parenteral study. It can be seen that sublingual administration of buprenorphine results in a gradual rise in plasma level, producing values similar to those following intravenous and intramuscular administration at the 80 min sampling time. At the 150 and 180 min sampling times the plasma concentration of buprenorphine was significantly higher than following parenteral administration (0.3 mg).

Table 2 contains the values obtained by averaging the stripped values computed as described in **Methods**, pharmacokinetic analysis, (**2**). There was large individual variation in the plasma buprenorphine profile following sublingual administration in contrast to the consistent decay profiles observed when the drug was administered parenterally (Bullingham *et al.*, 1980). An average peak level of 0.74 ng/ml was reached at 150 min, but four patients had not achieved a peak level by the end of the 3 h sampling period. One patient achieved peak level at 20 min.

Table 2 Plasma buprenorphine levels after sublingual administration

Time (min)	*Plasma buprenorphine (ng/ml)*
0	0
5	0
10	0
15	0
20	0.07 ± 0.12
40	0.10 ± 0.12
60	0.28 ± 0.15
80	0.41 ± 0.17
120	0.51 ± 0.13
150	0.74 ± 0.16
180	0.71 ± 0.14

Measured plasma levels minus computed contribution from the first (i.v.) dose. Results are mean ± s.e.mean, from the ten patients.

The systemic availability of the sublingual dose, relative to the intravenous dose, from 0 to 180 min, estimated from the area under the curve, was 31%.

Analgesia

A continuous record of demands against time was obtained for each patient. The minimum record was for 11.9 h, the maximum 17 h. The total demands made by each patient at 7 and 13 h after the sublingual dose is shown in Figure 2. There were no significant differences between the three groups for the number of demands made, at either 7 or 13 h after their respective postoperative buprenorphine doses (Mann-Whitney U test).

i) Duration of analgesia The median estimate of duration of action was 534 min from the time the sublingual dose was given.

ii) Sex differences Men made significantly more demands than women; the male demand rate (mg diamorphine $\times 10^{-3}$/patient/min) was 8.3 ± 0.1 (mean ± s.e.mean), and that for females was 1.5 ± 0.1. This difference in rate for 60 to 600 min of demand system use was highly significant ($P < 0.0001$).

Blood gas analysis

The blood gas results are shown in Table 3. Postoperatively the Pa_{CO_2} values were raised above the normal range; there were no differences between men and women.

Hormones and metabolites

The measured plasma glucose and cortisol are shown in Table 3. Plasma glucose concentrations rose dur-

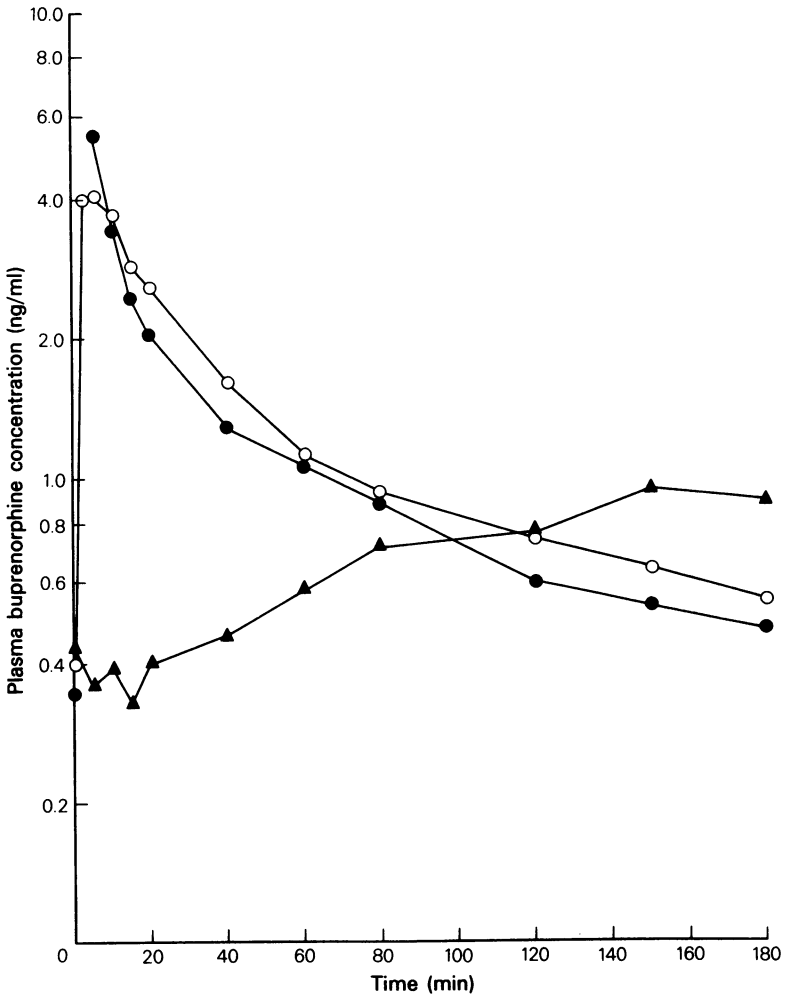

Figure 1 Mean measured plasma buprenorphine concentrations following administration of the second dose by different routes. (●) buprenorphine 0.3 mg i.v., (○) buprenorphine 0.3 mg i.m., (▲) buprenorphine 0.4 mg sublingually. Ten patients in each group: sublingual data as reported here and data after intravenous and intramuscular 0.3 mg doses from Bullingham *et al.* (1980). Plasma levels after the sublingual 0.4 mg dose were significantly higher ($P<0.01$) at the 150 and 180 min sampling points.

Table 3 Blood gas, cortisol and glucose values

Time (min)	*Pa_{CO_2} (kPa)*	*Pa_{O_2} (kPa)*	*Plasma cortisol (nmol/l)*	*Plasma glucose (mmol/l)*
0			337±53	4.46±0.09
30	4.90±0.18	23.4±1.2	439±86	5.56±0.40
150	5.90±0.38	15.4±1.1	832±33	7.03±0.46
190	6.27±0.22	15.4±1.1	923±53	7.23±0.45
240	6.39±0.19	16.0±1.1	927±51	7.15±0.43
300	6.11±0.20	15.3±1.3	1062±55	6.96±0.29
360	6.26±0.19	14.9±1.6	1022±32	6.65±0.25

Results are mean ± s.e.mean

ing operation and fell in the 3 h after the second dose by a mean of 0.58 mmol/l ($0.05>P<0.1$, paired *t*-test). This change was most apparent in the last hour of measurement, where the fall was 0.36 mmol/l, which was highly significant ($P<0.01$), using the paired data. Plasma cortisol levels rose during operation, but after the second dose of buprenorphine levels did not change significantly.

Discussion

The averaged kinetic data presented here for subling-

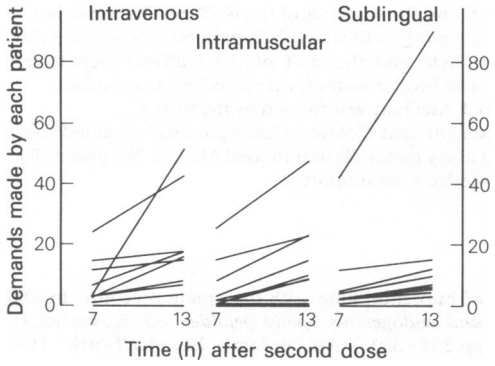

Figure 2 Postoperative analgesic demands made by each patient after a second dose of buprenorphine. Ten patients in each group. Data after postoperative intravenous and intramuscular doses from McQuay *et al.* (1980). No significant differences between the demands made by each group at the 7 and 13 h points (Mann-Whitney U test).

ual buprenorphine shows both delay in absorption and large intersubject variation in the buprenorphine plasma levels. These two observations would lead to the prediction of slow onset and variable efficacy.

In contrast, the analgesic onset time, duration and individual variation was not measurably different from that found after parenteral postoperative buprenorphine doses (McQuay *et al.*, 1980). Other analgesic measures have also shown sublingual buprenorphine to be effective in postoperative pain (Edge *et al.*, 1979). The surprising analgesic efficacy, despite low plasma levels, of the sublingual route may be explained by a general consideration of the dose-plasma level-response relation with respect to the sublingual route, and by specific features of buprenorphine.

Wagner (1969), in a theoretical paper, considered a single compartment model with a first order elimination rate constant (k_{el}) and a first order absorption rate constant (k_{ab}). He showed that as the ratio k_{el}/k_{ab} fell, the plasma profiles changed as anticipated, i.e. achieved lower, and later, peaks, but with more prolonged levels after peak. The change was most pronounced when k_{el}/k_{ab} became less than one. Assuming a drug receptor concentration/response relationship of a form analogous to the Michaelis–Menten relationship for enzyme kinetics, he also showed that the early responses could be alike despite the very different plasma profiles. In essence, this is because of the non-linear nature of the drug receptor concentration/response relationship.

The plasma curves presented here resemble the case when k_{el}/k_{ab} becomes less than one. Study of plasma levels beyond the 3 h reported here is required to estimate an absorption rate constant.

The limiting factor in this argument becomes the pharmacologically effective level of receptor occupancy. A high level of occupancy will require high drug levels at the receptor and thus implies high plasma levels, at least at some time during absorption. However, buprenorphine is very lipophilic and its association to the opiate receptor is relatively slow, but avid (Hambrook & Rance, 1976). Under these circumstances, a major determinant of loading of the opiate receptor is likely to be the time during which plasma buprenorphine levels are sustained. An effective level may be relatively low, and apparently variable, but it must be prolonged.

Thus the sublingual route may be particularly appropriate for buprenorphine, where the slow absorption rate combines with its associative properties with the opiate receptor to provide analgesia of long duration. An additional benefit may be that side-effects related to plasma level may differ by the sublingual route from those found with parenteral use. An indication of this was found here, where there was less sedation with sublingual buprenorphine. A similar effect has been noted for sublingual etorphine (Blane & Robbie, 1972).

The finding of a lower postoperative analgesic requirement in females was also true for parenteral administration (McQuay *et al.*, 1980). There was no difference in the plasma levels between the sexes in either study and there was no difference in the weights between the sexes. Other workers have seen a similar phenomenon with methadone (Kaiko *et al.*, 1977), and this suggests that the explanation lies in an intrinsic difference, rather than in a specific effect of the drug.

The Pa_{CO_2} levels were raised postoperatively and this was not surprising in view of the relatively elderly population studied. There was no significant difference between the values obtained in this study and those following parenteral buprenorphine (McQuay *et al.*, 1980).

The intraoperative rise in plasma glucose and cortisol was similar to that seen in other groups of patients (Brandt *et al.*, 1978). Plasma glucose concentrations started to fall after the second dose of buprenorphine, and although the fall in the first 3 h was not as dramatic as that seen with intramuscular buprenorphine (0.58 mmol/l *v* 1.51 mmol/l), the rate of fall was increasing and largest in the last hour of measurement. More prolonged observations (Moore, McQuay & Bullingham, 1980) show that these metabolic trends continue well beyond the 3 h study period. Plasma cortisol did not fall. A continued rise is expected (McQuay *et al.*, 1979; McQuay *et al.*, 1980), but did not occur after the sublingual dose.

This study has demonstrated substantial efficacy of sublingual buprenorphine given at a near parenteral

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