CLINICAL EFFECTS OF BUPRENORPHINE DURING AND AFTER OPERATION

H. J. McQuay, R. E. S. Bullingham, G. M. C. Paterson and R. A. Moore

SUMMARY

The analgesic, respiratory and hormonal effects of two doses of buprenorphine were studied during and after operation in 20 patients undergoing total hip replacement. The drug provided analgesia of long duration. The analgesic and hormonal effects of the drug were greater after i.m. than after i.v. administration. The postoperative analgesic requirement of women was less than that of men. The pharmacodynamic differences shown between the sexes and between the two routes of administration are discussed in relation to the pharmacokinetics of the drug.

Buprenorphine is a synthetic opiate analgesic with mixed agonist–antagonist properties and a low abuse potential (Heel et al., 1979). It has unusual receptor kinetics (Hambrook and Rance, 1976), and in clinical use has been shown to provide analgesia of long duration. This study was designed to determine the pharmacokinetics of buprenorphine in man when injected by either the i.v. or i.m. route, and to compare the i.v. pharmacokinetics in the same patient in both the anaesthetized and awake conditions (Bullingham et al., 1980). A secondary aim was to collect data on the analgesic effects of the drug, together with its effects on respiratory depression, plasma glucose concentration and endocrine function, and it is these results which are presented.

The inadequacy of existing regimens of analgesia after operation has been widely stressed (Keeri-Szanto and Heaman, 1972). Claims of prolonged action for any new analgesic merit careful assessment of analgesia; in this study patient-controlled demand analgesia was used.

A postoperative analgesic which provided long-lasting pain relief at the expense of unacceptable respiratory depression would have no advantage and, therefore, arterial blood-gas tensions were measured after operation.

It has been proposed that reduction of the stress response to surgery may be beneficial to the patient (Kehlet, 1979), and hormone and blood glucose concentrations have been measured to investigate the effects of buprenorphine on the stress response during and after operation.

PATIENTS AND METHODS

Ethics Committee approval was obtained for this study on patients undergoing elective total hip replacement at the Nuffield Orthopaedic Centre, Oxford. Twenty patients were divided into two groups, V and M, with six men and four women in each group. Both groups were given a first dose of buprenorphine i.v. at the induction of anaesthesia. Group V received a second dose of buprenorphine i.v. Group M received a second dose i.m. Patients were selected sequentially from operation lists if their age was between 45 and 75 yr and their weight less than 80 kg. Those with serious medical disorders or those taking antihypertensive drugs other than thiazides were excluded. A normal full blood count and biochemical examination before operation were conditions of entry to the trial. Signed consent to the study was obtained from each subject.

The patients were premedicated with diazepam 10 mg orally 2 h before surgery. A 1.6-mm i.d. cannula (Venflon) was inserted into an arm vein under local analgesia. All patients received thiopentone 4 mg kg⁻¹ and pancuronium 0.1 mg kg⁻¹. After tracheal intubation the lungs were ventilated with oxygen 33% in nitrous oxide and halothane 0.5% from a Fluotec Mk2 vaporizer. Ventilation to normocapnia was achieved using the Penlon version of the Bain co-axial breathing circuit with a total fresh gas flow of 70 ml kg⁻¹. The ventilator was adjusted to pro-
duce an expired tidal volume (measured at the endotracheal catheter connector) of 10 ml kg$^{-1}$ and respiratory frequency of 13 b.p.m. A 0.53-mm i.d. cannula (Longdwell) was inserted into the radial artery. Buprenorphine 0.3 mg diluted to 10 ml with normal saline was injected i.v. over 1 min.

Halothane 0.5% was continued until 10 min before antagonism of the neuromuscular blocking drug. Halothane was used to avoid any possibility of awareness and to suppress any autonomic effects which might have influenced the drug kinetics. No increment of any drug was given. All patients lay on warming blankets and direct arterial pressure, heart rate, rectal temperature and e.c.g. were monitored during anaesthesia. During anaesthesia 5 ml kg$^{-1}$ h of Hartmann's solution was given i.v. for the first 2 h, and thereafter blood was transfused to a specific plan depending on the pre-operative haemoglobin concentration, and blood loss assessed by swab weighing and suction.

At the end of surgery the anaesthetic gases were discontinued and residual neuromuscular blockade was antagonized with atropine 1.2 mg and neostigmine 2.5 mg i.v. The patients were transferred to the recovery room, and remained there until the following morning. All patients remained supine and breathed oxygen 28% from a Ventimask until at least 6 h from induction of anaesthesia.

At 3 h after the first dose of buprenorphine a further 0.3-mg dose was given; group V received this dose i.v. diluted to 10 ml and given over 1 min. Group M received 0.3 mg in 1 ml given by the nursing staff into the vastus lateralis muscle of the side opposite to hip operation. The second dose of buprenorphine was not given unless the patient was able to open the eyes to command. Six hours after the first dose of buprenorphine the patients were connected via a separate i.v. line (21-gauge Butterfly), to a demand analgesia system, the use of which had been explained to them on the previous day. The demand analgesia apparatus was constructed in the Nuffield Department of Anaesthetics from a modified Mill Hill infusion pump (Muirhead Ltd, 34 Croydon Road, Beckenham, Kent), delivering diamorphine 0.25 mg when the patient pressed a button. This was the only postoperative analgesic until the patient left the recovery room on the following morning. The demands for analgesia were recorded automatically over this period.

Arterial pH, $P_{CO_2}$ and $P_{O_2}$ were measured during operation, at 150 min after the first dose of buprenorphine and at 10, 60, 120 and 180 min after the second dose, using a Radiometer ABL2 blood-gas analysis system. Plasma cortisol concentration was measured by the method of Murphy (1976), modified by the use of Sephadex instead of Florisil; plasma prolactin concentration was measured using a kit obtained from CIS (U.K.) Ltd, and plasma glucose concentration by a standard glucose oxidase procedure. The samples were taken at the same times as blood was withdrawn for blood-gas analysis, with an additional sample before operation. Plasma buprenorphine concentrations were measured by the method of Bartlett and colleagues (1980), using a phosphate buffer. The kinetic analysis of the data appears elsewhere (Bullingham et al., 1980).

RESULTS

The patient data for the two groups are shown in table I. The age, weight, sex distribution, duration of surgery and $P_{CO_2}$ values during operation did not differ significantly for the two groups. The difference in blood loss was matched by transfusion. Anaesthesia was uneventful, with no unexpected changes in heart rate and arterial pressure.

After operation the patients were generally well, but one patient in group V was confused and hallucinating for 30 min, following administration of the second dose of buprenorphine (conversation with a non-existent person). Two patients in group V vomited once after the second dose was given and received metoclopramide 10 mg i.m. One patient in group M was nauseated following the second dose, but this resolved spontaneously.

Drowsiness was apparent in all the patients, such that they were clearly distinguishable from other patients in the recovery room who had received fentanyl-based anaesthetics. The patients...
slept for the first 2–3 h after operation, but were easily roused, and the drowsiness appeared to have no adverse effect. One patient in each group required an oropharyngeal airway for the first 30 min after anaesthesia. These patients then woke uneventfully and received their second dose of buprenorphine.

**Analgesia**

A continuous record of demands against time was obtained for each patient. The minimum record was for a period of 11.5 h, the maximum 18.6 h. A wide range of demand was observed; one patient in group V making no demands and another in group V making 88 demands (equivalent to diamorphine 22 mg). Such variability required the use of two methods of analysis. Analysis by averaging the data meant that the wealth of information obtained in the record of one patient, effectively a binary 2-min record over a period of at least 10 h, would not be put to best use. Thus the individual patient’s data were used in the estimation of duration of action. Mean data were used to compute the respective demands per patient per min for groups V and M.

The automatic recordings of each patient’s analgesic demands were analysed for the duration of action of buprenorphine.

Time to the fifth demand made by each patient was used to obtain the estimate of duration. The median value for all the patients was 480 min after the second dose was given.

A number of other criteria of duration of action including time to two, three and four demands and regression to zero demand axis at the time when demands became frequent were used also. These analyses gave median duration values which were very similar to the value obtained by analysis to fifth demand.

Using non-parametric methods, no significant difference was found in the duration of action for the two groups. There was no correlation (Spearman rank test) between the percentage absorption from i.m. administration and the duration of action. There was no correlation between the peak plasma buprenorphine concentration and duration, in either group.

**Route of administration and sex difference.** The difference in efficacy of buprenorphine i.v. and i.m. was shown by a comparison of the 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. Values between 0 and 60 min were excluded because the slopes in the 1st hour were markedly different from the succeeding 10 h.

Subdivision of the groups by sex allowed comparison of the demand rate shown in table II to be made between the men and women of groups V and M. The slope ratios shown in table III allow quantification of the relative effects of sex and route. In section 1 of table III, there is a 1.8–3.3-fold difference in the demand rate, the larger difference being in the i.m. group. In section 2, there is a 1.3–2.4-fold difference, the larger difference being in the females.

**Blood-gas analysis results**

Table IV shows blood-gas results at 30 min (during operation), 150 min (30 min before the second dose); 10 min and 1, 2 and 3 h after the second dose. $P_{aCO_2}$ values were increased after operation, but there were no significant differences either between the two groups or between men and women.
TABLE IV. Blood-gas analysis results. Combined groups V and M (kPa, mean ± SEM). Sample times are calculated from the time the first dose of buprenorphine was given. $F_{O_2}$ = 0.28, but 0.33 at 30-min sample time.

<table>
<thead>
<tr>
<th>Sample time (min)</th>
<th>30</th>
<th>150</th>
<th>190</th>
<th>240</th>
<th>300</th>
<th>360</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{aco_2}$ Range</td>
<td>5.45±0.21 (3.4-6.5)</td>
<td>6.65±0.03 (4.6-9.7)</td>
<td>6.81±0.26 (4.5-8.0)</td>
<td>6.98±0.31 (4.9-8.9)</td>
<td>6.84±0.26 (5.6-8.9)</td>
<td>6.58±0.24 (5.2-8.7)</td>
</tr>
<tr>
<td>$P_{a_o_2}$</td>
<td>19.85±0.85</td>
<td>14.69±1.01</td>
<td>14.25±0.89</td>
<td>14.36±0.90</td>
<td>14.23±0.80</td>
<td>14.26±0.74</td>
</tr>
<tr>
<td>$(P_{aco_2} - P_{a_o_2})$</td>
<td>6.9±0.91</td>
<td>6.25±1.16</td>
<td>5.51±0.94</td>
<td>5.54±0.85</td>
<td>5.89±0.98</td>
<td>5.94±0.94</td>
</tr>
</tbody>
</table>

women. Using a paired $t$ test, no significant increases in $P_{aco_2}$ were found following the second dose of buprenorphine, either at 10 min or 1, 2 or 3 h after the second dose. $(P_{a_o_2} - P_{aco_2})$ was calculated for all patients (Nunn, 1977). The mean difference was greater during, compared with after operation. Shunt values estimated from these mean values remained within the normal physiological range of 3–5%.

**Hormones and blood glucose**

Plasma glucose concentrations increased during the operation in both groups (fig. 1). Thereafter the concentrations did not change in group V, whilst group M patients showed a continuous decrease in plasma concentrations following the second dose of buprenorphine, with a mean decrease of 1.5 mmol litre$^{-1}$ over the 3-h period ($P<0.01$, paired $t$ test).

The increase in plasma cortisol concentrations during surgery was similar in both groups of patients (fig. 2). In group V plasma cortisol concentrations increased by a mean of 272 nmol litre$^{-1}$ ($P<0.01$, paired $t$ test) in the 3 h following the second dose. In group M, however, there was a mean decrease of 220 nmol litre$^{-1}$ ($P<0.01$, paired $t$ test) in the 1st hour following i.m. administration of the drug. Although the concentrations increased subsequently, they did not differ significantly at the end of the study period from those observed immediately after operation.
The changes in plasma prolactin concentration which accompany surgery were the same in both groups (table V). There was a seven-fold increase in concentration following operation. There was no significant difference between the groups at any time.

**DISCUSSION**

The evidence presented here supports the clinical profile of buprenorphine suggested by previous trials. Because this was primarily a kinetic study, the drug was administered twice and the effects might be expected to be greater than for a single administration.

**Analgesia**

The median duration of analgesia of 480 min resulted from the second dose of buprenorphine 0.3 mg. This is in accordance with single-dose studies which have shown a long duration using other methods of analgesia assessment (Kay, 1978). The explanation of this long duration compared with other opiates is not found in an increase in plasma buprenorphine concentrations, which decrease to very small values by 1 h after the dose is given (Bullingham et al., 1980). The kinetics are similar to those seen with fentanyl (McQuay et al., 1979), which does not give prolonged analgesia.

The slow dissociation constant of the buprenorphine drug–receptor complex (Hambrook and Rance, 1970) provides an explanation because, uniquely among opioid drugs, receptor occupancy will remain high for a long time. This distinction between pharmacokinetic and pharmacodynamic aspects, in which an effect continues at plasma concentrations where none would be anticipated is also seen with non-depolarizing neuromuscular blockers, and a slow drug–receptor dissociation constant is the explanation in that case (Feldman and Tyrell, 1970).

The smaller postoperative analgesic requirement of patients given the second dose of buprenorphine i.m. compared with i.v. was an unexpected finding. The bioavailability of this drug given i.m. is close to 100% (Bullingham et al., 1980), but this finding alone would suggest that there would be no difference between the two routes. For this drug the clue to the relative advantage of the i.m. route may lie in the kinetic analysis. The plasma concentrations following the same dose given by the two different routes show no significant difference after 10 min. Following administration i.v. a greater mass of the drug, initially in the plasma, will be removed by the liver in the first 10 min.

Thus administration i.m. results in the removal of less mass of drug in the initial 10 min, because less drug is in the plasma. Therefore, at 10 min, although the plasma concentrations in the two groups were the same, a greater mass of drug remained in the body in the i.m. case. This extra drug, stored in the tissues, subsequently returns to the plasma, and is available to be associated to the receptor. The receptor affinity of buprenorphine allows pharmacologically effective occupancy of the receptor at small plasma concentrations.

This is supported by current work on comparable patients using sublingual buprenorphine, which has provided excellent analgesia despite plasma concentrations which never exceeded 1 ng ml⁻¹ (unpublished observations). The extra drug resulting from i.m. administration caused no measurable change in plasma concentration, but exerted a pharmacological effect in terms of analgesic consumption.

The finding of a smaller analgesic requirement after operation in females substantiates the commonly held view that women need less postoperative analgesia than men, a view which has no support in the literature. The fact that there were no significant differences in the plasma concentrations of the drug between men and women suggests that the explanation lies in an intrinsic difference in the response to pain between men and women, rather than in a specific effect of the drug. This explanation is supported by work with methadone, which resulted in lower pain scores and higher pain relief scores in females compared with males, despite similar plasma concentrations in the two groups (A. B. Kaiko, personal communication). Furthermore, when the pain relief scores

**Table V. Plasma prolactin concentrations (mu. litre⁻¹) (mean±SEM)**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Group V</th>
<th>Group M</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>279±45</td>
<td>344±61</td>
</tr>
<tr>
<td>30</td>
<td>1896±468</td>
<td>1598±162</td>
</tr>
<tr>
<td>150</td>
<td>2074±398</td>
<td>2248±353</td>
</tr>
<tr>
<td>190</td>
<td>1652±344</td>
<td>1649±286</td>
</tr>
<tr>
<td>240</td>
<td>1230±233</td>
<td>1242±157</td>
</tr>
<tr>
<td>300</td>
<td>932±165</td>
<td>956±108</td>
</tr>
<tr>
<td>360</td>
<td>722±183</td>
<td>785±132</td>
</tr>
</tbody>
</table>
for men and women were the same, the plasma concentrations in the female group were less than in the male group. The difference between the sexes found with methadone was seen using classical pain scoring methods, and provides strong support for the difference using demand system analysis in the present study.

This difference is of importance in the testing of analgesics, because data on duration and efficacy obtained in single-sex studies, for example using the episiotomy pain model, may not be comparable with results from studies on both sexes.

Blood-gas analysis

$P_{acO_2}$ values were increased after operation. This was not surprising in view of the relatively elderly population studied, the fact that two doses of buprenorphine were used, and the use of diazepam for premedication with halothane as an anaesthetic supplement. There was no significant difference in the $P_{acO_2}$ values obtained in this study from those which result from single doses of fentanyl used in a similar group of patients and without the addition of halothane (unpublished observations). This does not support the specific interaction suggested with halothane in the manufacturer's report on the monitored release of buprenorphine, a suggestion which was based solely on measurements of respiratory rate.

That $P_{acO_2}$ does not increase following the second dose of buprenorphine is seen when the values at 150 min and at 190 and 240 min are compared. This shows that a proportionate increase dose not follow the second dose, and is evidence in man for a flat dose–response curve (Martin, 1979) which is of clinical importance if the increase in $P_{acO_2}$ is limited. One patient, however, who had a history of heavy tobacco smoking, had $P_{acO_2}$ values of 9 kPa after operation. No further increase was seen after the second dose, again suggesting that the drug has a flat dose–response curve, operating to the benefit of the patient in this instance of presumed respiratory disease.

**Hormones and blood glucose**

Group V patients showed changes in plasma concentrations of glucose and cortisol both during and after surgery which were typical of the changes seen in many other studies (Brandt et al., 1976, 1978; Hall et al., 1978; Cooper et al., 1979; McQuay et al., 1979). The substantial effect of i.m. buprenorphine on both cortisol and glucose concentrations was unexpected. Only high doses of fentanyl (Hall et al., 1978) or morphine (George et al., 1974) and extradural blockade (Brandt et al., 1978; Cooper et al., 1979), have been shown previously to obtund the stress response during and after surgery. Although the abrupt decrease in plasma cortisol concentrations was followed by an increase, there was no overall increase after operation in group M compared with group V and compared with the use of fentanyl (McQuay et al., 1979).

The decrease in plasma glucose concentrations was substantial, with a mean decrease of 1.5 mmol litre$^{-1}$ in the 3 h following buprenorphine i.m. The downward trend continued (fig. 1), and it is possible that the prolonged hyperglycaemia which occurs for up to 24 h following operation (Brandt et al., 1978) may be prevented by this route of administration.

There is no obvious explanation for this unique effect of therapeutic doses of i.m. buprenorphine but, just as with analgesic efficacy, i.m. buprenorphine had greater effect than the i.v. dose in reducing the stress response.

The changes in plasma prolactin concentration were of the same magnitude and duration as those shown by Brandt and colleagues (1976), and there was no difference in the rate of decrease of prolactin between the two routes of administration. Buprenorphine differs from the more commonly studied fentanyl and morphine in that it is a mixed agonist–antagonist rather than a pure agonist. There is growing interest in the specific neuro–endocrine effects of opiate drugs (Labrie et al., 1978), and such effects with buprenorphine cannot be excluded.

Buprenorphine, as used in this trial, clearly has little effect on the direct endocrine and metabolic response to surgery. The particular action of i.m. buprenorphine may have important implications for control of the long-term metabolic response to surgery (Brandt et al., 1978; Foster et al., 1979) and deserves investigation in this area.

We believe that buprenorphine has unique properties which, to obtain maximal benefit for the patient, may require that the route and times of administration take account of these properties. The potential benefit to patients suffering from pain after operation is such that further studies are indicated.
ACKNOWLEDGEMENTS
We thank the surgeons of the Nuffield Orthopaedic Centre for allowing us to study their patients, the nursing staff for their help and the staff of the Nuffield Department of Clinical Biochemistry for their technical assistance.

REFERENCES


EFFETS CLINIQUES DE LA BUPRENORPHINE AVANT ET APRES L'INTERVENTION CHIRURGICALE

RESUME
On a fait une étude sur les effets analgésiques, respiratoires et hormonaux qu'on produit de deux doses de buprenorphine, avant et après l'intervention chirurgicale effectuée sur 20 patients subissant un remplacement total de la hanche. Ce médicament a entraîné une analgésie de longue durée. Les effets analgésiques et hormonaux de ce médicament ont été davantage marqués après son administration par voie intramusculaire, qu'après l'administration par voie intraveineuse. Les besoins analgésiques postopératoires des femmes ont été moindres que ceux des hommes. Les différences pharmacodynamiques que l'on a constatées entre les sexes et les deux modes d'administration font l'objet d'un exposé comparatif avec la pharmacocinétique du médicament.

KLINISCHE WIRKUNGEN VON BUPRENORPHIN WÄHREND UND NACH DER OPERATION

ZUSAMMENFASSUNG

EFECTOS CLINICOS DE LA BUPRENORFINA DURANTE LA OPERACION Y DESPUES DE ESTA

SUMARIO
Durante la operación y después de ésta, se estudiaron los efectos analgésicos, respiratorios y hormonales de dos dosis de buprenorfinina, en 20 pacientes sometidos a sustitución total de la cadera. La droga provoó analgesia de larga duración. Los efectos analgésicos y hormonales de la droga fueron superiores después de la administración intramuscular, en vez de después de la administración intravenosa. El analgésico posoperatorio necesario para las mujeres fue inferior al de los hombres. Las diferencias farmacodinámicas entre los sexos y entre las dos rutas de administración se discuten en relación a las farmacocinéticas de la droga.