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BUPRENORPHINE: A NEW POTENT LONG-ACTING SYNTHETIC ANALGESIC. COMPARISON WITH MORPHINE

J. W. DOWNING, W. P. LEARY AND E. S. WHITE

SUMMARY

A new thebaine derivative, buprenorphine, 0.6 mg, was compared with morphine 15 mg in a double-blind trial, in patients recovering from elective Caesarean section. Within 1 h of administration analgesia was obtained with both drugs and was sustained for 7–8 h with buprenorphine, and 3–4 h with morphine. Buprenorphine caused a greater decrease in diastolic arterial pressure than did morphine, but arterial systolic pressure and heart rate were not influenced by either drug. No serious side-effects were encountered in this study.

Buprenorphine is a new synthetic analgesic agent, of high potency and prolonged action, derived from thebaine (Lewis, 1974) and closely related in structure to morphine (fig. 1). Buprenorphine exhibits powerful

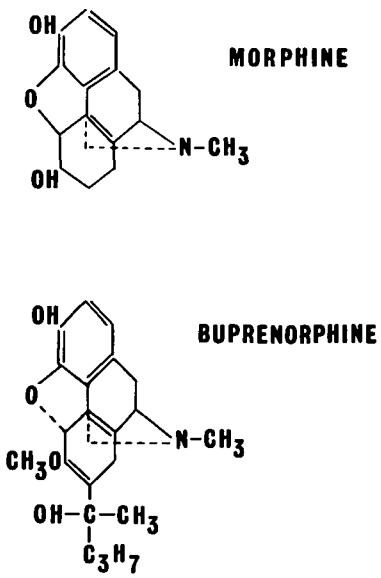

FIG. 1. Structural formulae.

agonistic activity combined with some antagonistic characteristics; chronic administration to monkeys and mice does not produce physical dependence. The duration of action of the drug may be twice that of morphine, while the potency in animals is 50–100 times that of morphine. Preliminary reports of clinical trials in man are encouraging, in that parenterally administered buprenorphine appears superior to other commonly used potent analgesics (Hovell, 1976; McQuillan, 1976; Rolly and Versichelen, 1976).

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MATERIALS AND METHODS

After operation, 58 women (group I), delivered by elective Caesarean section, received i.m. injections of morphine 15 mg or buprenorphine 0.6 mg in a double-blind clinical trial. The drugs were presented in identical coded ampoules, containing 2 ml of either morphine or buprenorphine, and were administered on a random basis. Fifteen similar patients (group II) received buprenorphine 0.6 mg in an open trial designed to assess its duration of action.

All the patients were in good health (American Society of Anesthesiologists rating 1), and were free of renal or hepatic disease. Consent for the investigation was obtained before surgery, and approval for the trial was granted by the relevant national and faculty control bodies.

Before operation the patients were prepared according to a standard protocol (Downing et al., 1976). Atropine 0.6 mg and metoclopramide 10 mg were injected i.v. before induction of anaesthesia.

Anaesthesia was induced with 1% ketamine administered i.v. (1–2 mg/kg body weight). The subsequent routine anaesthetic management has been described elsewhere (Downing et al., 1976). Enflurane 0.6% was added to the inspired gas mixture after delivery of the infant to maintain anaesthesia, but no parenteral analgesics were given during surgery.

On transfer to the recovery area, the patients were awake and co-operative. Pain assessment (Huskisson, 1974) and measurement of cardiopulmonary function were conducted by a single observer (E. S. W.).

The patients were asked to score both the degree of pain experienced and the level of pain relief achieved by analgesic injection. Pain was scored as none (1), slight (2), moderate (3) or severe (4) and pain relief as none (0), slight (1), moderate (2), extensive (3) or complete (4). The observer's assessment was recorded at the same time, thus providing both subjective and objective pain scores.

With each pain assessment, vital capacity (Ohio Vortex Respiration Monitor), expiratory peak flow (Peak flow gauge, M 400), arterial pressure (mercury manometer) and pulse rate (by palpation) were measured.

The assessments were made immediately after operation, 10 min after injection of the analgesic drug, and thereafter at hourly intervals up to 4 h in group I. The 15 women in group II were studied for 8 h.

An initial attempt to conduct the last phase of the trial double-blind failed, as patients who received morphine invariably required analgesic supplementation after 4–5 h. Patients were observed carefully for evidence of untoward drug effects throughout the investigations.

Statistical comparison of the results included calculation of Student's *t* test for the significance of the difference between two sample means, and the use of χ^2 contingency tables. Analyses were performed using a Hewlett–Packard Series 9810A (Model 10) calculator.

RESULTS

Patients in group I who received morphine were on average 2.8 yr older than those given buprenorphine ($P<0.05$) (table I).

TABLE I. *Clinical data of patients in groups I and II (mean and SD)*

Drug	Morphine	Buprenorphine
Group I		
n	29	29
Age (yr)	27.8 (±4.5)*	25.0 (±4.5)*
Body mass (kg)	71.3 (±12.4)	67.8 (±11.8)
Group II		
n		15
Age (yr)		26.0 (±3.8)
Body mass (kg)		69.3 (±15.0)

*$P<0.05$.

The mean subjective and observer pain scores fig. (2) indicate that buprenorphine provided significantly better analgesia than did morphine at 3 and 4 h after drug administration, at which time subjective pain relief (fig. 3) was also superior after buprenorphine injection. (Statistical analysis of the above data, applying χ^2 contingency tables, produced similar conclusions.)

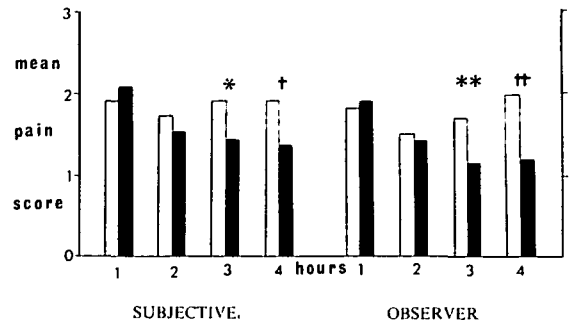

FIG. 2. Mean subjective and observer pain scores. □ Morphine; ■ Buprenorphine. *$P<0.05$; **$P<0.01$; †$P<0.005$; ††$P<0.001$.

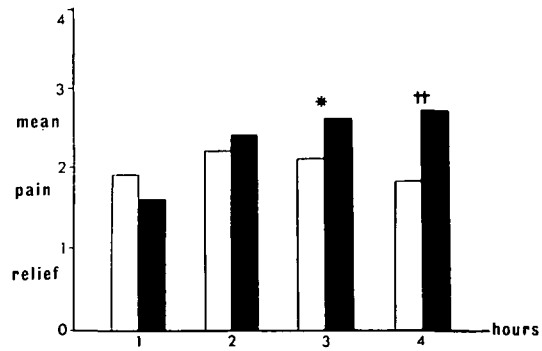

FIG. 3. Subjective assessment of pain relief. □ Morphine; ■ Buprenorphine. *$P<0.05$; ††$P<0.001$.

In group II (buprenorphine 0.6 mg) buprenorphine produced a significant reduction in pain (fig. 4), from 2 to 7 h after injection. Pain relief was significant over

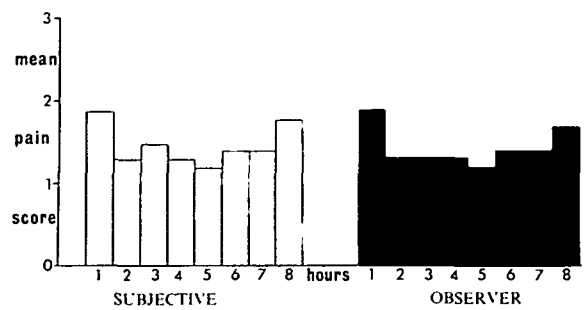

FIG. 4. Mean pain score, buprenorphine 8-h study.

the same period of time (fig. 5). Eight hours after the injection of buprenorphine the levels of analgesia and pain relief appeared to return towards those recorded 1 h after drug administration.

Morphine and buprenorphine were both associated with significant progressive increases, from "control" values after operation, in both vital capacity and peak flow over the 4 h of study (fig. 6). Buprenorphine was associated with a decrease in both systolic and diastolic arterial pressure 1 h after injection ($P<0.05$

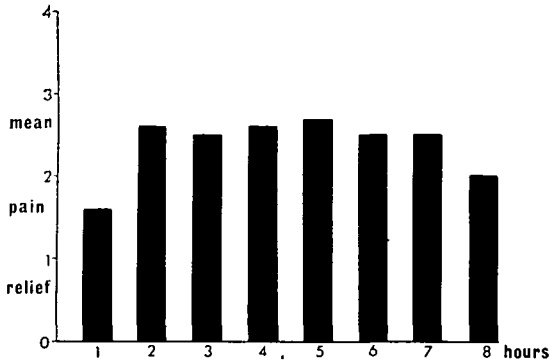

FIG. 5. Subjective assessment of pain relief, buprenorphine 8-h study.

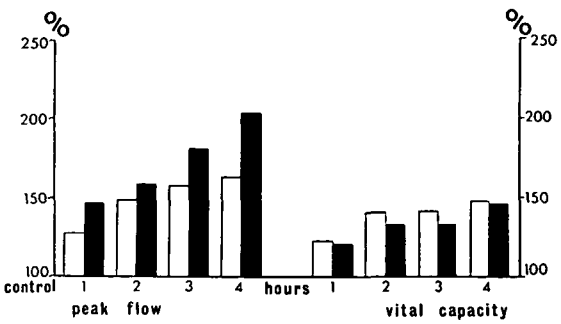

FIG. 6. % Increase in peak flow and vital capacity. □ Morphine; ■ Buprenorphine.

and $P<0.005$, respectively). Thereafter, there were significant decreases in mean diastolic pressure for the duration of the study, but mean systolic pressure was maintained. In group II, a significant decrease of diastolic pressure, from control values after operation, was noted, 2, 3 and 8 h after injection of buprenorphine ($P<0.05$).

Both morphine and buprenorphine caused highly significant slowing of the pulse from the control value, 1 and 2 h after injection of the drug. This change persisted with buprenorphine for 4 h. Significant decreases in mean heart rate were noted in group II up to 5 h after buprenorphine administration.

Morphine and buprenorphine produced no serious side-effects in this study.

DISCUSSION

The undesirable properties of morphine include respiratory depression and a significant potential for drug abuse. The search for a suitable alternative led to the exploration of a series of C-bridged thebaine derivatives (Lewis, 1974), of which buprenorphine is an example.

The chemistry and animal pharmacology of buprenorphine and its laboratory antagonist, diprenorphine, have been presented by Lewis (1974). Buprenorphine exhibits profound agonist properties, while possessing demonstrable antagonist characteristics. Diprenorphine, a relatively pure antagonist, reverses the effects of buprenorphine (Lewis, 1974).

Pharmacological studies of buprenorphine in animals led to the selection of the drug for clinical evaluation (Lewis, 1974) and encouraging results have been obtained in healthy human volunteers following both parenteral (Hovell, 1976; McQuillan, 1976; Rolly and Versichelen, 1976) and sublingual administration (Masson, 1976).

In addition, despite prolonged administration to monkeys and mice, buprenorphine failed to produce physical dependence (Lewis, 1974). Preliminary studies suggest that buprenorphine is 50–100 times more potent than morphine and acts for twice as long (Lewis, 1974). Dysphoria is not a feature of the drug, although side-effects, including nausea, sedation, miosis and constipation, may occur (Lewis, 1974).

The results of recent clinical trails of buprenorphine have been encouraging. Hovell (1976) reported that buprenorphine 4 and 8 μg/kg gave significantly more pain relief than pethidine 1 mg/kg or pentazocine 0.6 mg/kg. He demonstrated a dose–response relationship with buprenorphine, and showed that higher doses gave significantly more analgesia without a significant increase in side-effects.

McQuillan (1976) compared the analgesic effects of buprenorphine and an opium alkaloid for pain relief following Caesarean section under general anaesthesia. He claimed that i.v. buprenorphine, administered immediately after delivery of the baby, was superior. The degree of analgesia produced by the drug was profound and was associated with minimal maternal respiratory depression. Patients were fully alert and freely mobile within a few hours of surgery, and no serious side-effects were noted. Rolly and Versichelen (1976) reported satisfactory

analgesia in 73% of subjects 10–20 min after the administration of buprenorphine 4 μg/kg.

In this study, buprenorphine or morphine was administered i.m. to patients after elective Caesarean section. No preoperative medication or intraoperative parenteral analgesia was given. The mothers in group I, receiving morphine or buprenorphine on a random double-blind basis, were clinically comparable, although those in the morphine group were, on average, slightly older.

The time to onset of analgesia with the two drugs was similar, the degree of pain relief 1 and 2 h after injection being the same. Buprenorphine, however, appeared superior both on subjective and objective assessment at 3 and 4 h after administration. In the 15 women studied over an 8-h period (group II), good analgesia persisted for 7 h. At 8 h, the level of analgesia approached that observed 1 h after injection of the drug.

Measurement of respiratory function suggests that the improvement in vital capacity and peak flow with the two drugs was identical up to the 3rd hour after injection. More sophisticated studies, including blood-gas analysis and the effects of a carbon dioxide challenge, are required to assess the relative respiratory effects of the two drugs in greater detail.

Buprenorphine appeared to produce a slightly greater decrease in diastolic pressure than did morphine, while both drugs caused a significant decrease in heart rate, indicating that analgesia was adequate in most cases studied. No important undesirable side-effects were encountered with either drug in this investigation.

CONCLUSION

Buprenorphine 0.6 mg would appear to be as effective as morphine 15 mg in the first 3 h after administration. Thereafter, buprenorphine provides significantly better pain relief sustained over a period of 7 or 8 h. The respiratory and cardiovascular status of patients receiving the two drugs was similar, with the exception of the diastolic arterial pressure, which decreased more after buprenorphine. Our results suggest that buprenorphine represents a significant advance in the field of potent analgesics, having a length of action approximately twice that of morphine. Further evaluation of the influence of the drug on respiration is in progress.

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BUPRENORPHINE: NOUVEL AGENT ANALGESIQUE DE SYNTHESE, PUISSANT ET DE LONGUE DUREE. COMPARAISON AVEC LA MORPHINE

RESUME

Un nouveau dérivé de la thébaïne: la buprénorphine, en doses de 0,6 mg, a été comparé à la morphine en doses de 15 mg, au course d'une étude à double inconnue effectuée sur des opérés récupérant d'une césarienne effectuée à froid. Moins d'une heure après l'administration des doses, on a obtenu l'analgésie avec les deux médicaments et celle-ci s'est maintenue entre 7 et 8 h en ce qui concerne la buprénorphine, et entre 3 et 4 h en ce qui concerne la morphine. La buprénorphine a provoqué une baisse de la tension artérielle diastolique plus importante qu'avec la morphine, mais la tension artérielle systolique et le rhythme cardiaque n'ont été influencés par aucun de ces médicaments. On n'a rencontré au cours de cette étude aucun effet secondaire grave.

BUPRENORPHIN: EIN NEUES WIRKSAMES, LANGWIRKENDES SYNTHETISCHES ANALGETIKUM. VERGLEICH MIT MORPHIN

ZUSAMMENFASSUNG

Ein neues Thebainderivat, Buprenorphin, 0,6 mg, wurde mit 15 mg Morphin in einem Doppelblindtest in, sich vom wahlweisen Kaiserschnitt erholenden Patienten verglichen. Innerhalb einer Stunde nach der Verabreichung wurde mit beiden Drogen Analgesie erhalten und mit Buprenorphin 7–8 Stunden lang aufrechterhalten, und 3–4 Stunden lang mit Morphin. Buprenorphin verursachte eine grössere Abnahme im diastolischen, arteriellen Blutdruck als Morphin, der systolische, arterielle Blutdruck dagegen, sowie die Pulszahl wurden von keiner der beiden Drogen beeinflusst. Bei diesem Test wurden keine gefährlichen Nebenwirkungen gefunden.

BUPRENORFINA: UN NUEVO ANALGESICO POTENTE, SINTETICO Y DE LARGA ACCION. COMPARACION CON LA MORFINA

SUMARIO

Un nuevo derivado de la tebaina, la buprenorfina, 0,6 mg, fué comparado con morfina, 15 mg, en un ensayo a doble ciego, en pacientes que se recuperaban de sección cesarea electiva. Al cabo de 1 hora de administración, se obtuvo analgesia con ambos farmacos y se mantuvo durante 7–8 horas con buprenorfina, y 3–4 horas con morfina. Buprenorfina produjó un mayor descenso de la presión arterial diastólica que con la morfina, pero la presión arterial sistólica y el ritmo cardíaco no se vieron influenciados por ninguno de los dos farmacos. No se observó ningún efecto colateral de importancia en este estudio.