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SINGLE-DOSE COMPARISON OF BUPRENORPHINE 0.3 AND 0.6 MG I.V. GIVEN AFTER OPERATION: CLINICAL EFFECTS AND PLASMA CONCENTRATIONS

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SUMMARY

The plasma concentrations and clinical effects of a single i.v. dose of buprenorphine 0.3 or 0.6 mg were studied in patients recovering from surgery. Analgesic and hormonal effects were greater with the greater dose without a parallel increase in respiratory depression. A comparison with previous work suggests that increased efficacy results either from the use of the larger dose or equivalently if the first required postoperative dose of 0.3 mg has been preceded by a similar loading dose.

The pharmacokinetics of buprenorphine (Temgesic, Reckitt and Colman), a synthetic narcotic analgesic with agonist and antagonist properties, have recently been described (Bullingham et al., 1980, 1981). Results were presented for different routes of administration but only a single dose was used.

A trial was designed to study the kinetics of buprenorphine given at two different i.v. doses. Simultaneous measurements were made of the clinical effects.

This paper reports the analgesic, metabolic and respiratory effects in this trial. These are of particular interest because of the mixed agonist–antagonist properties of the drug, which may not produce straightforward dose–effect relationships (Houde and Wallenstein, 1956; Martin, Gorodetsky and Thompson, 1972).

PATIENTS AND METHODS

The study was conducted in nineteen patients undergoing elective total hip replacement for either osteo- or rheumatoid arthritis at the Nuffield Orthopaedic Centre, Oxford. Patients over the age of 80 yr and those with cardiovascular, respiratory, liver or kidney disease were excluded. Any patient taking drugs other than diuretics, oral analgesics or steroids was also excluded. All patients gave informed consent to the study which had been approved by the local Ethics Committee.

The patients were premedicated with diazepam 10 mg orally 2 h before operation. A 1.6-mm i.d. Venflon cannula was inserted i.v. under local analgesia. Anaesthesia was induced with thiopentone 4 mg kg^{-1} and maintained with nitrous oxide, oxygen (2 : 1) and halothane using a Bain co-axial breathing system with spontaneous ventilation through a mask and Guedel airway. The fresh gas flow was 100 ml kg^{-1}. The halothane concentration was increased initially to 2% and then reduced to 0.5% until 5 min before the end of surgery.

A lumbar extradural block was performed, with the patient in the left lateral position, at the L2–3 or L3–4 interspace. A Portex catheter was inserted and after a test dose of 0.5% bupivacaine 2 ml with 1 : 200 000 adrenaline, a further 13–17 ml of the same solution was injected with the patient supine. A 0.53-mm i.d. Longdwell was inserted into the radial artery after Allen's test had been performed, for direct arterial pressure monitoring and postoperative blood sampling.

Throughout the operation e.c.g., heart rate and arterial pressure were monitored and blood loss was assessed by swab weighing and measurement of suction loss. If the systolic arterial pressure decreased to less than 70 mm Hg, 3-mg increments of ephedrine were given. Fluid replacement was with Hartmann's solution 1000 ml followed by either blood or saline depending on blood loss and preoperative haemoglobin concentration.

After operation the patients were transferred to the recovery room where they breathed 28% oxygen through a Ventimask for at least 6 h.

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The patients were divided into two groups. Three hours after the start of surgery buprenorphine 0.3 mg (0.3-mg group) or 0.6 mg (0.6-mg group) diluted to 10 ml with normal saline was given i.v. over 30 s. Three hours later (6 h from the start of surgery) the patient was connected via a separate i.v. line (Butterfly 21-gauge) to a demand analgesia system which gave diamorphine 0.25 mg whenever the button was pressed. This system was constructed in the Nuffield Department of Anaesthetics from a modified Mill Hill infusion pump (Muirhead Ltd, 34 Croydon Road, Beckenham, Kent). It remained in place until the following morning and each demand was recorded automatically on a chart recorder. No other analgesia was given to the patient but metoclopramide 10 mg was given i.m. if the patient suffered from nausea or vomiting.

Arterial pressure, heart rate and breathing rate were recorded every 30 min initially and then hourly during the 6 h from the start of surgery. Pain intensity, degree of sedation and side-effects were recorded by the same investigator before, and at 30, 60, 120 and 180 min following the administration of buprenorphine. Pain intensity was measured on a four-point scale (0 = none, 1 = slight, 2 = moderate, 3 = severe). Sedation was assessed on a four-point scale (3 = asleep, 2 = moderately drowsy, 1 = mildly drowsy, 0 = alert).

Arterial blood-gases were analysed at 30 and 150 min after the start of surgery and at 10, 60, 120 and 180 min after the buprenorphine was given, using a Radiometer ABL2 blood-gas analysis system. Plasma glucose and plasma cortisol concentrations were measured before operation and at the same times as the arterial blood-gases. Plasma glucose was measured by a standard glucose oxidase procedure and plasma cortisol by the method of Beardwell, Burke and Cope (1968). Plasma buprenorphine samples were taken at 2, 5, 7.5, 10, 15, 20, 30, 40, 60, 80, 100, 120, 150 and 180 min after the administration of buprenorphine, and the concentrations were measured by the method of Bartlett and others (1980) using a phosphate buffer. Intra-assay and interassay variation at various plasma concentrations was less then 5%.

A continuous recording of the analgesic demands of each patient against time was obtained. This was analysed in two ways (McQuay et al., 1980). First, the time taken to the fifth demand by each patient was chosen to estimate the duration of analgesia and the median value for the patients in each group was compared. Second, to compare the requirement for further analgesia in the two groups, the number of demands made by each patient during each 15-min period from 0 to 540 min was averaged for each group. We took 540 min as it was the minimum time for which intact records were available.

These cumulative mean demands were plotted against time (fig. 1). Regression slopes were calculated and are shown drawn through the points in figure 1. The ratio between the slopes was obtained. This method of regression slope calculation was used to separate the effects of dose and sex.

RESULTS

There were no significant differences between the two groups in respect of age, sex ratio, height, time of surgery and blood loss (table I). There was a significant difference in weight, the heavier group receiving the larger dose of buprenorphine.

TABLE I *Patient data (mean ± SEM)*

	Group	
	0.3 mg	0.6 mg
Number	9	10
Age (yr)	66.2 ± 2.9	59.9 ± 3.8
Weight (kg)	62.7 ± 3.6	72.1 ± 3.9
Height (cm)	170.0 ± 2.4	167.3 ± 3.0
Surgery time (min)	86.7 ± 7.1	94.5 ± 11.4
Blood loss (ml)	329.0 ± 57.0	489.0 ± 89.0
Sex ratio	5M : 4F	5M : 5F

Two patients from the 0.3-mg group could not be included in the analgesia demand analysis because no recordings were obtained. One patient from each group was excluded from the analysis of metabolic results because they were on steroid medication.

Operating conditions were very good and there were no complications during the anaesthetic.

After operation the patients wakened quickly, and had pain intensity scores of 0 before the buprenorphine was given. After buprenorphine all the patients remained pain free (pain intensity

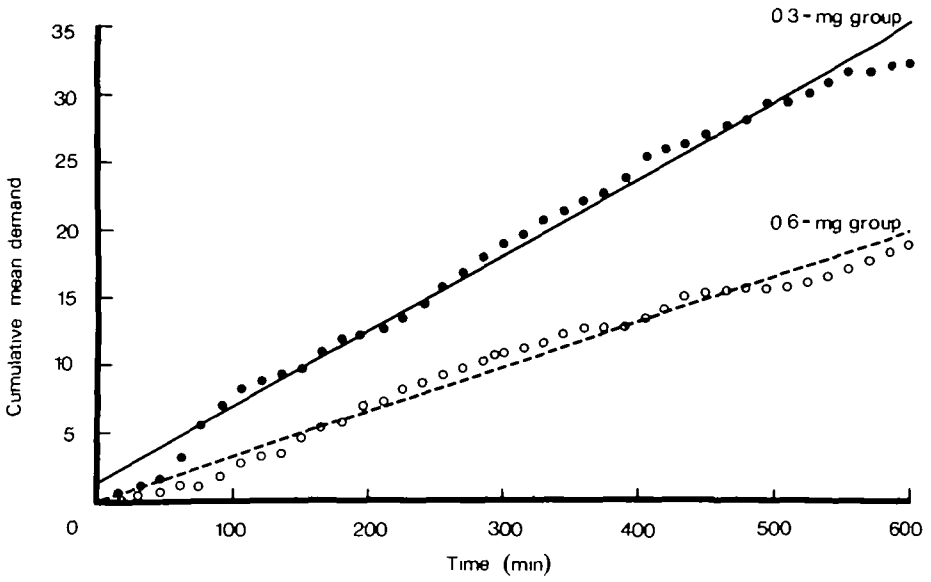

FIG. 1. Cumulative mean dose of diamorphine administered via demand system for the two groups 0 3-mg group: $n = 7$, $r = 0.994$, 0.6-mg group: $n = 10$, $r = 0.990$.

score 0) for at least 120 min. At 180 min, two-thirds of the patients had slight pain, and one-third had no pain, there being no difference between the two groups or between the sexes.

On wakening, the patients were all alert or mildly drowsy, with sedation scores of 0 or 1, except for one patient who was moderately drowsy. After buprenorphine, all the patients were either moderately drowsy or asleep (sedation scores of 2 or 3) for at least 120 min, but were easily roused. Again there was no difference, either between groups or between sexes. The only other side-effects noted were nausea and vomiting. Three patients in the 0.3-mg group were nauseated and one patient in the 0.6-mg group had nausea and vomiting. In each case this was relieved by metoclopramide 10 mg i.m.

There was no marked change in heart rate or arterial pressure in either group during the 3 h after buprenorphine administration.

Plasma buprenorphine

The mean plasma buprenorphine concentrations for the two groups are shown in figure 2. At each sampling time the ratio of the concentrations approximated to the ratio of the doses. The mean value of the ratio between the plasma concentrations (0.6-mg group : 0.3-mg group) was not significantly different from 2. Full kinetic analysis of the data will appear elsewhere.

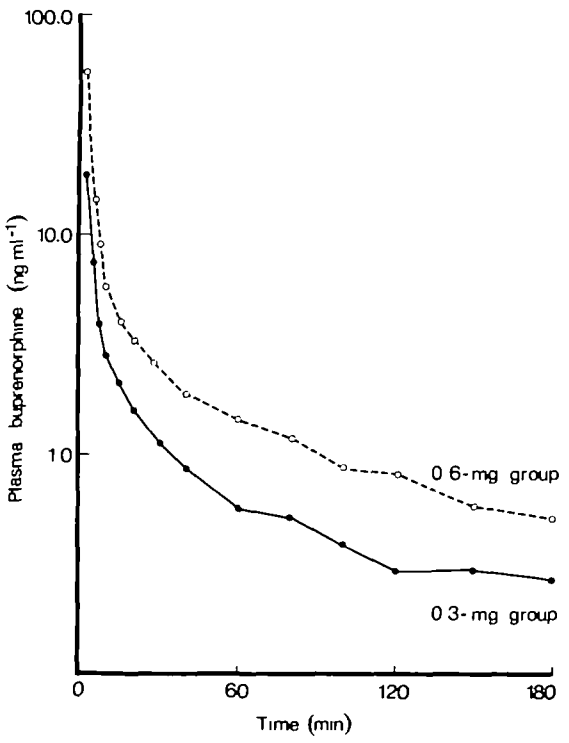

FIG. 2 Mean plasma buprenorphine concentrations on a logarithmic scale. $n = 9$ in the 0 3-mg group, $n = 10$ in the 0 6-mg group.

Glucose and cortisol

The plasma glucose and cortisol results are shown in table II. There was no significant difference between the glucose values of the two groups at any of the sampling times. Within the groups the plasma glucose continued to increase after operation after buprenorphine was given.

The 0.3-mg group had significantly greater cortisol values than the 0.6-mg group at 300 and 360 min ($P<0.05$, Student's t test), that is at 2 and 3 h respectively after the dose of buprenorphine was given. Within the groups, there was a significant mean increase in plasma cortisol in the 0.3-mg group at 300 min (154 nmol litre^{-1}, $P<0.1$, paired t test), and at 360 min (354 nmol litre^{-1}, $P<0.025$, paired t test). In the 0.6-mg group the increase was not significant (96 nmol litre^{-1} by 360 min).

Respiration

The arterial blood-gas results are shown in table III. There was no significant difference between the groups for Pa_{O_2}, Pa_{CO_2}, respiratory rate or $(PA_{O_2}-Pa_{O_2})$ at any of the sampling times. All of these measures showed wide ranges. The respiratory rate and Pa_{O_2} were reduced by about 30% in both groups within 10 min of giving the buprenorphine dose. Within the groups, there was a significant decrease in Pa_{CO_2} between the 300- and 360-min samples in the 0.3-mg group ($P<0.05$, paired t test), but not in the 0.6-mg group. $(PA_{O_2}-Pa_{O_2})$ difference was within normal limits at all times.

TABLE II. *Plasma glucose and cortisol values (mean ± SEM). Sample times calculated from the start of surgery Buprenorphine given at 180 min.* n = *8 for 0.3-mg group,* n = *10 for 0.6-mg group*

Sample time (min)	Glucose (mmol litre^{-1})		Cortisol (nmol litre^{-1})	
	0.3-mg group	0.6-mg group	0 3-mg group	0.6-mg group
0	4 50 ± 0.27	4 83 ± 0 17	303 ± 73	299 ± 40
30	5.44 ± 0.20	6.07 ± 0.40	558 ± 154	586 ± 69
150	6 75 ± 0.54	7 54 ± 0 78	862 ± 112	876 ± 98
190	6.81 ± 0 45	8.10 ± 0.81	873 ± 112	778 ± 100
240	7.39 ± 0 66	8 32 ± 0.61	923 ± 131	775 ± 126
300	7 21 ± 0.49	7 84 ± 0 35	1027 ± 131	774 ± 132
360	7.64 ± 0 78	8.39 ± 0.46	1227 ± 153	874 ± 120

TABLE III *Blood-gas analysis results. Mean ± SEM.* n = *9 for 0.3-mg group,* n = *10 for 0 6-mg group Sample times calculated from the start of surgery Buprenorphine given at 180 min.* FI_{O_2} = *0.28, but 0.33 at 30-min sample time Ranges in parentheses*

Sample time (min)	Pa_{O_2} (kPa)		Pa_{CO_2} (kPa)		Respiratory rate (b p.m.)		$(PA_{O_2}-Pa_{O_2})$ (kPa)	
	0.3-mg group	0.6-mg group	0.3-mg group	0.6-mg group	0.3-mg group	0.6-mg group	0.3-mg group	0.6-mg group
30	20.09 ± 1 5	17.29 ± 0.7	6.61 ± 0 4 (4.7–7 3)	6.38 ± 0.1 (3.7–6.4)				
150	17 51 ± 1 5	19 33 ± 1.1	5 57 ± 0.2 (4.7–7 3)	5.45 ± 0 3 (3.7–6.4)	16 7 ± 1.9	17.8 ± 1 1	2.19 ± 1.4	0.95 ± 1 1
190	12 60 ± 1.3	11.61 ± 1.9	6 60 ± 0.4 (5.0–8.6)	6.75 ± 0 3 (4 7–8 1)	12.8 ± 0 8	11.2 ± 1.0	5.94 ± 0.9	3.16 ± 0.9
240	13.41 ± 1 1	14.39 ± 0.9	6.98 ± 0.4 (5 6–9.7)	7 53 ± 0 3 (5 5–8.7)	10.8 ± 0.8	10.8 ± 1.0	4 64 ± 0.8	2 94 ± 0.8
300	13.36 ± 1 2	15 03 ± 0 9	6 80 ± 0 4 (5 6–9 8)	7.11 ± 0.4 (4.6–9 1)	11.2 ± 1.5	11.0 ± 0.8	4.16 ± 0.8	2.78 ± 0 6
360	12 43 ± 1.0	13 66 ± 0.9	5.88 ± 0.4 (4.3–8 1)	6.77 ± 0.3 (4.3–7.9)	13 0 ± 1.7	12.0 ± 0.8	5.56 ± 0 4	3 87 ± 0.7

TABLE IV *Analgesic demand analysis by group and by sex (mean ± SEM), for 0–540 min of connection to the demand system. All the values were significantly different ($P < 0.01$, d.f = 36) from all other values by comparison of the regression slopes*

	Demand rate for diamorphine ($mg \times 10^{-3}$ per patient per min)		Male/female ratio
	Males	Females	
0.3 mg i.v. ($n = 7$)	18.75 ± 0.5 ($n = 4$)	8.62 ± 0.25 ($n = 3$)	2.2
0.6 mg i.v. ($n = 10$)	13.00 ± 0.5 ($n = 5$)	4.25 ± 0.03 ($n = 5$)	3.1
0.3 mg : 0.6 mg ratio	1.4	2.0	

Analgesia

Duration of analgesia. The median time to the fifth demand for the 0.3-mg group was 250 min, compared with 492 min for the 0.6-mg group. This difference was significant ($P < 0.025$, Mann–Whitney U test).

Requirement for further analgesia. Table IV contains the regression slopes and demand ratios calculated as described. The analysis shows essentially independent effects of dose and sex. The 0.3-mg group made more demands than did the 0.6-mg group. Males made more demands than females. The influence of sex was more important than that of dose.

DISCUSSION

The relation between dose and response is fundamental to the optimal clinical use of any drug. The anticipated increase of response with increased dose does not necessarily occur with the opiates of mixed agonist-antagonist type (Martin, Gorodetsky and Thompson, 1972). These drugs can produce dose–response curves which display a maximum, minimum or the usual sigmoid-shaped response curve as the dose increases. The use of different doses of buprenorphine in this trial provided an opportunity to assess the dose–response curve for single doses in the recommended dose range.

The analgesic duration of buprenorphine 0.6 mg was twice that found with 0.3 mg. Similarly, the requirement for further analgesia after 0.6 mg was about half that after 0.3 mg. The greater dose also had greater effect than the smaller dose in preventing the anticipated increase in plasma cortisol after operation. The analgesic response to the two buprenorphine doses used, and the effect on plasma cortisol show that, in this dose range, a significant increase in response is achieved by doubling the dose.

The effect of both the doses on respiration was predictable; Pa_{CO_2} was increased and the respiratory rate decreased. There were, however, no significant differences between the groups, so that a straightforward dose–response relation was not obtained. The longer duration of the 0.6-mg dose, seen with analgesia, was also detected with respiration, because the Pa_{CO_2} values 3 h after the dose of buprenorphine had not decreased significantly from the values 1 h earlier, whereas a significant decrease was seen at this time in the 0.3-mg group.

These results show that buprenorphine produced significantly increased analgesia and hormonal response at the greater dose without an equivalent increase in respiratory depression.

The ability to differentiate the analgesic and respiratory potency of analgesics relies on the adequacy of the measurements. Most reported clinical studies of the effects of opiates involved different patient groups for the effects on respiration and analgesia. Laboratory studies either involved human volunteers who were not in pain or used animal pain models. Although refined respiratory measurements have been available, analgesic estimates have previously been relatively crude.

In this study the analgesic, respiratory and hormonal effects were measured simultaneously in patients recovering from surgery. The technique of demand analgesia used here has proved to be a sensitive method with small patient numbers as shown by the excellent linear correlation seen in figure 1. The use of Pa_{CO_2} as a respiratory measure is justified because it is still the primary physiological parameter which should determine clinical intervention. In addition, opiate drugs may cause measurable changes in hormone concentrations to occur (Moore, McQuay and Bullingham, 1980), and

these changes may be used to analyse dose–response relationships. Biochemical assays may be performed with convenience and precision on stored blood samples, in contrast to analgesic and respiratory measurements.

There is both clinical and experimental support for differentiating the dose–response curves for analgesia and respiratory depression. Clinically, large doses of buprenorphine (up to 8 mg) have been used to provide analgesia without evidence of serious respiratory sequelae (K. Budd, personal communication), and the repeated use of 0.3-mg doses of buprenorphine produced increased analgesia without parallel increase in respiratory depression (McQuay et al., 1980). Experimentally, Pasternak, Childers and Snyder (1980) and Pasternak, Zhang and Tecott (1980) distinguished opiate receptor populations in mice; those receptors with high affinity binding for morphine were correlated with analgesia, and those with low affinity binding with respiratory effects. This experimental dissociation between analgesia and respiratory depression indicates a potential mechanism for the distinction seen clinically in this trial.

The analgesic effect of two 0.3-mg doses given 3 h apart (McQuay et al., 1980) may be compared with those from a single 0.3- and 0.6-mg dose in this trial. The comparison shows that the requirement for further analgesia is different; a preliminary 0.3-mg i.v. dose lowers the subsequent analgesic requirement by a factor of two from 13 to 7 μg of diamorphine per patient per min, compared with a single 0.3-mg dose after operation. The effect of a single 0.6-mg dose (diamorphine 8.5 μg per patient per min) closely resembles that of the same dose split in two and separated by 3 h. For most drugs, splitting a dose into two equal parts would be expected to produce a substantial increase in clinical effect (Wagner, 1968). The increase seen in the comparison above is small, and is a result of two factors.

First, buprenorphine is lipophilic, and hence undergoes rapid tissue uptake. Low plasma concentrations are achieved quickly (fig. 2). The liver will eliminate most of the drug passing through it (Bullingham et al., 1980), but the absolute amount destroyed is small relative to the total quantity in the body. These extensive body stores maintain the plasma concentration over a long time period. The addition of a second dose, behaving independently, at a time interval small in comparison with the time scale of the plasma concentration decay, is little different from giving the two doses simultaneously. The plasma concentration 3 h after a single 0.6-mg dose of buprenorphine was given was no different from the concentration 3 h after a second 0.3-mg dose (Bullingham et al., 1980).

Second, buprenorphine is pharmacologically effective at low plasma concentrations. This is shown by the sublingual use of the drug, which works well at plasma concentrations of 1 ng ml^{-1} or less (Bullingham et al., 1981). It is this which is the unique feature of buprenorphine. Other lipophilic drugs such as fentanyl behave in an equivalent way with regard to kinetics (McQuay et al., 1979), but depend on high initial plasma concentrations for their analgesic action.

In summary, these results show that better analgesia may be obtained with buprenorphine as a postoperative analgesic either as the larger dose or by splitting this dose. This choice can be made with buprenorphine but not pure agonists because, with the latter, any increase in analgesia will necessarily incur further respiratory depression. Where an opiate premedication is desired, it would be both logical and convenient to choose the divided dose regimen, with the first dose as premedicant.

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COMPARAISON D'UNE DOSE UNIQUE DE BUPRENORPHINE DE 0,3 ET DE 0,6 mg I.V. ADMINISTREE APRES L'OPERATION: EFFETS CLINIQUES ET CONCENTRATIONS DANS LE PLASMA

RESUME

Des études ont été réalisées en ce qui concerne les concentrations dans le plasma et les effets cliniques d'une dose unique de buprénorphine de 0,3 ou de 0,6 mg i.v administrée à des patients en récuperation d'opérations. Les effets analgésiques et hormonaux ont été plus prononcés avec la dose plus élevée sans qu'il y ait une augmentation parallèle de la dépression respiratoire Une comparaison avec des expériences préalables indique que l'efficacité accrue découle soit de l'utilisation d'une dose plus forte ou, de même, lorsque la premiere dose postopératoire requise de 0,3 mg était précédée d'une dose de charge analogue

DOSISVERGLEICH ZWISCHEN 0,3 UND 0,6 mg BUPRENORPHIN, INTRAVENÖS NACH DER OPERATION VERABREICHT· KLINISCHE WIRKUNGEN UND PLASMAKONZENTRATIONEN

ZUSAMMENFASSUNG

Plasmakonzentrationen und klinische Wirkungen einzelner intravenöser Injektionen von 0,3 oder 0,6 mg Buprenorphin wurden bei Patienten studiert, die sich von einer Operation erholten Analgetische und hormonale Wirkungen waren bei der grösseren Dosis stärker—ohne gleichzeitigen Anstieg der respiratorischen Dämpfung Ein Vergleich mit früheren Arbeiten zeigt, dass die erhöhte Wirksamkeit entweder ein Ergebnis der höheren Dosis ist, oder davon, dass die erste postoperative Dosis von 0,3 mg nach einer gleichgrossen einleitenden Dosis erfolgte

COMPARACION DE DOSIS UNICA DE 0,3 Y DE 0,6 mg DE BUPRENORFINA I.V. DESPUES DE LA OPERACION. EFECTOS CLINICOS Y CONCENTRACIONES EN EL PLASMA

SUMARIO

Se llevó a cabo el estudio de las concentraciones en el plasma y de los efectos clínicos de una dósis única i v. de 0,3 ó de 0,6 mg de buprenorfina en pacientes bajo recuperación de una operación. Los efectos analgésicos y hormonales fueron mayores con las dosis mayores sin aumento paralelo en la depresión respiratoria. Una comparación con trabajos previos hace pensar que la eficacia mayor resulta ya sea del uso de una dosis mayor ya sea cuando la primera dosis postoperatoria necesaria de 0,3 mg fue precedida por una dosis de carga análoga.