A COMPARISON OF BUPRENORPHINE AND PETHIDINE IN ANALGESIC SUPPLEMENTED ANAESTHESIA

F A Khan, R S Kamal

ABSTRACT

A randomized trial comparing 2.5 and 5 micrograms/ kilogram body weight of buprenorphine and 0.8 milligram/ kilogram pethidine, intravenously for intraoperative use in a balanced anaesthetic technique, and for postoperative analgesia was carried out. Compared with pethidine, buprenorphine was shown to be a satisfactory analgesic for preoperative and postoperative use with little difference in the incidence of unwanted effects and much longer duration of action. Increasing the dose of buprenorphine did not give any significant advantage.

Keywords : Buprenorphine, pethidine, narcotic, preoperative and postoperative analgesia, postoperative pain

SINGAPORE MED J 1990; Vol: 31: 345 - 349

INTRODUCTION

Buprenorphine is a potent, semi-synthetic, centrally acting, partial agonist opiate analgesic, with a long duration of action [1]. Its use as a premedicant [2] and as a postoperative analgesic [3,4] is well documented, but very few studies have reported its intraoperative use for major surgery in comparison to other narcotic analgesics [5-7]. This study compares the cardiovascular effects, the intraoperative course and the postoperative analgesic requirements for buprenorphine 2.5 micrograms/ kilogram, 5 micrograms/kilogram and pethidine 0.8 milligram/ kilogram during and after major abdominal surgery.

METHODS

The protocol was approved by the Committee for the Protection of Human Subjects of the Aga Khan University Hospital. Informed consent was obtained from the patients before their entry into the trial. Seventy-five ASA class I and II patients undergoing upper abdominal surgery mainly of gall bladder and stomach were entered into the trial. They were aged between 20-60 years and none suffered from any cardiac, pulmonary, renal or hepatic disease which contraindicated the anaesthetic technique employed. They were randomly divided into three groups A, B and C.

Department of Anaesthesia
The Aga Khan University Hospital
Stadium Road
P O Box 3500
Karachi 74800
Pakistan

F A Khan, FFARCS
Assistant Professor

R S Kamal, FFARCS
Associate Professor

Diazepam 0.15 milligram/ kilogram was administered orally two hours before surgery in all groups. On arrival in the operating room, the pre-induction measurements of pulse rate, systolic and diastolic blood pressure were recorded using a noninvasive technique (Omega 1400 non-invasive BP monitor). Immediately prior to induction of anaesthesia with thiopentone, twenty-five patients received pethidine 0.8 milligram/ kilogram I/V (Group A) and fifty patients received either intravenous buprenorphine 2.5 micrograms/ kilogram (Group B) or 5 micrograms/ kilogram I/V (Group C).

Anaesthesia was induced with a sleep dose of 2.5% thiopentone followed by pancuronium 0.1 milligram/ kilogram to facilitate intubation. After ventilation of the lungs for three minutes with nitrous oxide and oxygen orotracheal intubation was performed. Readings of blood pressure and pulse rate were taken every minute for ten minutes after induction and every five minute interval throughout the procedure.

General anaesthesia was maintained with 66% nitrous oxide, 33% oxygen and 0.5% halothane. Normocapnia was maintained by monitoring the end tidal carbon dioxide with Engstrom Eliza Duo carbon dioxide analyser. Supplemental doses of pancuronium were given as indicated by the use of a peripheral nerve stimulator.

Supplemental doses of half the original dose of the test drug were given intravenously if two out of four of the following criteria were present i.e. systolic blood pressure exceeding the baseline by more than 15%, heart rate exceeding the baseline by more than 15%, sweating or lacrimation. Halothane was turned off approximately 15 minutes before the end of operation and residual neuromuscular relaxation reversed with atropine and neostigmine. Full reversal of block was ensured by the use of a nerve stimulator. All patients were observed in recovery for a minimum of two hours. During the recovery and postoperative period, analgesics were given by the anaesthesia resident when the patient complained of

moderate to severe pain, the patient being unaware of the analgesic or it dose used. All injections during the postoperative period were administered via the intramuscular route. All intraoperative and postoperative injections including dose, route, and time of administration were recorded. The time at which thiopentone was administered (induction time), time at which orotracheal intubation was done (intubation time) and the time at which incision was made (incision time) were also recorded. Recovery was assessed by the time of resumption of spontaneous respiration (breathing time), and the time of opening eyes on command (waking time), both times being measured from the time of reversal of muscle relaxation. All patients were followed and interviewed twenty-four hours postoperatively.

Numeric data was evaluated for statistical significance using analysis of Variance and Chi Square tests where appropriate.

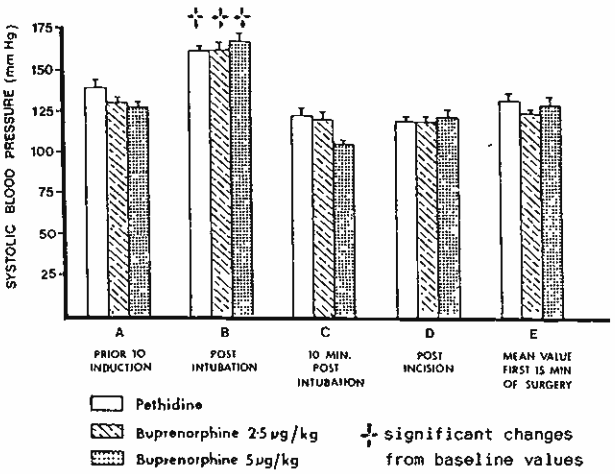
Table I
Demographic data,
Mean age, Mean weight and sex (± SEM)

	Group		
	A	B	C
Number	25	25	25
Sex, no. of males	7	11	14
Age (yrs)	44.4 ± 2.2	37.1 ± 2.1	42.5 ± 1.1
Weight (kg)	66.2 ± 2.4	62.9 ± 2.3	61.9 ± 3.3

RESULTS

Demographic data (Table I). With regards to age, sex and body weight the three groups were statistically comparable. The operations performed and their duration was also similar.

Fig 1
Comparison of Systolic Arterial Blood Pressure
(mean ± SEM values)

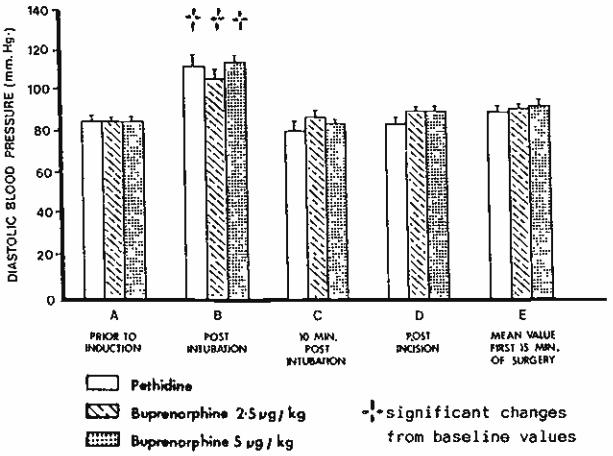


PREOPERATIVE COURSE

Blood pressure (Fig 1 & 2): Before induction of anaesthesia the arterial pressure was similar in all three groups.

Following intubation there was a significant rise in both systolic and diastolic pressures in all groups. The

Fig 2
Comparison of Diastolic Arterial Blood Pressure
(mean ± SEM values)



blood pressure readings after ten minutes of intubation, after incision and mean of first fifteen minutes after incision did not show a significant deviation from the baseline within each group.

Fig 3
Comparison of Heart rate changes
(mean ± SEM values)

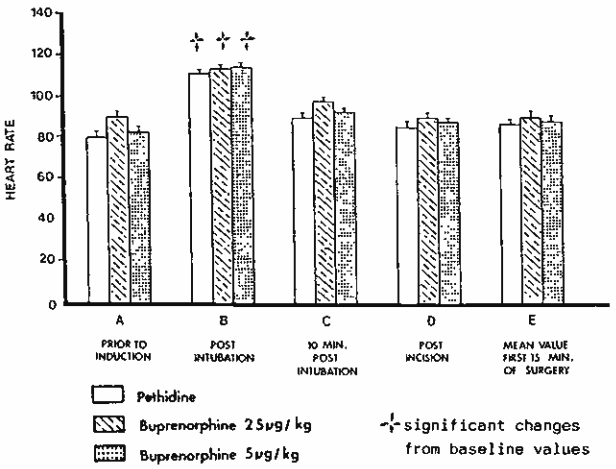


Table II
Supplemental Analgesia during maintenance of anaesthesia (Mean ± SEM)

	A n = 25	B n = 25	C n = 25	p
Patients requiring intraoperative supplement (%)	40.3	20	20	NS
Time from introduction to first intraoperative analgesic injection (mins)	53.5 ± 2.86	42.4 ± 4.69	48.8 ± 4.89	NS

NS = Not significant

The comparison of corresponding values in different groups did not show a significant difference.

Heart rate (Fig 3): The increase in heart rate from pre-induction to post-intubation values was significant in all three groups. The deviation of all other values from the baseline in each group did not show any statistical difference.

Analgesic supplement action (Table II): Ten patients in Group A, and five patients in Group B and C each, required additional narcotic analgesic during surgery.

The average time interval from the narcotic dose given at induction to the intraoperative supplement dose was 53.5 minutes ±2.86 SEM in Group A, 48.8 minutes ±4.89 SEM in Group B and 42.4 minutes ±4.69 SEM in Group C patients. This difference was not statistically significant.

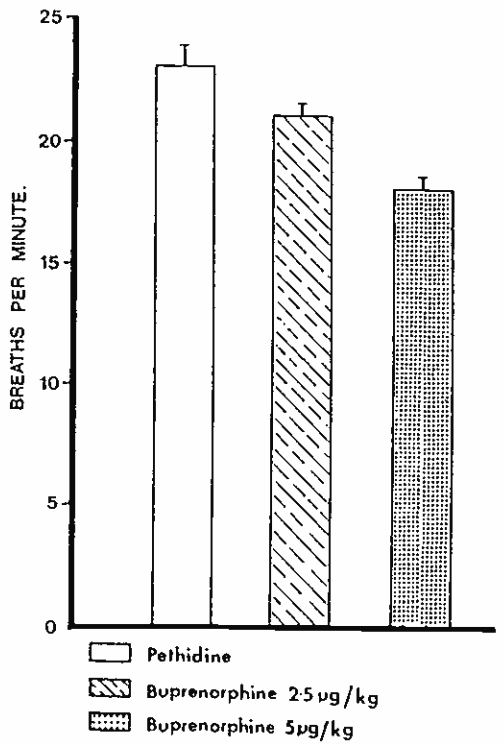
Unwanted effects: Heart rate of less than 60 per minute was observed in three patients in Group B and four patients in Group C.

Table III
Recovery from Anaesthesia
Mean time (± SEM) from reversal to spontaneous opening on command.

	A n = 25	B n = 25	C n = 25	p
Breathing time (mins)	2.0 ± 0.34	3.66 ± 0.55	3.67 ± 0.52	p<0.01 for difference between group A and B, and group A and C.
Waking time (mins)	3.80 ± 0.54	4.88 ± 0.71	4.70 ± 0.68	NS

NS = Not significant

Fig 4
Respiratory rate on arrival in recovery room (mean ± SEM values)



RECOVERY

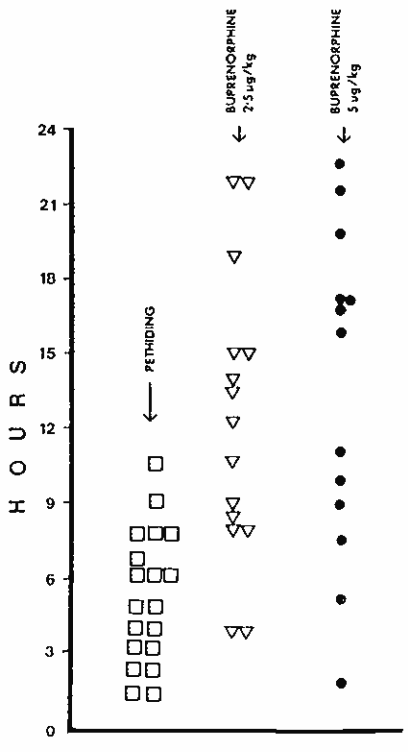
Breathing time (Table III) i.e., the mean time from reversal to onset of spontaneous respiration was 2 minutes ±0.34 SEM in Group A patients, 3.66 minutes ±0.55 SEM in Group B patients and 3.67 minutes ± 0.52 SEM in Group C patients. The difference between Group A and both Group B and C was statistically significant (P<0.01). *Waking time* i.e., the mean time from reversal to eye opening on command was 3.80 minutes ±0.54 SEM in Group A, 3.55 minutes ±0.71 SEM in Group B and 3.41 minutes ±0.68 SEM in Group C patients. This difference was not statistically significant.

Table IV
Incidence of unwanted side effects in the recovery room

	Frequency		
	A n = 25	B n = 25	C n = 25
Drowsiness	50%	28%	36%
Vomiting	-	-	8%
Nausea	1%	-	-
Respiratory rate less than ten	-	-	-
Heart rate less than 60/min	-	8%	12%

Respiratory rate on arrival in recovery was 23 per minute ±1.17 SEM in Group A, 21 per minute ±0.06 SEM in Group B, and 18 per minute ±1.05 SEM in Group C patients (Fig 4). This difference was not statistically significant.

Fig 5
Duration in hours between the last dose given in the operating room and the first post operative dose

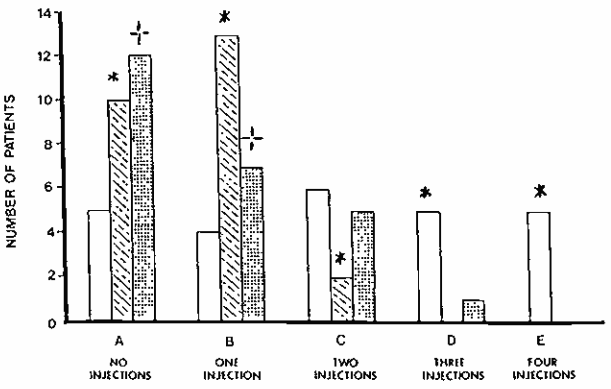


None of the patients in any group showed a respiratory rate of less than 10, or any abnormal respiratory pattern.

Unwanted effects (Table IV): The commonest side effect noted in recovery was drowsiness in all groups. Statistically there was no difference between the groups but clinically the incidence of drowsiness was lower with 2.5 micrograms/ kilogram buprenorphine. The incidence of nausea and vomiting was comparable in all three groups.

Bradycardia, i.e., heart rate less than 60 beats per minutes was observed in two patients in Group B and three patients in Group C, who responded to atropine.

Fig 6
Comparison of post operative analgesia requirements over 24 hours



Pethidine

Buprenorphine 5 µg/kg

Buprenorphine 2.5 µg/kg

* significant changes from between pethidine group and buprenorphine 2.5 micrograms/kg

+ significant changes from between pethidine group and buprenorphine 5 micrograms/kg

Table V
Incidence of unwanted side effects within 24 hours post-operatively

	Frequency		
	A n = 25	B n = 25	C n = 25
Vomiting	46%	40%	44%
Nausea	42%	48%	24%
Respiratory rate less than 10/mins	0	0	0
Headache	8%	4%	8%
Dizziness	-	-	-
Sweating	4%	-	-
Dry mouth	8%	-	-
Rash	-	-	-
Tinnitus	-	-	-

POSTOPERATIVE COURSE

Analgesia requirements (Fig 5): The mean time interval from the last narcotic analgesic injection received in the operating room to the first postoperative dose was 5.81 hours ±0.15 SEM of r pethidine group, 12.55 hours ±1.50 SEM in Group B and 14.40 hours ±1.57 SEM in Group C patients. Eighteen patients in Group A required postoperative analgesia within 24 hours compared to 15 patients in Group B postoperative and 12 patients in Group C. The average number of injections required over 24 hours are presented in Fig 6.

Unwanted effects (Table V): The commonest side effects in the postoperative period were nausea and vomiting. The comparative incidence of vomiting was statistically insignificant in all three groups, but the incidence of nausea was higher with pethidine and buprenorphine 2.5 micrograms/ kilogram compared to buprenorphine 5 micrograms/ kilogram.

DISCUSSION

One of the major problems in developing countries in the specialty of anaesthesia is the availability of drugs. Fentanyl is not available in our country, and the only other narcotic analgesics available for intraoperative use are pethidine and morphine, the availability of which can be a problem as both these drugs are subjected to the Controlled Drugs Act with only a certain quota released to the hospitals at variable intervals. The potency of the locally manufactured drugs has also been questioned at times due to lack of quality control. Buprenorphine being an uncontrolled drug in Pakistan is easily avialable. Its low abuse potential[8], its cardiovasular stability [9], longer duration of action and its potential safety in overdosage [10] outweigh its disadvantages especially in major surgery and in situations where shorter acting drugs are not available.

Buprenorphine has been compared to fentanyl [5,11], pentazocine [7] and morphine [6,12] for intraoperative and postopertive use, and to pethidine for postoperative use [13,14] but none of the studies have compared it to pethidine for intraoperative use in a balanced anaesthesia technique.

The problem in the use of buprenorpine in anaesthesia is the choice of an appropriate dose. The agonist/ antagonist nature of the drug limits its analgesic effect but the dose at which ceiling occurs is not known. Different authors have recommended different doses varying from 4 micrograms/ kilogram to 10 micrograms/ kilogram for intraoperative use [5,11]. None of the studies used 0.5% halothane as part of a balanced anaesthetic technique. We used 0.5% halothane throughout the procedure as part of our techique and also to reduce any chance of awareness. It may also allow a smaller narcotic dose to be used. We therefore selected a dose of 2.5 micrograms/ kilogram and 5 micrograms/ kilogram of buprenorphine for our study.

A lower percentage of patients in the buprenorphine groups (20% in each group) required intraoperative supplementation compared to 40% in the pethidine group. The analgesic requirements were not statistically different in the two buprenorphine groups, although clinically the patients receiving 2.5 micrograms/ kilogram of buprenorphine required intraoperative supplements earlier.

The cardiovascular parameters in all three groups remained stable. Recovery was significantly quicker in the pethidine group as compared to buprenorphine, and none of the patients showed any significant depression of ventilation in any groups.

Drowsiness was the commonest side effect observed during recovery by several authors. In comparing it with pethidine and pentazocine for postoperative use Hovell [12] found no difference in sedation produced. Our findings are similar to Kamel [13] who reported a higher incidence with pethidine. Although halothane 0.5% was stopped in all groups approximately 15 minutes before the end of surgery it is clinically difficult to rule out its contribution in the incidence of drowsiness. However, one hour into recovery, three patients in the pethidine group, three patients in the buprenorphine 25 microgram/ kilogram and two patients in the buprenorphine group 5 micrograms/ kilogram, were still drowsy.

Rolly [3] pointed out that drowsiness may indicate a state of relaxation in the presence of good postoperative pain suppression. We also did not consider it a disadvantage as all our patients were easily rousable. A small percentage of patients, in both buprenorphine groups had a heart rate of less than 60 per minute. This effect has been observed in other studies. [15] with buprenorphine and could be either due to direct depression of conduction or a stimulant action on the vagal nucleus similar to morphine.

The commonest side effect in the delayed recovery period was nausea and vomiting. There was no significant difference among the groups except for nausea where surprisingly the incidence was less with 5 micrograms/ kilogram buprenorphine. The incidence of the above complaints can probably be reduced by giving a prophylactic antiemetic along with the analgesic injection.

A significant advantage with buprenorphine was the carry over effect of analgesia into the postoperative period.

With pethidine, 85% patients required postoperative analgesia. The mean time interval to the first postoperative analgesia dose was more than 12 hours in both the buprenorphine groups with the majority of patients only requiring one or two injections within 24 hours.

In conclusion, this investigation indicates that buprenorphine 2.5 microgram/ kilogram proved to be an adequate analgesic supplement to nitrous oxide, oxygen and relaxant anaesthesia with 0.5% halothane, for upper abdominal surgery in the majority of patients. The patients remained stable intraoperatively. Excessive cardiovascular responses to surgical stimuli were sufficientaly suppressed and the technique provided satisfactory analgesia in the postoperative period. Recovery and side effects were not different from pethidine. Although pethidine produced similar results, there was increased intraoperative and postoperative supplements required.

Increasing the dose of buprenorphine from 2.5 micrograms/ kilogram to 5 micrograms/ kilogram did not prove advantageous. There was no statistical difference between the analgesic effect, but there was a higher incidence of side effects with 5 micrograms/ kilogram buprenorphine.

REFERENCES

1. Heel RC, Brogden RN, Speight TM, Avery GS: Buprenorphine – A review of its pharmacological properties and therapeutic efficacy. Drugs 1979; 17: 81-110.
2. Devan PLT, Macnee CM, Orwin JM: An open multicentre study of buprenorphine used as the sole analgesic in the pre-, per- and postoperative periods. In: Paul L, Beven T, Firsh M, eds. Buprenorphine and Anaesthesiology. Royal Society of Medicine International Congress and Symposium Series No 65. London : Royal Society of Medicine, 1984: 89-94.
3. Rolly G, Versichelen L: Buprenorphine as postoperative analgesic. Acta Anaesthesiol Belg 1976; 27: 183-6.
4. Dobkin BD, Esposito B, Philbin C: Double blind evaluation of buprenorphine hydrochloride for postoperative pain. Can J Anaesth 1977; 24: 195-202.
5. Kay B: A double blind comparison between fentanyl and buprenorphine in analgesic supplemented anaesthesia. Br J Anaesth 1980; 52: 453-6.
6. Green DW, Sinclair JR, Mikhael MS: Buprenorphine versus morphine – A comparison of intraoperative and postoperative analgesia. Anaesthesia 1985; 40: 371-5.
7. Carl P, Crawford ME: A comparison between buprenorphine fentanyl and pentazocine in analgesic supplemented flunitiazepam nitrous oxide anaesthesia. In: Paul L, Beven T, Firth M, eds. Royal Society of Medicine International Congress and Symposium series No 65. London : Royal Society of Medicine, 1984: 71-6.
8. Jasinski DR, Pevnick JS, Griffith JD: Human pharmacology and abuse potential of the analgesic buprenorphine. Arch Gen Psychiatry 1978; 35: 501-16.
9. Orwin JM, Orwin J, Price M: A double blind comparison of buprenorphine and morphine in conscious subjects following administration by the intramuscular route. Acta Anaesthesiol Belg 1976; 27: 171-5.
10. Rance MJ: Animal and molecular pharmacology of mixed agonist antagonist analgesic drugs. Br J Clin Pharmacol 1979; 7: 2815-65.
11. Abrahamson J, Niemand D, Olsson AK, Tornelrandt K: Buprenorphine (Temgesic) as preoperative analgesic, a multicentre study. Anaesthetist 1983; 32: 75-9.
12. Hovell BC, Ward AE, Pain relief in the postoperative period - A comparative trial of morphine and new analgesic buprenorphine. J Int Med Res 1977; 5: 417-21.
13. Kamel MM, Geddes IC: A comparison of buprenorphine and pethidine for immediate postoperative pain relief by the I/V route. Br J Anaesth 1978;50: 599-03.
14. Hovell BC: A comparison of buprenorphine, pethidine and pentazocine for the relief of pain after operation. Br J Anaesth 1977; 49: 913-5.
15. Rosenfeldt FL: Haemodynamic effects of buprenorphine after heart surgery. Br Med J 1978; 2: 1602-4.