Indian J Physiol Pharmacol 1997; 41(4) : 361–368

BUPRENORPHINE PHARMACOKINETIC PARAMETERS DURING CORONARY ARTERY BYPASS GRAFT SURGERY

AKRAM AMANI, THANGAM JOSEPH* AND KANTI BALASARASWATHI

Department of Anaesthesiology, M. S. R. Medical College, Bangalore – 560 054 and **Department of Pharmacology, St. John's Medical College, Bangalore – 560 034*

(Received on November 21, 1996)

Abstract : The pharmacokinetic parameters of buprenorphine (BN) after a single bolus dose of 10 μg/kg i.v. was investigated in 6 male patients whose age averaged 59 ± 9.8 years and body weight of 65.8 ± 5.7 kg undergoing coronary artery bypass graft surgery (CABG). The unbound BN plasma concentrations were detected using ultrafiltration and high performance liquid chromatography/electro-chemical detection (HPLC/ECD) method. During cardiopulmonary bypass (CPB) there was a fall in BN plasma concentrations, observations similar to reports on fentanyl, sufentanil and alfentanil. This is probably due to haemodilution, hypothermia and hydrophobic sequestration of drug on to the CPB tubing. After CPB the concentrations rose to values higher than during CPB, though it did not attain pre CPB concentrations. These variations were not statistically significant indicating that plasma levels were adequately stable during CPB. The plasma concentraion time curves were biexponential and the pharmacokinetic parameters obtained were : distribution half-life 37.24 ± 6.57 min, elimination half-life 482.69 ± 79 min, clearance 1221.97 ± 209.42 ml/min, and volume of distribution 736.46 ± 71.25 L. BN in the dose used follows the pharmacokinetic pattern of other commonly used narcotics during CABG. The mean ± SEM plasma BN concentration during CPB was 0.51 ± 0.03 ng/ml which was adequate for the maintenance of analgesia and anaesthesia, as none of our patients expressed the signs and symptoms of awareness during surgery. Further, unlike the other narcotics muscle rigidity was absent. Thus BN is a safe and good alternative to other narcotics for patients undergoing CABG.

Key words : anaesthesia, buprenorphine, pharmacokinetics, coronary artery

INTRODUCTION

Observations by Lowenstein et al (1) about the safety and efficacy of high dose morphine lead to a conceptual leap of administering large doses of narcotics as sole anesthetics in cardiac surgery. First morphine (2) followed by fentanyl (3) and sufentanil (4) are extensively used as sole anesthetics with oxygen for coronary artery bypass surgery (CABG). Their pharmacokinetics have been studied extensively (5 – 8). Factors like cardiopulmonary bypass (CPB) cause a number of changes in pharmacokinetics of a drug (9, 10). This may be particularly

*Corresponding Author

important for highly protein bound drugs, as introduction of the priming fluid, changes in the plasma volume and perfusion, all can alter the protein binding and distribution of drugs.

Buprenorphine (BN) is a highly protein bound (96%) opioid agonist/antagonist, 25–50 times more potent than morphine (11). Its high potency, long duration of action and low cost make it a suitable analgesic for intra-and postoperative analgesia.

The purpose of this study was to investigate the pharmacokinetics of a high dose of BN in CABG and to see if there was adequate BN plasma concentrations during CPB. The information obtained will provide guidelines for the anaesthesiologists to use and adjust analgesic and anaesthetic regimens.

METHODS

With the approval of the Medical Ethics Commitee of the M.S. Ramiah Medical College Hospital, 6 male patients with normal hepatic and renal function scheduled for elective CPB entered the study after informed consent. Their age, mean ± SEM was 59 ± 9.8 years (range 34–71) and body weight 65.8 ± 5.7 kg. All patients had angiographically proven coronary artery disease with ejection fractions ranging from 0.4–0.6%.

All patients were premedicated with 10 mg oral diazepam along with other cardiac medicaments 1 h before transport to surgery. On arrival in the operating room, the peripheral vein, radial artery and right internal jugular vein were cannulated under local anaesthesia. Through the internal jugular vein sheath, quadruple lumen thermister tipped pulmonary artery catheter was floated and positioned to wedge on balloon inflation. Patients were oxygenated for 5 min and steady state haemodynamic parameters, both monitored and derived were noted.

Anaesthesia was induced with sodium pentothal 4 mg/kg along with pancuronium bromide 0.12 mg/kg as required by clinical criteria. Atraumatic intubation was facilitated within 5 min. Anaesthesia was maintained with oxygen and 0.2–0.4% isoflurane and mechanical ventilation. Before initiation of CPB, anaesthesia was supplemented with 5 mg diazepam and 2-4 mg pancuronium iv. In the post CPB period, patients were ventilated with oxygen only and isoflurane as required. Post operatively, all patients were ventilated electively with 0.4% isoflurane and weaned systematically. Monitoring of blood pressure, electrocardiogram, body temperature, end-tidal CO_2 and fluid administration was maintained throughout the 24 h study period. Intermittent measurements of blood gases, pH, electrolytes, hematocrit and urine volumes were made, throughout the study, period.

Before induction of anaesthesia, BN 10 μg/kg body weight was diluted 10 ml with normal saline and injected iv as a single bolus dose over a period of 1 min. Samples of 10 ml blood were withdrawn through the central venous catheter into heparinised glass tubes at 5 min before and at 5, 35, 65, 125, 185, 320, 380 and 800 min after BN injection. Time intervals referred to different stages e.g. 35 min (sternotomy), 65 min (beginning of bypass), 125 min (mid

bypass), 185 min (end bypass), 320 min (at closure), 380 min (connecting to ventilators), and 800 min (post-operative period). The sampling times were selected to obtain 2 samples before CPB, 3 samples during CPB and 3 samples after CPB. Plasma was separated by centrifugation and stored at –22°C until analysis. For drugs like BN which are highly protein bound the effects are principally dependent on the free (unbound) fraction, and hence in this study only, the unbound plasma level (free fraction) was estimated.

Sample analysis: BN plasma concentrations were detected using ultrafiltration and High Performance Liquid Chomatography/Electrochemical detection (HPLC/ECD). The separation of BN into the protein bound and free fraction (unbound) was done with the help of an ultrafiltration (12) system (MPS Company, Amicon). This system consists of a specimen container (capacity maximum 1.2 ml), which is connected at its lower end with the membrane support through a washer or gasket by means of two clamps. The isotropic and hydrophilic YMT membrane used in this system had a minimal separation limit at a molecular weight of 30,000 Daltons. Its diameter was 14 mm and was spun at 2000 g. To obtain an optimum centrifuging time and filtrate value, the filtrate value was kept constant at 25°C. The ultrafiltrates were stored at –22°C and analysed biochemically within 3 days.

Extraction: 1.00 ml of ultrafiltered plasma was mixed with 0.1 N HCl (1 ml) and the new solution was agitated for 5 min, then incubated at 56°C for 1 h. The solution was neutralized with 0.1 N NaOH (1 ml) and addition of 1 ml of phosphate buffer pH 8.5. The drugs were extracted with 5 ml toluene. After agitation and centrifugation, the organic phase was purified by an additional acidic extraction with 1 ml of 1N HCl. The aqueous layer was re-extracted after the addition of 1 ml of 0.1 N NaOH and 1 ml of phosphate buffer pH 8.5 with 5 ml of toluene. After agitation and centrifugation, the organic phase was taken off and evaporated to dryness. The residue was reconstituted in 50 µl of mobile phase and injected into the HPLC column. The HPLC conditions of this assay were the same as reported before (13). The drug was detected connecting the HPLC (Waters 590 U.S.A.) to an ECD (Waters 460) with 2 electrodes. The working electrode was set at a potential of 0.5 V and the second electrode was a reference electrode.

Data on BN plasma concentration of each sample was integrated using a computer based data station integrator. Areas of peak interest were collected from the data station. Calculation was done by PC-AT 286 Computer. The correlation between concentration and area was statistically evaluated. The detection limit of BN plasma concentration was 0.03 ng/ml with correlation coefficient (r) more than 0.99 per cent.

Pharmacokinetic analysis : Pharmac–okinetic variables were estimated by standard non linear least square regression. Unbound drug plasma levels were fitted to a sum of exponential curves using the computer programme 'Pharmkit' based on a stripping method.

Statistical analysis: All values are expressed as mean ± SEM. The paired 't' test with Bonferroni correction was applied to determine which time points were

significant in relation to baseline (time 5 min) and significance validated at $P<0.05$.

RESULTS

The mean demographic data for the six patients are shown in Table I. There were no significant differences between any of these patients for any of the variables.

TABLE I : Demographic data (Mean ± SEM) of patients.

No. of patients	6
Age in years	59 ± 9.83
Sex	All males
Weight in kg	65.8 ± 5.7
Height in cm	165.4 ± 3.2
Surface area (M2)	1.67 ± 0.2
Dose (µg/kg, iv)	10

The BN plasma-concentrations (all concentrations refer to unbound fractions) at the various time points obtained in the individual patients and the mean ± SEM are shown in Table II and Fig.1. 5 min after BN 10 µg/kg, iv, the plasma concentration in most patients (5 out of 6) were below 2 ng/ml. In one patient, the concentration was higher, viz. 3.02 ng/ml (patient 1). The mean ± SEM concentration at this time point was 1.69 ± 0.29 ng/ml. The plasma concentration declined gradually as expected over the first 65 min (pre bypass period). After initiation of CPB there was a fairly rapid decline from 65 min to 125 min in all patients, the time corresponding to mid bypass; the value at mid bypass being 47.4% lower than pre bypass level. By the end of bypass (185 min) the drug concentration rose to higher than levels at mid bypass, though they failed to attain pre bypass concentrations. None of these changes were statistically significant indicating that the plasma concentrations remained adequately stable during CPB. The concentrations in the post bypass period declined slowly into the post-operative period and was significantly lower from pre CPB levels only from 380 min.

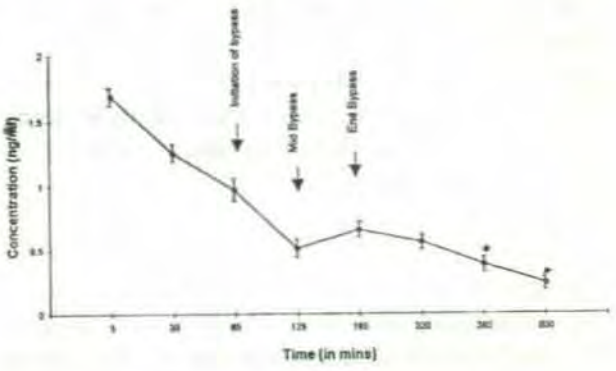

Fig. 1: Unbound buprenorphine plasma concentration (Mean ± SEM) after 10 µg/kg iv bolus in patients undergoing coronary artery bypass surgery (n = 6).

*Indicates significance from baseline (i.e. 5 min) concentration using t–tests with Bonferroni correction.

The plasma-concentration-time curve fitted into a biexponential decay except in one patient (patient 5) where it fitted to a mono-exponential curve. Since the difference was small, a biexponential analysis was used on this data also. The pharmacokinetic parameters are given in Table III.

DISCUSSION

Drugs such as BN have limited efficacy and should be regarded as partial µ opioid agonist (14). BN also binds to other receptor subtypes. Indeed, occupancy of low affinity receptors at high concentrations may cause antagonism of µ mediated analgesia. Keeping this in mind, this study was designed to look at the pharmacokinetics

TABLE II : Unbound buprenorphine plasma concentration ng/ml (Mean ± SEM) for patients undergoing CABG.

Patients	*1*	*2*	*3*	*4*	*5*	*6*	*(Mean ± SEM)*
Control	*0*	*0*	*0*	*0*	0	0	
5	1.50	3.02	1.90	1.40	1.28	1.05	1.69 ± 0.29
35	1.26	1.82	1.25	1.10	1.24	0.88	1.25 ± 0.12
65	0.72	1.82	0.82	0.77	0.89	0.82	0.97 ± 0.16
125	0.54	0.63	0.41	0.57	0.44	0.49	0.51 ± 0.03
185	0.66	0.72	0.82	0.64	0.55	0.57	0.66 ± 0.04
320	0.57	0.76	0.76	0.42	0.41	0.49	0.56 ± 0.06
380	0.33	0.36	0.58	0.32	0.24	0.45	0.38 ± 0.04
800	0.27	0.30	0.28	0.32	0.03	0.21	0.23 ± 0.04

TABLE III : Buprenorphine pharmacokinetic parameters after 10 µg/kg bolus dose for 6 patients undergoing CABG.

Patients number	$t½_{\alpha}$ *(min)*	$t½_{el}$ *(min)*	*Vd (litre)*	*Cl ml/min*	C_{max} *ng/ml*	*AUC ng/ml/hr*
1	36.15	496.12	812.99	1135.80	1.25	581.07
2	56.93	532.17	658.06	857.40	2.87	758.37
3	16.26	630.48	818.04	899.00	2.39	744.98
4	35.60	682.80	785.11	796.85	1.46	12.55
5	–	140.00	425.42	2105.82	1.35	289.61
6	41.30	414.59	919.16	1536.40	0.97	494.56
Mean	37.24	482.69	736.46	1221.97	1.71	480.19
±SEM	±6.53	±79.17	±71.25	±209.42	±0.30	±117.77

Abbreviation : $t½_{\alpha}$ = Distribution half life; $t½_{el}$ = Elimination half life; Vd = Volume of distribution; Cl = Total body clearance; C_{max} = Maximum concentration; AUC = Area under concentration versus time curve.

TABLE IV : Comparative pharmacokinetic parameters of buprenorphine (Mean) with those reported in literature.

Parameters	*Present study*	*Bullingham et al. Ref. 17*	*Hand et al. Ref. 20*	*Hand et al. Ref. 20*
Type of patients	Anaesthetised (CPB)	Anaesthetised (Healthy)	Anaesthetised (Healthy)	Anaesthetised (Renal failure)
Age (yrs)	59.0	64.0	49.0	34.7
Weight (kg)	65.8	67.7	61.8	62.0
No. of pts.	6	24	6	9
M : F	M	14 : 10	1 : 5	5 :4
$t½_{\alpha}$ (min)	37.24	11.2		
t½ el (min)	482.69	139.6	397.7	239.2
Vd (L)	736.46	97.3	312.7	200.5
Clearance ml/min	1221.97	901.3	650.5	987.6

Abbreviation : $t½_{\alpha}$ = distribution half-life; $t½_{el}$ = elimination half-life; Vd = Volume of distribution; Cl/total = Total body clearance.

and dose requirement for patients undergoing CABG to provide stress free anaesthesia.

After intravenous injection of a drug, the arterial plasma concentration rises to a peak within one circulation time, with the rise time dependent on the degree of pulmonary uptake. In case of lipophilic drugs like opioids uptake into lung tissue is a major factor, with approximately 75% of the dose extracted during the first phase (15) BN appears to behave similar to other opioids.

The percentage free base is the unionised fraction in a protein free aqueous solution at pH 7.4 (16), the unbound fraction is the unbound drug in plasma at pH 7.4 expressed as a percentage. The diffusible fraction is the percentage of total drug in plasma which is both unbound and unionised at pH 7.4. Unbound and unionised drug is the form that readily diffuses across cell membranes and the free drug in the tissues will easily equilibrate with free drug in the plasma. Since BN is 96% bound to plasma proteins, only the free fraction would show changes during and post CPB without any detectable change in total concentration. Hence in this study only free fraction of BN was estimated.

The changes in plasma BN concentrations followed a biexponential pattern as reported by Bullingham et al (17). Following a bolus iv injection of 10 µg/kg BN, the mean concentration change in the pre bypass period was from 1.69 ± 0.29 ng/ml at 5 min to 0.97 ± 0.12 ng/ml at 65 min. The plasma level of BN declines very rapidly with a distribution half-life of 2 min as expected for this very lipophilic drug (17). Since we did not measure the actual concentration of free BN in the first 5 min after bolus injection, we cannot compare our values with this earlier report. On initiation of CPB, BN concentration fell by about 47.4% at mid bypass which is similar to the reports on fentanyl, alfentanil, and sufentanil (9) wherein concentrations were found to fall to between 30–60% of pre CPB levels. The reasons explained for this decline during CPB are haemodilution, hypothermia, hydrophobic sequestration on to CPB tubing (18). Inspite of the fall in BN plasma concentrations to 0.51 ± 0.03 ng/ml, at mid bypass none of our patients complained of awareness during surgery indicating that the concentration achieved is adequate for the maintenance of analgesia and anaesthesia during CPB. At the end of CPB (185 min) plasma levels rose to 0.66 ± 0.04 ng/ml, a concentration higher than at mid bypass but slightly lower than pre bypass levels, which shows that very little drug was lost in CPB circuit or due to metabolism and that the levels remain adequately stable during CPB. The decay in the post bypass period was slow and significantly lower levels from baseline were noted only after 380 mins, indicating that the analgesic effect was prolonged.

Though haemodynamic parameters of BN in cardiac patients have been reported earlier (19), the pharmacokinetic parameters of BN in CABG has not been studied before, hence we cannot compare our findings with any similar study. However, the pharmacokinetic parameters obtained in this study are compared to kinetics obtained by previous investigators on normal healthy volunteers (17) and subjects with normal and impaired renal function undergoing

surgery (Table IV). In our study the distribution t½ (37.24 ± 6.53 min) was longer than that reported by Bullingham et al (17). The elimination t½ in our study is 482.69 ± 79.17 min and is comparable to that reported in anaesthetised patients (20). Bullingham et al (17) however, reported shorter t½ in a similar group. The volume of distribution in our study which is 736.46 ± 71.25 L is much larger than that reported by the others (17, 20). The total clearance in this study is 1221.97 ± 209.42 is similar to that in healthy human subjects (17), while different from that reported by Hand et al (20) in anaesthetised patients. These differences may be due to different surgical conditions, age and calculation of the kinetic parameters based on the free fraction in this study, while others seem to have based their calculation on total plasma concentration and also the technique used to measure the drug concentrations. We have used HPLC/ECD while others have used Radioimmunoassay techniques.

Despite the limitations imposed by the fewer number of blood samples in our study, the concentrations and kinetics do not vary much in comparison to the other most commonly used narcotics like fentanyl, sufentanil or alfentanil during CABG. Buprenorphine 10 µg/ml has been reported to be a good anaesthetic and analgesic for abdominal surgery, in fact it was found to be better than fentanyl (21). In our study a concentration of 0.51 ng/ml produced good analgesia and no respiratory depression. Because the decay is prolonged and since it is our practice to ventilate all the patients in the post CPB period, we find BN a safe and very good alternative to other narcotics. Moreover, unlike the other narcotics, muscle rigidity, intraoperative awareness (except one patient # 457 in the series) were not present.

ACKNOWLEDGEMENTS

The authors are grateful to Prof. P.S. Sastry, Former Chairman of Biochemistry Department of Indian Institute of Science, for laboratory facilities and for supervising the drug analysis. Our thanks are also due to Prof. Alfred Mascarenhas (Former Principal of St. John's Medical College) and Dr. Kurpad, Associate Professor of Physiology of the same College for HPLC facilities. We also thank Dr. Rao for computer programming and Mr. Louis D'Souza for computer type setting.

This research is supported by a Research Fellowship (Ministry of Health and Education of I.R. of Iran) for a Ph.D Programme in M.S. Ramaiah Medical College to the first author Akram Amani.

REFERENCES

1. Lowenstein E, Hallowell P, Levin FH, Daggert WM, Austin WG, Laver MB. Cardiovascular response to large doses of intravenous morphine in man. *New Engl J Med* 1969; 281 : 1389–1393.
2. Hasbrouck JD. Morphine anaesthesia for open-heart surgery. *Ann Thoracic Surgery* 1970; 10 : 364–369.
3. Stanley TH, Philbin DM, Coggins CH. Fentanyl–oxygen anaesthesia for coronary artery surgery : Cardio vascular and anti diuretic hormone responses. *Canad Anaesth Soc J* 1979; 26 : 168–172.
4. Sebel PS, Bovill JG. Cardiovascular effects of sufentanil anaesthesia. *Anesth Analg* 1982; 61 : 115–117.

5. Hug CC (Jr), Murphy MR, Rigel EP, Olson WA. Pharmacokinetics of morphine injected intravenously into the anaesthetized dog. *Anaesthesiology* 1981; 54: 38–47.

6. Murphy MR, Olson WA, Hug CC (Jr). Pharmacokinetics of ^{3}H-fentanyl in the dog anaesthetized with enflurane. *Anaesthesiology* 1979; 50: 13–19.

7. McClain DA, Hug CC (Jr). Intravenous fentanyl kinetics. *Clin Pharmacol Ther* 1980; 28: 106–114.

8. Bovill JG, Sebel PS, Blackburn CL, Heykantz J. Kinetics of alfentanil and sufentanil : A comparison. *Anaesthesiology* 1981; 55: A-174.

9. Gedney JA, Ghosh S. Pharmacokinetics of analgesics, sedatives and anaesthetic agents during cardiopulmonary bypass. *Br J Anaesth* 1995; 75: 344–351.

10. Holly FO, Fonganis KV, Stanski DR. Effect of cardipulmonary bypass on the pharmacokinetics of drugs. *Clin Pharmacokinetics* 1982; 7: 234–251.

11. Reisine T, Pasternak G. Opioid analgesics and antagonists. In : Goodman & Gilman's The Pharmacological Basis of Therapeutics. Eds. Hardman G, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, McGraw-Hill, 1996, p548.

12. Adams HA, Biscoping J, Ludolf K, Borgmann A, Bachmann MB, Hemplmann Gl. The quantitative analysis of amide local anaesthetics using high pressure liquid chromatography and ultraviolet detection. *Reg - Anaesth* 1989; 12: 53–57.

13. Kintz P. Determination of Buprenorphine and its dealkylated metabolite in human hair. *J Anal Toxicol* 1993; 17: 443–444.

14. Boas RA, Villiger JW. Clinical actions of fentanyl and buprenorphine : The significance of receptor binding. *Br J Anaesth* 1985; 57: 192–196.

15. Roerig DL, Kotrly KJ, Vucims EJ, Ahif SB, Dawson CA, Kampine JP. First pass uptake of fentanyl, meperidine and morphine in the human lung. *Anaesthesiology* 1987; 67: 466–472.

16. Kaufman JJ, Semo NM, Koski WS. Micro-electrometric titration measurements of the pka's and partition and drug distribution coefficients of narcotics and narcotic antagonists and their pH and temperature dependence. *J Med Chem* 1975; 18: 647–655.

17. Bullingham RES, McQuay HJ, Moore A, Bennett MRD. Buprenorphine kinetics. *Clin Pharmacol Ther* 1980; 28: 667–672.

18. Bently JB, Conahan TJ, Cork RC. Lung sequestration of fentanyl during cardio pulmonary bypass. *Anaesthesiology* 1982; 57 (Suppl): A 244.

19. Okutani R, Kono K, Kinoshita O, Nakamura H, Ishida H, Philbin DM. Variations in haemodynamic and stress hormonal response in open heart surgery with Buprenorphine/diazepam anaesthesia. *J Cardiothorac Anaesth* 1989; 34: 406.

20. Hand CW, Sear JW, Uppington J, Ball MJ, Mc Quay HJ, Moore RA. Buprenorphine disposition in patients with renal impairment : single and continuous dosing, with special reference to metabolites. *Br J Anaesthesia* 1990; 64: 276–282.

21. Kay B. A double blind comparison between fentanyl and buprenorphine in analgesic supplemented anaesthesia. *Br J Anaesth* 1980; 52: 453–457.