Br. J. clin. Pharmac. (1989), **28**, 202–204

Pharmacokinetics of intravenous buprenorphine in children

KLAUS T. OLKKOLA[1], EEVA-LIISA MAUNUKSELA[2] & REIJO KORPELA[2]
[1]Department of Clinical Pharmacology, University of Helsinki, Paasikivenkatu 4, SF-00250 Helsinki and [2]The Children's Hospital, University of Helsinki, Stenbäckinkatu 11, SF-00290 Helsinki, Finland

Buprenorphine (3 μg kg^{-1}) was given intravenously as premedication to small children (age 4–7 years) undergoing minor surgery. Because of the rapid decline of the plasma buprenorphine concentrations, the terminal elimination half-life could not be estimated reliably. Given this constraint, values of clearance appeared to be higher than those in adults but values of V_{ss} were similar.

Keywords buprenorphine pharmacokinetics children

Introduction

Buprenorphine is a synthetic opioid analgesic which seems to be at least as effective as morphine in the treatment of postoperative pain in children (Maunuksela *et al.*, 1988a,b). Its pharmacokinetics have been studied in adults but not in children. The present study investigated the kinetics of buprenorphine administered intravenously to small children.

Methods

This was an open, single dose study with buprenorphine given as premedication to patients undergoing minor surgery. The demographic data of the 10 patients who participated in the study are presented in Table 1. The local ethics committee approved the study protocol. Informed consent for participation was obtained from the parents of each patient. Children considered to be poor anaesthetic risks were excluded from the study.

Administration of buprenorphine and anaesthetic procedure

The same anaesthetic technique was used for all patients. Local anaesthetic cream EMLA®

Table 1 Characteristics of the patients and the pharmacokinetic parameters based on biexponential functions describing the decline of plasma buprenorphine concentrations following an intravenous injection of 3 μg kg^{-1} of buprenorphine base

Patient number	*Age (years)*	*Weight (kg)*	*Duration of surgery (min)*	$t_{1/2,1}$ *(min)*	$t_{1/2,2}$ *(min)*	V_{ss} *(l kg^{-1})*	*CL (ml min^{-1} kg^{-1})*
1	5.0	18.5	24	3	49	3.1	59
2	6.4	19.7	50	6	79	3.4	44
3	4.6	19.1	3	4	57	3.9	72
4	5.6	20.0	24	7	126	8.3	64
5	6.7	25.0	27	2	21	1.9	99
6	6.4	21.3	25	4	46	2.1	53
7	4.6	23.7	30	3	35	2.3	65
8	7.5	23.1	35	2	15	1.2	68
9	5.3	20.5	17	6	59	2.8	52
10	6.8	23.0	20	13	134	3.1	26
Mean	5.9	21.4	26	5	62	3.2	60
s.d.	1.0	2.2	12	1	13	2.0	19

Correspondence: Dr Klaus T. Olkkola, Department of Clinical Pharmacology, University of Helsinki, Paasikivenkatu 4, SF-00250 Helsinki, Finland

(Astra, Sweden) was applied over suitable peripheral veins on both hands 1 h before the cannulation. The children were brought to the recovery room, where they were made comfortable in their hospital beds with cartoons and toys. The monitoring equipment was attached and recording was started.

Peripheral veins on both hands were cannulated with Venflon 1.0 cannulae (Viggo®, Sweden). Buprenorphine (3 μg kg^{-1} of buprenorphine base) was given for premedication as a 2 min intravenous injection. The cannula in the contralateral hand to that in which buprenorphine had been administered was used for blood sampling. Blood samples (1 ml) were taken immediately prior to administration of buprenorphine and after 2, 5, 15, 30, 45, 60 min and 2, 4, 6, and 8 h. Blood was collected into lithium-heparin tubes. The plasma was separated immediately and stored at −20° C until analysis.

After the 2 h blood sample was taken the surgical procedure was performed. Prior to induction of anaesthesia i.v. glycopyrrolate (5 μg kg^{-1}) was administered. Anaesthesia was induced with thiopentone (3–5 mg kg^{-1}) and intubation was facilitated with suxamethonium (1.0–1.5 mg kg^{-1}). For maintenance of anaesthesia nitrous oxide/oxygen (2:1) and halothane were used. Spontaneous ventilation was assisted according to end-expiratory CO_2 concentration. At the end of the operation the child was extubated while asleep and brought to the recovery room. In the recovery room intravenous indomethacin (350 μg kg^{-1}) was given for postoperative pain if necessary.

Assay of buprenorphine and pharmacokinetic analysis

Plasma concentrations of buprenorphine were measured by a specific radioimmunoassay procedure (Bartlett *et al.*, 1980). Sensitivity was 0.05 ng ml^{-1} and the coefficient of variation of repeated determinations was better than 8%. The individual plasma drug concentration-time profiles were fitted by a biexponential function using nonlinear least-squares regression (Metzler & Weiner, 1980). A weighting value of $1/c^2$ was used. The goodness of the fit was determined by comparison of the sum of squares of weighted residual errors, and by assessment of randomness of 'scatter' of actual data points about the fitted function (Boxenbaum *et al.*, 1974). 'Fast' and 'slow' half-lives ($t_{½,1}$ and $t_{½,2}$), steady-state volume of distribution (V_{ss}) and clearance (CL) were calculated according to standard formulae (Wagner, 1976).

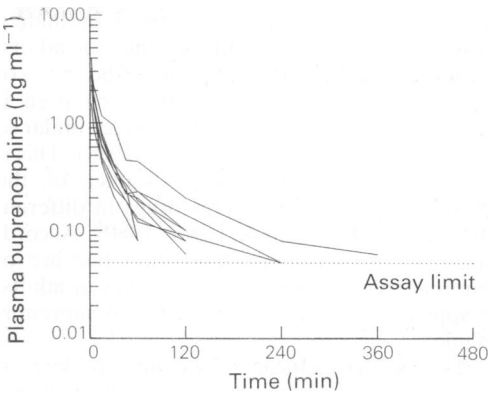

Figure 1 Semilogarithmic plot of plasma buprenorphine concentrations after intravenous buprenorphine administration in 10 children.

Results

The plasma concentrations of buprenorphine could be described by a biexponential function in all patients. The mean estimated $t_{½,1}$ and $t_{½,2}$ values were 5 and 62 min. Mean CL was 60 ml min^{-1} kg^{-1} and V_{ss} varied from 1.2 to 8.3 l kg^{-1}. None of the kinetic parameters was correlated with age, body weight or body surface area. Characteristics of the patients and the calculated pharmacokinetic parameters are shown in Table 1. The time course of plasma drug concentrations is shown in Figure 1.

Discussion

Plasma buprenorphine concentrations fell below the assay limit in seven of the 10 patients at 240 min after drug administration. In the present study the mean 'slow' half-life was approximately 1 h, which is considerably less than the terminal elimination half-life of 2–6 h reported earlier in adults (Bullingham *et al.*, 1980, 1982). However, the estimation of the elimination half-life of buprenorphine was unreliable and $t_{½,2}$ probably did not represent the true elimination half-life of buprenorphine. This problem could have been avoided, if larger doses of buprenorphine had been given. However, this was not ethically acceptable, since the drug was given as premedication to awake children. Buprenorphine was not given during general anaesthesia, because it would have biased the estimation of pharmacokinetic parameters.

The estimation of CL and V_{ss} might have been affected by the rapid decline of the buprenorphine plasma concentrations below the assay limit,

too. In the present study the mean CL in children was about three times higher than in adults, which is understandable because the ratio of hepatic weight to body weight in children is higher than in adults. V_{ss} values were similar to those in adults (Bullingham *et al.*, 1980). This is in agreement with previous studies of the pharmacokinetics of various drugs in different age groups (Rowland & Tozer, 1980). Accordingly, if the terminal elimination half-life of buprenorphine is really shorter than in adults, it appears to be due to a higher CL of buprenorphine.

The analgesic efficacy of 1.5 and 3 $\mu g\ kg^{-1}$ of buprenorphine in children has been well established (Maunuksela *et al.*, 1988a,b). There appears to be no direct relationship between the plasma concentration of buprenorphine and the pharmacologic effect which is in agreement with the findings of Hambrook & Rance (1976). The low plasma concentrations of buprenorphine do not exclude analgesic effect. The elimination of buprenorphine in children appears to be at least as fast in children as in adults. Accordingly, there are no pharmacokinetic contraindications for its use as an analgesic in children.

This study was supported by the Paulo Foundation. We thank Reckitt and Colman (UK) for the measurement of the plasma buprenorphine concentrations.

References

Bartlett, A. J., Lloyd-Jones, J. G., Rance, M. J., Flockhart, I. R., Dockray, G., Bennett, M. R. D. & Moore, R. A. (1980). The radioimmunoassay of buprenorphine. *Eur. J. clin. Pharmac.*, **18**, 339–345.

Boxenbaum, H. G., Riegelman, S. & Elashoff, R. M. (1974). Statistical estimations in pharmacokinetics. *J. Pharmacokin. Biopharm.*, **2**, 123–148.

Bullingham, R. E. S., McQuay, H. J., Moore, A. & Bennettt, M. D. R. (1980). Buprenorphine kinetics. *Clin. Pharmac. Ther.*, **28**, 667–672.

Bullingham, R. E. S., McQuay, H. J., Porter, E. J. B., Allen, M. C. & Moore, R. A. (1982). Sublingual buprenorphine used postoperatively: ten hour plasma drug concentration analysis. *Br. J. clin. Pharmac.*, **13**, 665–673.

Hambrook, J. M. & Rance, M. J. (1976). The interaction of buprenorphine with opiate receptor. In *Opiates and endogenous opioid peptides*, ed. Kosterlitz, H. W., pp. 295–301. Amsterdam: Elsevier/North Holland Biomedical Press.

Maunuksela, E.-L., Korpela, R. & Olkkola, K. T. (1988a). Double-blind, multiple-dose comparison of intravenous buprenorphine and morphine in postoperative pain of children. *Br. J. Anaesth.*, **60**, 48–55.

Maunuksela, E.-L., Korpela, R. & Olkkola, K. T. (1988b). Comparison of buprenorphine with morphine in the treatment of postoperative pain in children. *Anesth. Analg.*, **67**, 233–239.

Metzler, C. M. & Weiner, D. L. (1985). *PCNONLIN user's guide.* Edgewood, USA: Statistical Consultants Inc.

Rowland, M. & Tozer, T. N. (1980). Individualization. Age and weight. In *Clinical pharmacokinetics: Concepts and applications*, vol. **1**, ed. Rowland, M. & Tozer, T. N., pp. 218–229. Philadelphia: Lea & Febiger.

Wagner, J. G. (1976). Linear pharmacokinetic equations allowing direct calculation of many needed pharmacokinetic parameters from the coefficients and exponents of polyexponential equations which have been fitted to the data. *J. Pharmacokin. Biopharm.*, **4**, 443–467.

(Received 7 February 1989, accepted 21 April 1989)