ORIGINAL ARTICLES

Alfentanil pharmacokinetics in preterm infants

N Marlow, A M Weindling, A Van Peer, J Heykants

Abstract

The pharmacokinetics of alfentanil were studied during the first four days after birth in 22 ventilated preterm infants who were all receiving muscle relaxants. Five minutes after a single dose of 20 μg/kg alfentanil median serum concentration was 66 ng/ml (range: 20–606). The median clearance ws 0·87 ml/kg/min (range: 0·4–9·62) and median elimination half life 321 mins (64–1251). There were wide differences in the manner in which individual infants handled the drug and transient depression of blood pressure and heart rate was observed. These data were used to calculate an infusion dosage. In four infants 20 μg/kg alfentanil given by infusion over 30 minutes followed by 5 μg/kg/hour produced steady state median alfentanil concentrations of 54·5 ng/ml (range: 7–73 ng/ml) with no evidence of drug accumulation.

There is a dichotomy of opinion among paediatricians as to whether newborn infants receiving mechanical ventilation should receive sedative drugs, either to improve the match between the infant's own respiratory effort and that of the ventilator or to relieve their perceived discomfort. In 1984 only 8% of British neonatal units routinely administered sedation to ventilated newborn infants.[1] In a recent postal questionnaire survey involving 32 regional and district newborn intensive care units this figure had risen to 18%, a further 50% using sedation on an occasional basis and 32% using no sedation at all (J Waugh, personal communication, 1988). The use of analgesics has recently been thrown into relief by several recent publications concerning the response of the preterm child to surgical stress.[2 3] These data have been used to suggest that medical intensive care of the newborn should also be accompanied by sedation or analgesia,[3 4] even on a priori grounds without supporting data.[5]

Published data relate to how the term infant handles sedative and analgesic drugs. These data are derived from single dose studies, performed around planned surgical procedures. Fentanyl, for example, has an appreciably prolonged elimination half life and diminished clearance when given to preterm infants.[6] This is accompanied by a wide variation between subjects. Monitoring drug effect and preventing toxicity are thus problematical, especially if muscle relaxants are used. In view of these uncertainties we have studied the pharmacokinetics of a short acting, synthetic opioid, alfentanil, in order to assess the practicability of opiate infusions for ventilated newborn infants.

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Patients and methods

This study was conducted in two phases: first, alfentanil pharmacokinetics were established in preterm infants after a single dose; secondly, these data were used to calculate a dose for infusion and alfentanil concentrations were determined during continuous infusion.

PHASE I—SINGLE DOSE STUDY

A total of 20 μg/kg alfentanil (Rapifen, Janssen Pharmaceutical) was administered by peripheral intravenous infusion over two minutes to 22 subjects, by one investigator (NM). All were preterm infants receiving mechanical ventilation with a clinical diagnosis of hyaline membrane disease. No mother had received alfentanil during the perinatal period. All infants were receiving pancuronium 80 μg/kg at a frequency sufficient to abolish visible movement. All infants had indwelling arterial catheters. Heart rate, mean blood pressure, and transcutaneous oxygen tension were recorded continuously and noted before and at one minute intervals after the injection, for up to 15 minutes. Informed parental consent was obtained for all infants.

Arterial blood (0·4 ml) was withdrawn at the following time points: 0 (control), 5, 15, 60, 90, 180, 300, and 420 minutes after injection. Blood gases (0·2 ml blood) were measured before the injection and five minutes after. Thereafter measurements were taken as clinically indicated, at least every four hours. The maximum number of samples taken was eight, three being omitted where the birth weight was 1000 g or less. Samples were spun, separated, and deep frozen until analysis. Serum concentrations of alfentanil were determined in 0·1 ml aliquots of serum using a standard radioimmunoassay technique (Janssen Biotech). The detection limit of the assay was 1 ng/ml.[7]

Measurement of drug concentrations and calculation of pharmacokinetic data for the first phase were made by Janssen Pharmaceutical Ltd (AVP). Alfentanil plasma concentration-time data after the bolus dose were fitted to a one or two compartment model by using non-

Table 1 Pharmacokinetic data after single dose of alfentanil

	Median	*Range*
Dose given (mg/kg)	19·7	17·8–22·1
Half life (mins)		
α	7·6	2·0–38·1
β (elimination)	321	64·0–1251
Clearance (ml/kg/min)	0·87	0·4–9·62
Volume of distribution (ml/kg)	501	125–1039

linear least squares regression analysis and weighting by the inverse of the plasma concentration.[8]

PHASE II—INFUSION STUDY

The single dose pharmacokinetic data were used to calculate a suitable infusion regime. Because of the wide interpatient variability three schedules were evaluated with analysis of samples between each trial. Alfentanil was administered to a further 14 infants using the following regimes: a loading infusion of 15 μg/kg followed by 3 μg/kg/hour (five infants), a loading infusion of 20 μg/kg and 3 μg/kg/hour (five infants), and 20 μg/kg followed by 5 μg/kg/hour (four infants). The loading dose was given by continuous infusion over 30 minutes by a syringe driver (Model SP44 or IP5, Vickers Medical). Continuous monitoring of heart rate, blood pressure, and transcutaneous oxygen tension was performed as previously. Samples (0·4 ml) were taken before and at the completion of the loading infusion and twice daily for 48 hours or until muscle relaxants were discontinued when the alfentanil infusion was also stopped. The samples were handled as above. Serum alfentanil was again measured by radioimmunuoassay.

This study was approved by the district ethics committee.

Results

PHASE I—SINGLE DOSE STUDY

The median gestational age of the 22 infants was 30 weeks (range 25–36 weeks) and birth weight 1343 g (690–4084 g). Twelve infants were studied in the first 24 hours after birth, five at between 25 and 48 hours, and five between 49 and 96 hours. There were seven girls. At the time of sampling 16 infants had a serum creatinine concentration >100 μmol/l, three were jaundiced (bilirubin >150 μmol/l), and four had dopamine infusions running. One child was macrosomic after a pregnancy complicated by diabetes mellitus. Subsequently, four infants still required added oxygen at 28 days and four died. No deaths occurred during the period of data collection or were felt to be related to the administration of alfentanil.

The median dose of alfentanil given was 19·8 μg/kg (range: 17·8–22·1). The median alfentanil concentration five minutes after injection was 66 ng/ml (range: 20–606 ng/ml) (fig 1). Wide difference between patients were noted in terms of peak serum concentration and rate of decay, and in all related pharmacokinetic variables. Basic pharmacokinetic data are shown in table 1. No association between birth weight, gestation, age at testing, or gender and elimination half life or clearance could be demonstrated. Injection over two minutes was associated with a transient fall in blood pressure, heart rate, and arterial oxygen tension. These data have been reported previously.[9]

PHASE II—INFUSION STUDY

The results of the infusion studies are shown in table 2. Concentrations after loading with 15 μg/kg infusion at 3 μg/kg/hour were frequently unsatisfactory. After 20 μg/kg alfentanil given over 30 minutes followed by 5 μg/kg/hour satisfactory concentrations were obtained without significant change in cardiorespiratory variables. No significant accumulation of alfentanil was observed (fig 2).

Discussion

Before the administration of potent opioid

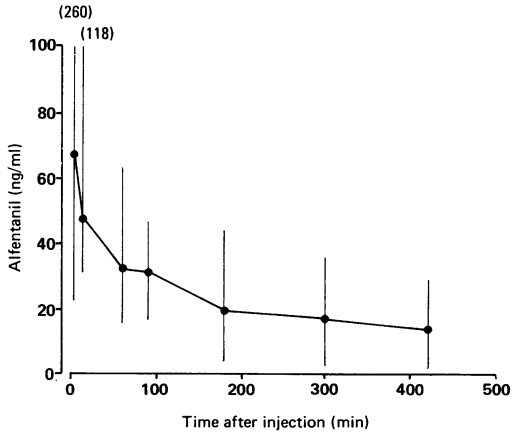

Figure 1 Alfentanil concentrations after single dose. Values shown are median, 10th and 90th percentiles.

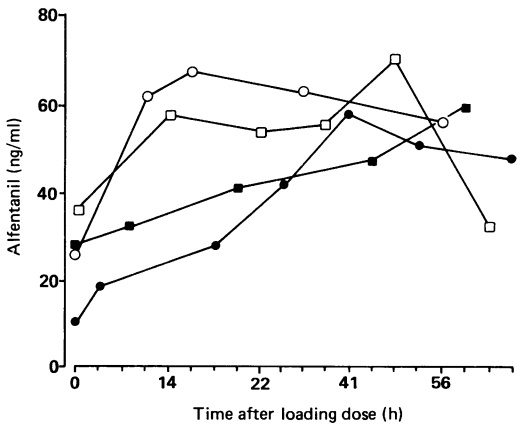

Figure 2 Alfentanil concentrations during infusion (four patients).

Table 2 Alfentanil concentrations during infusion

Loading dose (μg/kg)	*Infusion rate (μg/kg/hour)*	*No of subjects (No of samples)*	*Alfentanil concentration*	
			After loading dose: median (range)	*During infusion: median (range)*
15	3	5 (35)	18·5 (18–26)	17·8 (1–104)
20	3	5 (19)	20·0 (10–41)	29·0 (6–76)
20	5	4 (24)	27·0 (11–36)	54·5 (7–73)

drugs to sick preterm infants receiving mechanical ventilation becomes mandatory, it is necessary to collect background pharmacokinetic data and to demonstrate that such medication is both efficacious and safe. Clinical monitoring of frequency of administration of sedatives, such as chloral hydrate, may rapidly produce undesirably high levels (L Harris, presentation to Paediatric Research Society, October 1988), and there is no evidence that clinical monitoring of pethidine or morphine is any better. The routine adminstration of muscle relaxants, as on our unit, removes any possibility of clinical monitoring.

There was great variability in the handling of alfentanil in our study. Peak serum concentrations and clearance varied widely between subjects. This variability has been noted in pharmacokinetic studies of fentanyl[6 10] and morphine.[11] It is difficult to extrapolate from these studies, however, because all were performed in infants undergoing surgery, frequently for congenital heart disease, at varying postnatal ages. Compared with both older children and adults,[12 13] preterm infants have reduced clearance, prolonged elimination half life, and a greater volume of distribution of alfentanil.

The sick preterm newborn infant has multisystem illness with immature hepatic and renal function. Opiates are metabolised by the non-specific monoamine oxidases present in liver. Inactive metabolites are then excreted in the urine. Variation in hepatic and renal function may therefore exert a significant effect upon the metabolism of alfentanil. In this study no relation was observed between broad markers of hepatic and renal function (serum bilirubin and serum creatinine, respectively) and elimination half life or clearance. Bilirubin is only a crude indicator of liver function and clearly does not identify inadequate hepatic degradation of the drug.

In adults concentrations of alfentanil between 35 and 50 ng/ml are recommended for sedation during mechanical ventilation, although for analgesia during surgery concentrations of 200 ng/ml and higher are recommended. Although the regimen described in this paper achieved adequate sedative concentrations of alfentanil, it is important to remember that these levels are not analgesic for adults. The insertion of chest drains and other painful procedures must still be covered by adequate local and perhaps parenteral analgesia.

This study shows that it is possible to administer alfentanil without appreciable cardiovascular effects and with no accumulation over a 48 hour period. As both hepatic and renal function improve at the same time as the preterm child recovers from hyaline membrane disease one might expect improved opioid clearance and elimination. One study had observed shortening of elimination half life and increasing clearance of a similar drug, sufentanil, in infants returning for a second operation.[14] These improvements in drug handling are, however, not yet predictable and further studies are necessary to establish their time course. As yet, routine monitoring of serum concentrations for any of the commonly used analgesics is not practicable with current methodologies. The serum concentrations in this study are unlikely to lead to toxicity but low concentrations, and therefore inadequate treatment, are possible.

Although we have demonstrated that alfentanil infusions are possible in sick preterm infants, we have not established that adult equivalent sedative doses are effective in reducing the stress of mechanical ventilation, nor have we established that such a reduction of stress is beneficial. Further studies are in progress to establish these points.

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