Title: THE CORRELATION BETWEEN FENTANYL PHARMACOKINETICS AND PHARMACODYNAMICS IN PRETERM INFANTS DURING PDA LIGATION

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Introduction: There is little information available on the use of high dose Fentanyl (F) anesthesia in preterm infants. No pharmacokinetic study has been reported, and no correlation made between pharmacokinetics and pharmacodynamics. The aim of this study is to establish the pharmacokinetics of F in preterm infants and to correlate it with the observed pharmacodynamics.

Method Nine infants with a patent ductus arteriosus were studied. Gestational age was 23-38 wks (mean ±SD 26.9±4.5). Age at surgery was 27-43 wks (31.8±4.7). The weight was 710-1625 gms (1100±305). Prior to surgery, 8/9 infants required mechanical ventilation for cardiorespiratory failure. Each patient received a F bolus of 30 ug/Kg IV. Neuromuscular blockade was established in 7 infants with 0.1 mg/Kg IV of pancuronium (P); the remaining 2 received a higher dose (see results). The infants were mechanically ventilated with oxygen-enriched air and the inspired oxygen concentration was adjusted to give a transcutaneous oxygen saturation of 80-90%. Heart Rate (HR), systolic blood pressure (BP), transcutanous oxygen saturation and rectal temperature were continuously monitored and were recorded at the following times: baseline; post F/P induction; at skin incision; post-ligation of PDA; at skin closure and on return to the neonatal intensive care unit. 3 blood samples were drawn at ½, 2 and 6 hours. F plasma concentrations were analysed by the gas-liquid chromatography method of Gillespie.[1] F elimination half life ($T_{\frac{1}{2}\beta}$), the volume of distribution (VD) and F total body clearance (Cl) were calculated from the decay curve concentration time data.

Statistical Analysis: The difference in HR and BP were compared for each patient by the student's t-test for paired results. The correlation between F $T_{\frac{1}{2}\beta}$ and Cl was studied by linear regression.

Results

	BP (mm Hg)	HR, min
Baseline	67± 7	158±11
Postintubation	69±11	158±11
Incision	71±11	159±12*
PDA Ligation	69±12	165±16
Closure	69±13	173±15*
Post-op.	73±22	155±10

TABLE Mean±S.D. *P < 0.05
Pharmacodynamics of F in Preterm Infants with PDA

F Pharmacokinetics & Pharmacodynamics

30 minutes after the bolus injection of 30 ug/Kg of F the plasma levels were 7.7-13.6 ng/ml. Thereafter, levels decreased gradually yielding $T_{\frac{1}{2}\beta}$ of 6-32 hours (17.7±9.3) VD of F was between 2206-3896 ml/Kg (2904±517). F Cl was between 1-4.1 ml/Kg/min (2.4±1.3). There was good correlation between $T_{\frac{1}{2}\beta}$ and Cl ($r = 0.89$, $P < 0.01$). BP remained stable throughout surgery. However, there was a gradual increase in HR from 159±12/min. at the time of incision to 173±15/min. at the time of closure ($p < 0.05$) (Table). These findings correlated well with the clinical impression that towards the end of the operation anaesthesia became lighter The operating time was from 85-165 mins. (130±27). Spontaneous movement was seen in all patients at the time of reversal of neuromuscular blockade. In 7 who received 0.1 mg/Kg of P, this occurred at the end of the operation, but in the other 2, who received higher doses (0.2 and 1.0 mg/Kg), the reversal was prolonged (3½ hr and 11 hr). In these 2, the profile of BP and HR was similar to the rest of the group.

Discussion: Our studies indicate that F pharmacokinetics in the preterm infant with PDA is significantly different from adults[2] or older children with cyanotic heart disease.[3] The prominent characteristic is the prolonged $T_{\frac{1}{2}\beta}$ (17.7±9.3 hr) which is explained by the significantly lower Cl of F in preterm infants (2.4±1.3 ml/Kg/min) as compared to adults or older children (12 ml/Kg/min). Lower clearances of many other drugs are known in preterm infants and are associated with immaturity of liver enzymatic processes. The VD of F in our patients is similar to adults[2] and significantly larger than in older children with cyanotic heart diseases.[3] This is probably due to hypoperfusion in the cyanotic patients. The haemodynamics were relatively stable throughout surgery with none of the instability previously observed with the use of potent inhalational anaesthetic agents. It appeared that there was some lightening by the time of skin closure. The lack of correlation between the elimination of the drug and the termination of its pharmacodynamic effect is of particular interest. At the end of surgery, most of the infants moved or breathed spontaneously despite F plasma concentrations being virtually unchanged due to the prolonged $T_{\frac{1}{2}\beta}$. This has been previously shown in adults and animals and is explained by redistribution of F from the brain into fat and muscle.[4]

Our studies suggest that a bolus of 30 ug/Kg of F may not be adequate to cover the increased stimulus of skin closure. It seems reasonable to give a higher dose of F or a concomittant continous infusion. Any delayed onset of spontaneous respiration which may then occur is not a problem as current treatment includes maintaining mechanical ventilation in these infants in the immediate post-operative period.

References:

1. Gillespie et al. J. Anyl Toxicol 5:133-137, 1981
2. McClain et al. Clin Pharm Ther 28:106-114, 1980
3. Crean et al. Anaesthesiol 59:A448, 1983
4. Hug et al. Anaesthesiol 55:369-375, 1981