Title: FENTANYL ANESTHESIA FOR CARDIAC SURGERY IN CHILDREN: a) FENTANYL-OXYGEN vs FENTANYL-$N_2O$; b) RELATIONSHIP BETWEEN DRUG CONCENTRATIONS AND PHARMACODYNAMICS.

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Introduction: Fentanyl (F) has become widely popular as primary anesthetic in patients undergoing cardiac surgery. While there are many reports on F pharmacokinetics and pharmacodynamics in adults, there is only sparse information in children. In the present studies we aimed to a) compare the pharmacodynamics of F oxygen vs F $N_2O$ in order to assess whether F can be used as a single agent b) to assess the relation between F plasma levels and pharmacodynamics.

Patients and Methods: The study protocol was approved by the Human Experimentation Committee of the hospital. Fourteen children undergoing cardiac surgery were included. Their mean age was 3.9 ± 2.8 yr (range 0.5 - 8.25 yr) and mean weight 14.1 ± 7.5 kg (range 3.5 - 29.5 kg). They suffered from tetralogy of Fallot (7), A-V canal (2) and transposition of the great arteries (5). In order to continuously monitor systolic and diastolic blood pressure (BP) and heart rate, an intraarterial catheter was placed in the radial artery. The patients were premedicated with 0.1 - 0.2 mg atropine and muscle relaxation was achieved with 0.1 mg/kg of pancuromium bromide. Anesthesia was induced with an intravenous bolus of 30 μg/kg F given over 1 minute. Maintenance of anesthesia was achieved with continuous F infusion of 0.3 μg/kg/min with oxygen (7 patients) or with $N_2O$ (7 patients). The $N_2O$ was given as $N_2O/O_2$ 50/50. The two groups were comparable in their ages and in their diagnostic entities. Systolic and diastolic BP and heart rate were recorded prior to the induction of anesthesia, after 2 minutes of 100% $O_2$ breathing, and then before and ½, 1, 1.5, 2 and 5 min after induction, intubation, incision, and sternotomy. Heparinized venous blood samples for F concentration were drawn in various time points throughout surgery, including 2-5 minutes after induction and at the times of intubation, incision and sternotomy. Samples were centrifuged and plasma kept in -20°C until analyzed within 1 month. A modification of the gas liquid chromatography of Gillespie (1) with sufentanyl as an internal standard was used to measure F plasma levels. The coefficient of variation within a day was 2.55%. Recovery of F from plasma varied between 81.5% for 2 ng/ml and 85% for 25 ng/ml.

Statistical Analysis: The percentage of change in systolic and diastolic BP and in heart rate relative to the baseline (time 0) were computed and compared between the two groups ($F+O_2$ vs $F+N_2O$) by the student's t-test for unpaired results. The correlation between the % of maximal change in each parameter and the plasma F levels was studied by linear regression.

Results: F levels were similar in the two groups ($F+O_2$ vs $F+N_2O$) at the time of intubation (52.3 ± 6.15 vs 56.0 ± 7.1 ng/ml) (mean ± SE) incision (34.2 ± 2.5 vs 32.3 ± 3.4 ng/ml) and sternotomy (34.2 ± 2.5 vs 30.8 ± 4.1 ng/ml). There were no significant differences between the two treatment groups in most parameters (Table). There was however a significantly higher increase in systolic BP after sternotomy in the $F+O_2$ group compared to $F+N_2O$ group. Moreover, in 6/7 patients receiving $F+O_2$ there were events of sudden increase in BP during various other stages of surgery. Two of these patients needed an additional 5-10 μg/kg bolus of F, and two received droperidol 0.1 μg/ml. F levels at the time of the BP elevations were in the adult therapeutic range (19.4 - 40 ng/ml). No such events were recorded in the $F+N_2O$ group.

There was a significant negative correlation between F levels and the percentage change in systolic BP following intubation ($r=0.9$, $p<0.05$). No correlation could be checked after incision or sternotomy largely because most patients had almost identical F levels (between 31-38 ng/ml).

| | Syst BP | | Diast BP | | Heart Rate | |
|---|---|---|---|---|---|---|
| | $F+O_2$ | $F+N_2O$ | $F+O_2$ | $F+N_2O$ | $F+O_2$ | $F+N_2O$ |
| Induction | -12.2 ± 3 | -14.3 ± 4.5 | -10.4 ± 7.6 | -20 ±2.6 | 9.6± 12.8 | 14 ±2.9 |
| Intubation | 11 ± 38 | 15.4 ± 6.9 | 9.5 ± 6.9 | 9 ±5.3 | 5 ±1.5 | 9.1 ± 4 |
| Incision | 11.2 ± 12 | 16.2 ± 5.3 | 11.2 ± 7.5 | 17.6 ±5.1 | 2 ±3.4 | 8.8 ±3.6 |
| Sternotomy | 7.7* ±3.7 | 1.9 ± 3.4* | 4.5 ± 1.4 | 4 ±1.5 | 1.2 ±2.5 | 4.9 ±3.7 |

*$P<0.05$

Maximal pharmacodynamic changes (% mean ± SE) following the various stimuli in the two study groups.

Discussion: Our comparative studies indicate that $F+O_2$ may not guarantee satisfactory anesthesia for cardiac surgery in children. There was a significant increase in systolic BP during sternotomy as compared to $F+N_2O$ anesthesia. Moreover, in most $F+O_2$ cases there were events of BP elevation which necessitated the use of additional anesthesia. F levels were similar in the two groups during the various stages of surgery. During all stages including the BP elevation in the $F+O_2$ group, plasma levels of F were high above the adult therapeutic range (2). This may be explained by a) lower sensitivy of pediatric patients to F, b) because of the significantly smaller distribution volume of F in these patients less drug is available in the peripheral compartment despite the higher plasma concentrations (3), c) no correlation between plasma levels and pharmacodynamic effect because only small amounts of the F stay in the blood. While there are no direct data to support or reject (a) or (b), our experiments indicate that there is a concentration-response curve in these children at least during the distribution phase (at the time of intubation). Our studies indicate that F bolus of 30 μg/kg with F continuous infusion of 0.3 μg/kg/min should be combined with $N_2O/O_2$ inhalation in order to guarantee stable anesthesia.

References:

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