Fentanyl-oxygen versus fentanyl-N₂O/oxygen anaesthesia in children undergoing cardiac surgery

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Fentanyl-oxygen (fentanyl-O₂) anaesthesia was compared to fentanyl-nitrous oxide/oxygen (fentanyl-N₂O/O₂) anaesthesia in 14 children undergoing cardiac surgery. Children were randomly assigned to one of the two techniques studied, with seven patients in each group. The mean age (mean $\pm$ SE) was 3.9 ± 0.75 years (0.5–8.25 years) and mean weight 14.7 ± 2 kg (3.5–29.5 kg). Patients were premedicated with IM atropine $0.02 \text{ mg}\cdot\text{kg}^{-1}$ and morphine $0.2 \text{ mg}\cdot\text{kg}^{-1}$ 1 hour preoperatively. They received a fentanyl bolus of $30 \mu\text{g}\cdot\text{kg}^{-1}$ with a concomitant continuous infusion of $0.3 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Pancuronium $0.1 \text{ mg}\cdot\text{kg}^{-1}$ was administered immediately following the fentanyl bolus. Fifty per cent nitrous oxide was given with oxygen in one group and 100 per cent oxygen was administered to the other group. Fentanyl plasma concentrations were similar in the two groups at the various stages of surgery. There were no significant differences between the two treatment groups in systolic

and diastolic blood pressure or in heart rate in response to induction, intubation, and incision. There was a significantly greater increase in systolic blood pressure after sternotomy in the fentanyl-O₂ group. In addition, in six of seven patients receiving fentanyl-O₂ there were events of sudden increase in blood pressure during various stages of surgery before the bypass, necessitating an additional fentanyl bolus or the addition of droperidol in four cases. Similar phenomena were not documented in the fentanyl-N₂O/O₂ group. Our studies suggest that fentanyl-O₂ anaesthesia in the schedule described, in children undergoing elective cardiac surgery for Tetralogy of Fallot, A-V canal, and transposition of the great arteries, is not sufficient to prevent elevation in systolic blood pressure despite fentanyl plasma concentrations in excess of $20 \text{ ng}\cdot\text{ml}^{-1}$. The addition of nitrous oxide prevents this phenomenon.

Key words

SURGERY: cardiac; ANALGESICS: fentanyl;
ANAESTHETICS, GASES: nitrous oxide; ANAESTHESIA: paediatric.

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Fentanyl has become a popular anaesthetic agent for cardiac surgery in both adults¹ and children^{2,3} due to its relative maintenance of cardiovascular stability.⁴ A variety of techniques have been described which employ a fentanyl bolus or a bolus combined with a continuous infusion of fentanyl.^{1,2,5–7} Some investigators have used fentanyl with 100 per cent oxygen,^{5,8} whereas others have combined it with other agents.^{1,6,7} Different preanaesthetic medication further hampers the ability to compare the various studies.

In the present studies we compared the pharmacodynamics of fentanyl/oxygen to fentanyl-nitrous oxide/oxygen anaesthesia in order to assess whether fentanyl can be used as a single anaesthetic agent with oxygen in children undergoing cardiac surgery.

Methods

This study protocol was approved by the Human Experimentation Committee of the hospital. We studied 14 children undergoing cardiac surgery for the correction of Tetralogy of Fallot (7), A-V-canal (2) and transposition of the great arteries (5). Their mean age was 3.9 ± 0.75 years (range 0.5–8.25 years) and mean weight 14.1 ± 2 kg (range 3.5–29.5 kg). Table I summarizes the patients' characteristics and diagnostic entities.

The children were premedicated with atropine $0.02 \text{ mg} \cdot \text{kg}^{-1}$ and morphine $0.2 \text{ mg} \cdot \text{kg}^{-1}$ one hour preoperatively. Anaesthesia was induced with an intravenous bolus of $30 \mu\text{g} \cdot \text{kg}^{-1}$ fentanyl over one minute. Muscle relaxation was achieved with $0.1 \text{ mg} \cdot \text{kg}^{-1}$ of pancuronium. Maintenance of anaesthesia was achieved with a continuous infusion of $0.3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ of fentanyl with oxygen breathing (seven patients) or with nitrous oxide/oxygen (seven patients) in proportions of 50/50.

Patients were randomly assigned to one of the two treatment groups. With local anaesthesia an intra-arterial catheter was inserted in the radial artery to monitor blood pressure and blood gases. A second catheter was inserted through the most accessible site to measure CVP. Systolic and diastolic blood pressure and heart rate were recorded prior to the induction of anaesthesia, after two minutes of 100 per cent O_2 breathing, and then before and 0.5, 1, 1.5, and 5 minutes after induction, intubation, incision and sternotomy. In addition these parameters were recorded at various times between and after the above mentioned events. Central venous pressure (CVP) was recorded once during each event. When blood pressure or heart rate rose by more than 20 per cent above baseline levels an additional bolus of $5\text{--}10 \mu\text{g} \cdot \text{kg}^{-1}$ fentanyl or a bolus of droperidol $0.1 \text{ mg} \cdot \text{kg}^{-1}$ was given intravenously. All studies were accomplished before connecting the patients to the cardiopulmonary bypass.

Heparinized venous blood samples for measurements of fentanyl plasma concentrations were drawn at various time points throughout surgery, including two to five minutes after induction, and at the time of intubation, incision and sternotomy. To avoid erroneously high or low readings of fentanyl, blood was drawn from the arm opposite to the site of infusion of the drug. The sampling site was consistent throughout the study. Samples were centri-

TABLE I Patients' characteristics and clinical diagnoses

Patient	Age (yr)	Weight (kg)	Diagnosis
Fentanyl + N_2O			
1	0.5	3.5	A-V-Canal
2	1.25	7.9	TGA
3	0.75	9.3	TGA
4	1.2	8.2	TGA
5	7.25	23.3	TOF
6	8.25	21.5	TOF
7	4.2	12.0	TOF
(Mean $\pm$ SE)	3.3 ± 1.2	12.2 ± 2.8	
Fentanyl + O_2			
1	8	29.5	TOF
2	3.5	13.1	TGA
3	3.8	16.6	TOF
4	0.75	6.5	A-V-Canal
5	5.1	17.8	TOF
6	6.25	14.5	TOF
7	0.5	3.5	TGA
(Mean $\pm$ SE)	4.0 ± 1	14.5 ± 3	

TGA = Transposition of great arteries.

TOF = Tetralogy of Fallot.

fuged and plasma kept at -20° until analyzed within a month. A modification of the gas liquid chromatography method of Gillespie⁹ was employed with sufentanil as an internal standard to measure fentanyl plasma concentrations. The coefficient of variation within a day was 2.55 per cent. Recovery of fentanyl from plasma varied between 81.5 per cent for $2 \text{ ng} \cdot \text{ml}^{-1}$ and 85 per cent for $25 \text{ ng} \cdot \text{ml}^{-1}$.

Statistical Analysis

The percentages of change in systolic and diastolic blood pressure and in heart rate relative to the baseline (time 0) of each event (induction, intubation, incision and sternotomy) were computed and compared between the two treatment groups (fentanyl + O_2 vs. fentanyl + $\text{N}_2\text{O}/\text{O}_2$) by Student's *t* test for unpaired data. Similarly, the mean fentanyl plasma concentration during each event was compared between the two treatment groups by Student's *t* test for unpaired data. Results are expressed as mean $\pm$ SE.

Results

The two groups were comparable in their ages, diagnostic entities (Table I), and in their arterial gases prior to induction while breathing air, and

TABLE II Arterial gases and pH before induction while breathing air and after 2 minutes of breathing 100% O₂ in the two study groups.

	PO ₂ (mmHg)		PCO ₂ (mmHg)		pH	
	F + O ₂	F + N ₂ O	F + O ₂	F + N ₂ O	F + O ₂	F + N ₂ O
Pre induction; breathing air	47.2 ± 2.7	43.6 ± 3.9	38.0 ± 2.4	41.3 ± 1.9	7.37 ± 0.02	7.3 ± 0.02
After 2 minutes of breathing 100% O ₂	66.3 ± 1.1	60.8 ± 4.3	37.8 ± 1.8	42.4 ± 3.0	7.35 ± 0.03	7.32 ± 0.02

after two minutes of breathing 100 per cent O₂ (Table II). There were no significant differences between the two treatment groups in most parameters (Figure). There was, however, a significantly larger increase in systolic blood pressure after sternotomy in the fentanyl-O₂ group than in the fentanyl-N₂O/O₂ group.

In six of seven patients receiving fentanyl-O₂ there were events of sudden increase in systolic blood pressure at various points during surgery. Two of these patients needed an additional 5 to 10 µg·kg⁻¹ bolus of fentanyl, and two received droperidol 0.1 µg·kg⁻¹.

Fentanyl plasma concentrations were similar in the two treatment groups (fentanyl-O₂ vs. fentanyl-N₂O/O₂) at the time of intubation (52.3 ± 6.15 vs. 56.0 ± 7.1 ng·ml⁻¹ respectively), incision (34.2 ± 2.5 vs. 32.3 ± 3.4 ng·ml⁻¹) and sternotomy (34.2 ± 2.5 vs. 30.8 ± 4.1 ng·ml⁻¹). Fentanyl plasma concentrations at the time of blood pressure elevations were in the adult therapeutic range (19.4–40 ng·ml⁻¹). No elevations in blood pressure were recorded in the fentanyl-N₂O/O₂ group.

Discussion

We compared the pharmacodynamics of fentanyl as a single anaesthetic agent with morphine pre-medication to fentanyl with morphine pre-medication in conjunction with nitrous oxide-oxygen anaesthesia. Our two randomized groups were comparable with respect to age, weight, diagnosis and operative techniques. Moreover, the two groups had similar plasma concentrations of fentanyl during the various stages, indicating that putative pharmacodynamic differences between them cannot be attributed to pharmacokinetic variability.

The loading dose of fentanyl used by us was smaller than dose-schedules employed in adults. This is due to our previous observations that while using the adult regimen, levels are 2–3-fold higher in these children than in adults² due to a smaller distribution volume. The continuous infusion rate of fentanyl was comparable to adult regimens due to a similar clearance rate of the drug. There was a significant increase in systolic blood pressure during sternotomy with fentanyl-O₂ anaesthesia as compared to fentanyl-N₂O/O₂ anaesthesia; however, this difference was small and hardly significant in the biological or clinical sense. More importantly, in most cases, patients anaesthetized with fentanyl-O₂ needed additional doses of anaesthetic agents because of increased blood pressure in

FIGURE No differences in blood pressure and heart rate during skin incision (left panel) and sternotomy (right panel) were identified between the two study groups except for higher systolic BP during sternotomy in the fentanyl-O₂ group (●—●). No changes were found during induction and intubation, before starting N₂O.

various stages. During all stages of this study, including episodes of elevation of blood pressure, plasma concentrations of fentanyl were above the adult therapeutic range.¹⁰ This may be explained by several different mechanisms:

- a It is possible that children have lower sensitivity to fentanyl than adults, similar to observations made with digoxin and other drugs.¹¹
- b In children with congenital heart disease undergoing cardiac surgery the volume of distribution of fentanyl has been shown to be significantly smaller than in adults, possibly due to tissue hypoperfusion or decreased extra-cellular fluid volume.² Therefore it is conceivable that higher plasma concentrations of fentanyl do not necessarily reflect higher brain concentration of the drug in these patients.
- c Fentanyl has been shown to undergo redistribution from brain tissue into fat and other pharmacodynamically inert regions.¹⁰⁻¹² Consequently, a correlation may not exist between plasma concentrations and pharmacodynamic effects of fentanyl.¹³ Thus the acceptance of the concentrations of fentanyl which are regarded as therapeutic must be questioned. This is of particular importance because being a drug with a large distribution volume, only small amounts of fentanyl remain in the blood during steady state.

Our studies suggest that in order to prevent episodes of excessive elevation in blood pressure in children undergoing elective cardiac surgery, the described schedule should be combined with another anaesthetic agent. We have demonstrated that N₂O/O₂ may provide the necessary stability in blood pressure. However, the relative risk of N₂O in worsening the consequences of air embolism after the cardiopulmonary bypass must be considered,¹⁴ and another choice may be found more suitable. Our studies were focused on the pre-bypass period and therefore could not address this question. Further studies comparing combinations of fentanyl with other anaesthetic agents in larger groups of children are necessary.

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Résumé

L'anesthésie au fentanyl-oxygène (fentanyl-O₂) a été comparée au fentanyl-protoxyde d'azote/oxygène (fentanyl-N₂O/O₂) chez 14 enfants devant subir une chirurgie cardiaque. Les enfants ont été choisis au hasard par rapport à l'agent utilisé et divisés en deux groupes de sept. L'âge moyen (moyenne ± SE) était de 2.9 ± 0.75 ans (0.5–8.25 ans) et le poids moyen 14.7 ± 2 kg (3.5–29.5 kg). Les patients étaient prémédiqués avec l'atropine 0.02 mg·kg⁻¹ et la morphine 0.2 mg·kg⁻¹ deux heures avant l'opération. Ils ont reçu du fentanyl en bolus de 30 µg·kg⁻¹ suivi d'une perfusion continue de 0.3 µg·kg⁻¹·min⁻¹. Le pancuronium 0.1 mg·kg⁻¹ a été administré immédiatement après l'injection du bolus de fentanyl. Cinquante pour cent de protoxyde d'azote a été administré avec l'oxygène pour un groupe et 100 pour cent d'oxygène pour l'autre. Les concentrations plasmatiques de fentanyl ont été similaires dans les deux groupes aux différentes étapes de la chirurgie. Il n'y avait aucune différence significative entre les deux groupes tant qu'à la pression artérielle systolique et diastolique ni dans la fréquence cardiaque en réponse à l'induction, l'intubation ou l'incision. Il y avait cependant une augmentation significative de la pression artérielle systolique après sternotomie pour le groupe fentanyl-O₂. En plus chez six des sept patients recevant du fentanyl-O₂ on observa des épisodes d'augmentation de la pression artérielle durant les différentes étapes de la chirurgie avant la CEC, nécessitant une administration additionnelle de bolus de fentanyl ou l'administration de dro-péridol chez quatre patients. Des phénomènes identiques n'ont pas été documentés chez les groupes recevant le fentanyl-N₂O/O₂. Nos études suggèrent que l'anesthésie au fentanyl-O₂ tel que décrite chez les enfants subissant une chirurgie cardiaque pour une Tétralogie de Fallot, un canal A-V, ou une transposition des gros vaisseaux n'est pas suffisante afin de prévenir l'élévation dans la pression artérielle systolique malgré les concentrations plasmatiques de fentanyl en excès de 20 ng·ml⁻¹. L'addition de protoxyde d'azote prévient ce phénomène.