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Double-blind Comparison of Oral Transmucosal Fentanyl Citrate with Oral Meperidine, Diazepam, and Atropine as Preanesthetic Medication in Children with Congenital Heart Disease

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The effectiveness of oral transmucosal fentanyl citrate (OTFC) as preanesthetic medication was compared with oral meperidine, diazepam, and atropine (MDA) in 40 pediatric patients scheduled to undergo repair of congenital heart defects. In a double-blinded manner, patients received a fentanyl lollipop (20–25 μg/kg) and a placebo oral solution (0.4 ml/kg) (n = 20) or a placebo lollipop and an oral solution (0.4 ml/kg) of meperidine (1.5 mg/kg), diazepam (0.2 mg/kg), and atropine (0.02 mg/kg) (n = 20). The patient's vital signs, systolic and diastolic blood pressures, heart rate, respiratory rate, and oxyhemoglobin saturation (Sp_{O_2}), as well as activity and apprehension scores were evaluated and recorded at baseline and at 10-min intervals. The patient's emotional status at the time of parental separation and at induction of anesthesia were also assessed. Side effects and onset of action were observed. After OTFC, onset of sedation was significantly faster than with the oral solution of meperidine, diazepam, and atropine. In both groups there was no significant change in heart rate. Although systolic blood pressure, diastolic blood pressure, and respiratory rate showed statistically significant decreases, these changes were not clinically significant. The child's emotional status at the time of separation from the parents and during induction was similar in both groups. Side effects with OTFC were more frequent: nose itching occurred in 65%, body itching in 10%, and vomiting in 30%. Two patients (10%) in the OTFC-treated group became hypoxemic (Sp_{O_2} < 90) and required supplemental oxygen. In the group receiving oral meperidine, diazepam, and atropine, 10% had mild facial pruritus and 5% complained of a dry mouth. When compared with oral meperidine, diazepam, and atropine, OTFC in the dosage used is readily acceptable, provides more rapid sedation, but has considerably more preoperative side effects. Consequently, OTFC in the dose used in this study cannot be recommended as a preanesthetic medication for patients with congenital heart disease. (Key words: Analgesics: fentanyl. Anesthesia: pediatric. Preanesthetic medication: fentanyl, oral transmucosal.)

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ANESTHESIA AND SURGERY can invoke enormous stress and anxiety for the child undergoing an operative procedure and the child's family members. The anxiety and fear that the child experiences before and during induction of anesthesia can cause prolonged psychologic problems.[1] Both psychologic support and pharmacologic agents are useful in allaying the anxiety and stress associated with surgery. Although preoperative visits with the anesthesiologist have been shown to be effective in diminishing stress, pharmacologic adjuncts are better than placebo in reducing patient anxiety.[2,3] Even with the advent of numerous anxiolytic agents, the ideal preanesthetic medication for children is not yet available. Preanesthetic medication administered through intramuscular injections can, in itself, create fear and anxiety, whereas oral preanesthetic medications may be erratic in their absorption and consequently their desired effect. Oral transmucosal fentanyl citrate (OTFC) is a nonthreatening alternative preanesthetic medication in children. In prior studies with healthy patients, OTFC (15–20 μg/kg) has been shown to be safe, efficacious, and acceptable for pediatric patients having minor surgery.[4–6] The purpose of this study was to compare in a double-blinded fashion the effectiveness of high-dose OTFC (20–25 μg/kg) and oral meperidine, diazepam, and atropine (MDA) in pediatric patients with known congenital heart disease who were about to have cardiothoracic surgery. We chose 20–25 μg/kg fentanyl citrate as our dosing level with the thought that the lower dosage (15–20 μg/kg) found to be optimal in healthy ASA Physical Status 1 and 2 outpatients might be insufficient in sedating hospitalized patients for major cardiovascular surgery. The MDA preanesthetic medication was chosen based on prior reported studies and our familiarity with the preanesthetic medication.[7]

Materials and Methods

This study was approved by the hospital's Human Rights Committee, and written informed consent from the patients' parents was obtained. The 40 children studied were between the ages of 2 and 12 yr, ASA Physical Status 2 and 3. All patients had congenital heart disease

TABLE 1. Scoring Systems

	Score	Status
Preoperative activity	1	Asleep; not easily arousable
	2	Asleep; slowly responds to verbal commands and/or gentle stimulation
	3	Drowsy; readily responds to verbal commands and/or gentle stimulation
	4	Awake; calm and quiet
	5	Awake; active
Preoperative apprehension	1	None
	2	Little: slight or minimal expression of fear or apprehension
	3	Moderate: expression of fear or apprehension
	4	Excessive: vocal display of fear or apprehension
Emotional status at separation from parents and during induction	1	Excellent: patient unafraid, cooperative, or asleep
	2	Good: slight fear and/or crying; quiet with reassurance
	3	Fair: moderate fear and crying; not quiet with reassurance
	4	Poor: crying, need for restraint

and were scheduled to have elective cardiovascular procedures. They were randomly divided into two equal groups, both of which received a form of preanesthetic medication and a placebo. Group 1 (OTFC) received OTFC†† (20–25 μg/kg) and 0.4 ml/kg placebo oral solution, whereas group 2 (MDA) received 0.4 ml/kg oral solution of meperidine (1.5 mg/kg), diazepam (0.2 mg/kg), and atropine (0.02 mg/kg) along with a placebo lollipop.

Approximately 1 h before the anticipated beginning of surgery, the patient and parents were brought to the anesthesia holding area. Baseline measurements of systolic and diastolic blood pressures, oxyhemoglobin saturation (Sp_{O_2}), heart rate, and respiratory rate were recorded. The systolic and diastolic blood pressures were recorded by a Dinamap[6] (Critikon), the Sp_{O_2} by a Nellcor pulse oximeter, the heart rate by radial artery palpation, and respirations by chest wall observation. The child's levels of apprehension and activity were scored and recorded. The medication was then administered in a double-blinded manner. The scoring was done by three people, all of whom were blinded to the medication administered. All measurements and scores were recorded again every 10 min until induction of anesthesia. Sp_{O_2} was monitored continuously. Emotional status at separation from parents and at anesthetic induction was recorded (see table 1 for scoring systems). Supplemental oxygen was administered if Sp_{O_2} decreased to less than 90% in children with acyanotic heart disease and if Sp_{O_2} decreased by more than 10% from baseline in children with cyanotic heart disease.

If, immediately before the induction of anesthesia, the attending anesthesiologist believed the child was unsatisfactorily premedicated (*i.e.*, the child was either too anxious or too active), then additional medication (intramuscular midazolam or rectal methohexital) was administered. The incidence and duration of side effects, including nausea, vomiting, and facial and body scratching, were recorded. During induction of anesthesia, the incidence of airway obstruction and laryngospasm was recorded. Anesthesia induction techniques varied. Children younger than 10 yr received an inhalation induction with nitrous oxide, oxygen, and halothane by a face mask unless an intravenous induction was deemed safer for medical reasons. Children older than 10 yr were offered a choice of either inhalation or intravenous induction. After induction of anesthesia, at the time of intubation, oral secretions were assessed. The following rating scale was used: 1 = none; 2 = mild; 3 = moderate; and 4 = excessive.

Data were analyzed with the use of chi-squared and ordered chi-squared (Mantel-Haenszel) tests, the Mann-Whitney test, and repeated-measures analysis of variance where appropriate. Statistical significance was assumed for $P < 0.05$.

Results

All results are reported as mean ± standard deviation. Patients in the two groups were similar with respect to age, sex distribution, weight, race, ASA Physical Status, height, cyanosis, and baseline hemodynamics (table 2). Forty-one children were enlisted in the study. No patient was receiving any regular medications that may have affected the preanesthetic medication side effects or seda-

TABLE 2. Demographic and Baseline Hemodynamic data

Variable	OTFC	MDA
Age (yr)	5.43 ± 2.74	5.79 ± 3.03
Sex ratio (male/female)	8/12	10/10
Weight (kg)	18.8 ± 8.6	19.4 ± 9.0
Heart rate (beats per min)	102.9 ± 20.6	102.8 ± 18.8
Respiratory rate (breaths per min)	20.4 ± 2.6	20.1 ± 1.8
Systolic blood pressure (mmHg)	105.6 ± 12.4	113.2 ± 13.7
Diastolic blood pressure (mmHg)	61.7 ± 9.7	64.3 ± 12.9
Sp_{O_2} (%)	95.5 ± 6.6	94.0 ± 9.0

Data are means ± SD.

†† Oral transmucosal fentanyl citrate and the placebo lollipops are manufactured by Anesta Corporation, 825 North 300 West, Suite 200, Salt Lake City, Utah 84103.

TABLE 3. Distribution of Congential Heart Lesions

Type of Lesion	OTFC	MDA
Atrial septal defect (ASD)	2	8
Atrioventricular septal defect	1	3
Ventricular septal defect	2	1
Patent ductus arteriosus	2	1
Pulmonary artery stenosis	1	0
Left ventricular outflow obstruction	2	0
Mitral valve regurgitation	1	0
Double inlet left ventricle	1	0
Tetralogy of Fallot	4	0
Coarctation of aorta	1	3
Right atrial appendage	1	0
Pacemaker placement	1	0
Left atrial myxoma	1	0
Aortic stenosis	0	1
Hypoplastic right ventricle	0	2
Pulmonary atresia, ASD	0	1

Data are number of patients.

tion. One patient (2.5 yr old) was eliminated from analysis because of refusal of both the lollipop and the oral solution. Cardiovascular lesions for which the patients required surgery are shown in table 3. Both groups included patients with left-to-right, right-to-left, and bidirectional cardiac shunts, as well as patients with obstructive lesions. By randomization, there were significantly ($P \leq 0.05$) more patients with atrial septal defects in the MDA-treated group.

There was no significant difference between the two groups with respect to acceptability of the lollipop. Eight children chewed a portion of the lollipop. Eleven patients needed encouragement to take the lollipop, and 15 patients required coaxing to drink the oral solution. In patients receiving OTFC, the mean (±SD) time to consume the lollipop was 28 ± 17 min. The range was 4–70 min.

Time between the patients' receipt of preanesthetic medication and separation from their parents varied from 30 to 100 min. Two children were evaluated for 30 min, 2 for 40 min, 13 for 50 min, 14 for 60 min, and the remaining nine for 70–100 min. Thus, all patients were observed for at least 30 min after preanesthetic medication. Statistical analysis was performed on data obtained up to 50 min after the patients received medication, which involved 90% of the patients. In both groups heart rate did not change significantly, but systolic blood pressure, diastolic blood pressure, and respiratory rate all decreased significantly (figs. 1 and 2).In acyanotic patients receiving OTFC, the decline in Sp_{O_2} was greater (97.5 ± 1.5 to 95.0 ± 2.1) than in those in the MDA-treated group (98.7 ± 1.1 to 97.1 ± 1.0) (see fig. 3). However, these differences were not clinically significant. After preanesthetic medication, two children in the OTFC-treated group (10%) were hypoxemic ($Sp_{O_2} < 90\%$) and required supplemental oxygen. Although both children had a decreased respi-

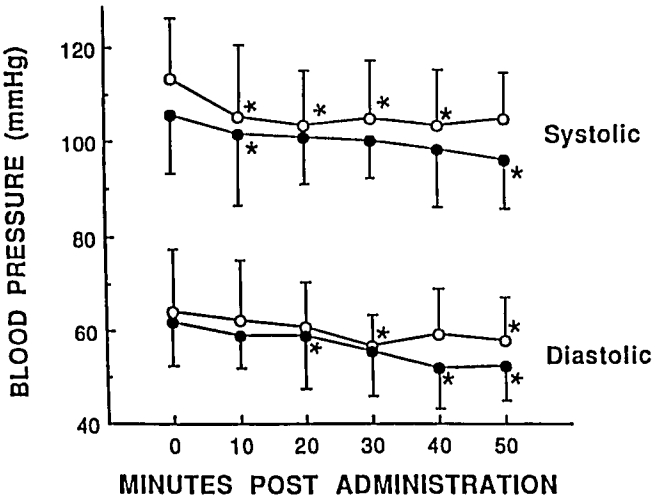

FIG. 1. Systolic and diastolic blood pressures after preanesthetic medication in both OTFC (filled circles) and MDA (open circles) patients. *$P < 0.05$ from control values.

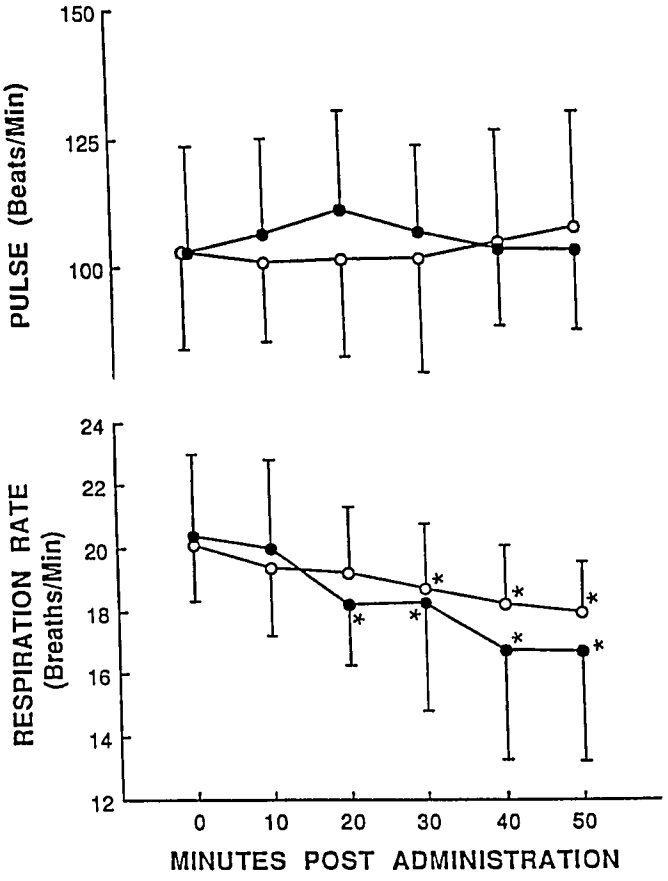

FIG. 2. Heart rates and respiratory rates after preanesthetic medication in OTFC (filled circles) and MDA (open circles) patients. *$P < 0.05$ from control values.

ratory rate that increased on command, in neither child did the Sp_{O_2} increase with an increase in respiratory rate. Only seven children with cyanotic heart disease were entered into the study. Two children received OTFC, and five were assigned to the MDA-treated group. With preanesthetic medication, Sp_{O_2} increased in both patients in the OTFC-treated group and in four of the five patients in the MDA-treated group (see fig. 3).

Activity scores showed that more patients were asleep and drowsy ($P \leq 0.05$) in the OTFC-treated group between 30 and 60 min (see fig. 4). Compared with baseline, patients receiving OTFC showed a greater decrease ($P \leq 0.05$) in activity from 30 to 60 min than the patients receiving MDA. Decreases in the apprehension score from baseline also occurred earlier in the OTFC-treated group, with significance at 30, 40, and 50 min ($P \leq 0.05$). There was no statistically significant difference between the two groups in emotional status at separation from parents and during anesthetic induction (see figs. 5 and 6). At separation from parents, 85% of OTFC-treated patients and 80% of MDA-treated patients had scores of 1 or 2 (excellent or good); at induction, 70% of OTFC-treated and 80% of MDA-treated patients had scores of 1 or 2.

The incidence of side effects was greater ($P \leq 0.05$) in the OTFC-treated group and included facial pruritus (65%), body pruritus (10%), nausea (25%), and vomiting (38%). In group-2 patients, 10% had facial pruritus, and 5% complained of a dry mouth. Two children, one in each group, were believed to be insufficiently sedated and required supplemental preanesthetic medication before the induction of anesthesia.

During the induction of anesthesia, there was no instance of laryngospasm in either group and there was no significant difference between the two groups in the incidence of airway obstruction. The amount of oral secretions was significantly greater in the OTFC-treated group.

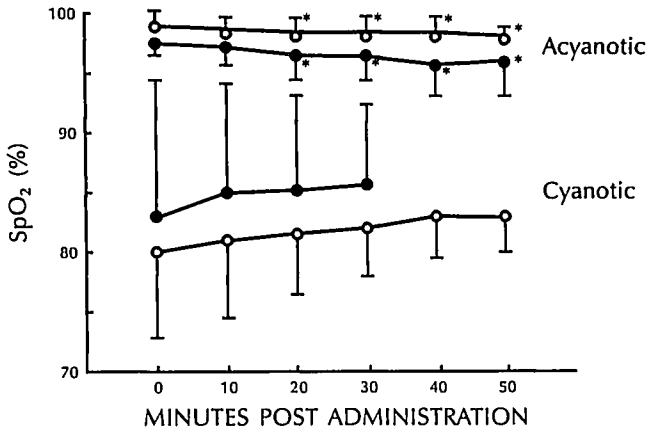

FIG. 3. Oxygen saturations in cyanotic and acyanotic patients after preanesthetic medication with either OTFC (filled circles) or MDA (open circles). *$P < 0.05$ from control values.

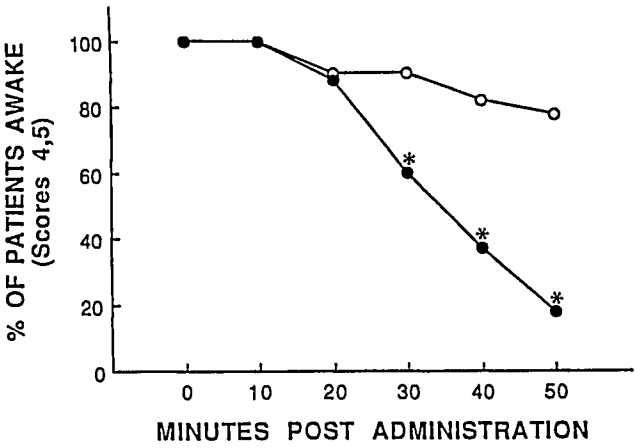

FIG. 4. Activity level (*i.e.*, scores of 4 and 5) (percentage of children awake) after preanesthetic medication with OTFC (filled circles) or MDA (open circles). *$P < 0.05$ between groups.

Four of the five children older than 10 yr had intravenous catheters inserted without a struggle before the operation. Three of the 35 (8.6%) children younger than 10 yr of age had an intravenous catheter inserted for induction at the discretion of the attending anesthesiologist. All three children were significantly upset by the placement of the intravenous catheters.

Discussion

In a study of outpatients, Desjardins *et al.*[8] concluded that outpatients should not receive preanesthetic medication, not because of overwhelming risk, but rather because of the lack of any appreciable benefit. We believe that the major goals of preanesthetic medication in pediatric patients should be to make the experience of surgery less traumatic; to ease the emotional difficulty in parental separation; and to facilitate a safe and smooth induction of anesthesia. Despite the availability of numerous preanesthetic medication drugs, an ideal agent has not yet been developed. Because the effectiveness of a pre-

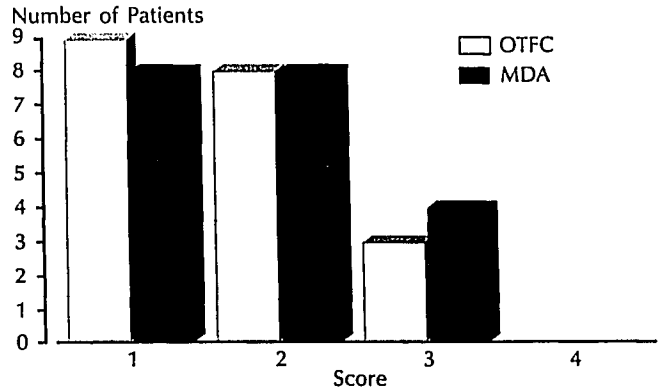

FIG. 5. Patients' emotional status at the time of parental separation with OTFC and MDA.

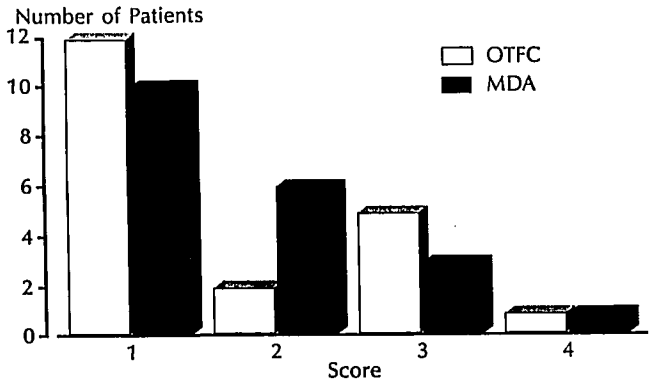

FIG. 6. Patients' emotional status at induction with OTFC and MDA.

anesthetic medication depends on dose, time, and route of administration, such medication may or may not be effective at the time of the child's induction of anesthesia. With oral, intramuscular, and rectal administration of drugs, variability in drug absorption rates, coupled with the administration of these drugs on a weight basis, frequently results in either inadequate or excessive sedation. With intramuscular injections, the anticipatory fear and associated pain may inflict additional psychologic trauma.[9]

The transmucosal route of administration provides an alternative to intramuscular administration. The transmucosal delivery of opioids may provide equal or enhanced bioavailability of the drug when compared with oral and intramuscular delivery. In addition, OTFC appears nonthreatening. In previous nonblinded studies, OTFC has been a readily acceptable, safe, and effective form of preanesthetic medication.[4,5] In blinded studies comparing OTFC with placebo, Feld *et al.*[6] reported that OTFC provided better separation and anxiety scores and a better quality of anesthesia induction in healthy ASA Physical Status 1 and 2 patients. Our double-blinded study compared OTFC with an effective and frequently administered oral solution of meperidine, diazepam, and atropine in patients with congenital heart disease who were about to have cardiothoracic surgery. The oral regimen used was that devised by Brzustowicz *et al.*,[7] and we believed that comparison with a well-known and used preanesthetic medication was an appropriate choice. However, we recognize the limitations of our study in that single-dose regimens were used. Consequently, patients may not have been receiving equipotent doses of MDA and OTFC. Although the anesthesiologist's visit can allay anxiety and fear, and itself has been equated to the effect of a preanesthetic medication,[2,9] we believed that the addition of a third group, with placebo only, to separate out the influence of the psychologic component of the anesthesiologist's interaction, would be inappropriate in patients about to have cardiothoracic surgery.

Although in both groups of patients statistically significant decreases in systolic blood pressure, diastolic blood pressure, and respiratory rate occurred, these changes were not clinically significant. Two patients in the OTFC-treated group had a significant decline in Sp_{O_2}. Both of these patients had a decreased respiratory rate, but their Sp_{O_2} did not increase when the respiratory rate increased with command. These findings are similar to those of Feld *et al.*[6] but differ from the findings of Streisand *et al.*[5] In the study by Streisand *et al.*,[5] 3 of 12 children receiving OTFC (20–25 μg/kg) experienced a $Sp_{O_2} < 90\%$, but all 3 of these patients responded to command with an increase in respiratory rate and an increase in Sp_{O_2}. Thus, it appears that in patients receiving 20–25 μg/kg doses of OTFC, Sp_{O_2} monitoring is required. Of particular concern is the continuing decline of the Sp_{O_2} and respiratory rate in the OTFC-treated group. It is unclear whether this would have continued if the preanesthetic period had been prolonged.

Side effects were significantly more frequent in the OTFC-treated group. We recorded an incidence of 65% of facial pruritus, which compares with an incidence of 50–80%[4,10] in outpatients receiving 15–20 μg/kg OTFC, and an incidence as high as 85–100%[5] in patients receiving 15–25 μg/kg of OTFC. More significantly, 6 of 20 OTFC-treated patients in our study vomited before induction of anesthesia. The vomiting occurred within 23–61 min after the preanesthetic medication was given to the patient, and it usually occurred concomitant with the onset of sedation. This vomiting before induction of anesthesia is in contrast to the other studies, in which vomiting associated with OTFC occurred in the postoperative period. Preoperative vomiting necessitated changing the anesthetic induction technique in 8.6% of the total of patients. Whether the vomiting resulted from the use of a higher fentanyl dose, the 0.4 ml/kg placebo oral solution, or the combination is not known. Previous studies in outpatients receiving OTFC in dose ranges of 15–20 μg/kg and 20–25 μg/kg have shown that side effects were more common in the higher dose range.[5] However, in the study by Nelson *et al.*,[4] 1 of 20 patients receiving 15–20 μg/kg OTFC vomited before induction. In addition, at the time that our study was begun, limited information was available regarding the side effects seen at the various OTFC doses.

The findings regarding Sp_{O_2} in the seven children with cyanotic heart disease are intriguing. Two patients receiving OTFC and four of five patients receiving MDA had an increased Sp_{O_2}. Although there were too few patients in our study to allow us to draw any conclusions, possible explanations include a decreased oxygen consumption secondary to sedation and/or salutary effects of sedation on the pulmonary vascular bed.‡‡

‡‡ DeBock TL, Davis PJ, Tome J, Petrilli R, Siewers RD, Motoyama EK: Effect of premedication on arterial oxygen saturation in children with congenital heart disease. J Cardiothorac Anesth 4:425–429, 1990

It is not surprising that the OTFC-treated group had significantly more secretions at the time of intubation than the MDA-treated group, whose preanesthetic medication included atropine. However, the secretions caused no increase in airway difficulties or obstruction in the OTFC-treated group, and one patient in the MDA-treated group complained about a dry mouth. We did not evaluate gastric residual volumes or gastric *p*H. Stanley *et al.*[12] found that OTFC did not change gastric *p*H and produced nonsignificant increases in gastric volume.

In summary, OTFC provided more rapid decreases than MDA in preoperative anxiety and activity. However, emotional status at the time of separation from parents and anesthetic induction was similar in the two groups. It is possible that a lower dosage of OTFC may be as sedating with fewer side effects or that an antiemetic administered concomitantly would surmount the problem of nausea and vomiting. At present, because of the high incidence of preinduction vomiting, high doses of OTFC (20–25 μg/kg) cannot be recommended as a preanesthetic medication for children with congenital heart disease.

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