Anesthesiology
70:616-621, 1989

Comparison of Oral Transmucosal Fentanyl Citrate and an Oral Solution of Meperidine, Diazepam, and Atropine for Premedication in Children

Paul S. Nelson, M.D., James B. Streisand, M.D.,† Sandra M. Mulder, drs.,‡*
Nathan L. Pace, M.D.,§ Theodore H. Stanley, M.D.§

The safety and efficacy of premedication with oral transmucosal fentanyl citrate (OTFC) was compared with that of an orally administered solution of meperidine, diazepam, and atropine and no premedication in 59 children about to undergo elective operations. The patients were randomly assigned to receive no premedication (n = 19); 0.25 ml/kg of the oral solution (containing meperidine, 1.5 mg/kg, diazepam, 0.2 mg/kg, and atropine, 0.02 mg/kg, n = 20); or OTFC (15–20 μg/kg, n = 20). Children had activity (sedation) and anxiety scores, vital signs (including systolic and diastolic arterial blood pressures and heart and respiratory rates) and pulse oximetry determined oxygen saturation measured before and at 10-min intervals after premedication until they were taken to the operating room. Quality of induction and recovery was evaluated using scoring schedules; recovery times were measured and side effects noted. OTFC was readily accepted and provided significant reductions in preoperative activity (sedation) and anxiety starting after 30 min. After OTFC, sedation and anxiolysis were significantly greater than in children having no premedication but similar to children having the oral solution for premedication. Vital signs and oxygen saturations remained unchanged preoperatively in all groups. Induction and recovery evaluations and recovery times were similar in the three groups, although children having OTFC had the lowest requirements for narcotics in the recovery room. OTFC caused an 80% incidence of mild preoperative facial pruritus and a higher overall incidence of postoperative vomiting (37%) than premedication with the oral solution (5%) or no premedication (18%). The results demonstrate that OTFC is readily accepted, safe, more effective than no premedication, and at least as effective as premedication with an oral solution of meperidine, diazepam, and atropine in children. (Key words: Analgesics: fentanyl, meperidine. Hypnotics: diazepam. Premedication, oral transmucosal: fentanyl.)

IN CHILDREN, emotional trauma associated with parental separation and induction of anesthesia may result in an increased incidence of postoperative behavioral problems.[1] Psychologic preparation and/or premedication can reduce the emotional distress experienced by children before and during anesthetic induction.[2,3] However, achieving adequate rapport with a child often proves difficult in a busy day surgery facility.[3,4] An ideal anesthetic premedication regimen in children would provide adequate sedation and relief of anxiety without prolonging postoperative recovery and without reliance upon a painful or threatening method of administration.[4]

Oral transmucosal absorption *via* a fentanyl-impregnated lollipop (OTFC) is a new, pleasant, nonthreatening method of delivering preanesthetic medication to children.[5,6] The objectives of this study were to compare the safety and efficacy of premedication with OTFC with that of an orally administered solution of meperidine, diazepam, and atropine.[7]

Methods

Approval was received from the Food and Drug Administration and the University of Utah Human Institutional Review Board, and consent was obtained from the parents of 75 ASA physical status 1–2 children 2–15 yr of age scheduled as outpatients and inpatients for a variety of elective ophthalmologic, otolaryngologic (ENT), urologic, and orthopedic operations. After consent was obtained, the children were randomly assigned to one of three groups: group 1, no premedication; group 2, oral premedication (0.25 ml/kg) with an aqueous solution in which the patients received meperidine, 1.5 mg/kg, diazepam, 0.2 mg/kg, and atropine, 0.02 mg/kg; and group 3, premedication with a fentanyl lollipop (OTFC), which contained 15–20 μg/kg of fentanyl citrate. The lollipops were made by heating a candy base and adding 100, 200, 250, 300, 400, 500, 700, or 1,000 μg of fentanyl citrate crystals. Following mixing, the candy–fentanyl mixture was poured into molds, a stick was added, and the lollipop was allowed to cool and harden before removal from the molds. All lollipops were the same size (1.6 ml) irrespective of the dose of fentanyl they contained. No attempt was made to blind the study because of the limited experience with OTFC in children and the potential risk (vomiting and aspiration) from consumption of both a lollipop and oral solution. Thus, some evaluations (activity and anxiety indices, induction scores, and vital sign determinations) were made by an investigator who was aware of the patient's group, whereas others (recovery times and emergence scores) were made by an individual unaware of the premedication.

* Fellow in Anesthesiology.
† Assistant Professor of Anesthesiology.
‡ Research Assistant in Anesthesiology.
§ Professor of Anesthesiology.

Received from the Department of Anesthesiology, University of Utah School of Medicine, Salt Lake City, Utah. Accepted for publication November 21, 1988. Supported in part by the Stanley Research Foundation.

Address reprint requests to Dr. Stanley: Department of Anesthesiology, University of Utah School of Medicine, 50 N. Medical Drive, Salt Lake City, Utah 84132.

Although 75 children were recruited into the study, data for only 59 (group 1, 19; groups 2 and 3, 20 each) were evaluated. The remaining 16 patients were eliminated from analysis because they refused to take the premedication; were not held in the holding area at least 30 min before being taken to the operating room; were given incorrect premedication; or had their operation canceled. Emergence data were obtained from all 59 patients but only evaluated from 56 because three children (two receiving no premedication and one receiving OTFC) were given morphine during the operation.

Approximately 1 h before the scheduled beginning of the operation each child (accompanied by his or her parents) was brought to the preoperative holding area adjacent to the operating room. Following examination of the patient's oral mucosa, baseline systolic and diastolic arterial blood pressures, heart rate, respiratory rate and hemoglobin saturation (Sp_{O_2}) were measured by a standard manual pediatric blood pressure cuff, radial artery palpation, observation of the chest wall, and use of a Criticare Systems Model 501® pulse oximeter, respectively. The patients then received either OTFC, the oral premedication solution, or no premedication. Children in group 3 were asked to rapidly suck the lollipop without biting or chewing it, and the time required for complete consumption of the candy was recorded.

Sp_{O_2} was continuously measured, and heart rate, systolic and diastolic blood pressures, and respiratory rate remeasured every 10 min throughout the preanesthetic evaluation period until the children were taken to the operating room. Activity and anxiety scores (table 1) were determined prior to administration of the premedication and every 10 min thereafter until the children were taken to the operating room to evaluate the effectiveness of the premedication. Children taken to the operating room within 30 min of receiving premedication were considered unsuitable for evaluation. Prior to departure to the operating room, the patient's oral mucosa was reexamined.

Anesthesia was induced with halothane (0.25–3.0%) and N_2O (60%) in oxygen *via* a face mask by an anesthesiologist unaware of the group allocation of the patient. Ventilation was at first spontaneous, then assisted, and finally controlled as the patient lost consciousness. Following loss of consciousness an iv infusion of 5% dextrose and 0.25% normal saline or lactated Ringer's solution was started in a hand or arm vein. The trachea was intubated without the use of a muscle relaxant unless laryngeal exposure was difficult or other anatomic considerations suggested that paralysis would significantly facilitate tracheal intubation. In these circumstances succinylcholine (1.0–1.5 mg/kg iv) was used for relaxation. The ease and quality of anesthetic induction was evaluated according to an anesthetic induction score (table 1). Anesthesia was maintained with halothane (0.1–2.5%)

TABLE 1. Preoperative Activity (sedation), Anxiety, Anesthetic Induction, and Emergence Scoring Schedules

Preoperative activity
- 1 = Asleep, not readily arousable
- 2 = Asleep, slowly responds to verbal commands
- 3 = Drowsy, readily responds to verbal commands
- 4 = Awake, calm and quiet
- 5 = Awake and active

Preoperative anxiety
- 1 = None
- 2 = Little (demonstrates some fear or uneasiness but does not cry)
- 3 = Moderate (clearly fearful, cries but becomes quiet with reassurance)
- 4 = Excessive (crying, uncooperative, does not become quiet with reassurance)

Induction
- 1 = Excellent (patient unafraid, fully cooperative, compliant, not at all resistant; an uneventful induction)
- 2 = Good (mostly cooperative, compliant, some anxiety or crying but becomes quiet with reassurance)
- 3 = Fair (moderate fear or crying, not quiet with reassurance)
- 4 = Poor (combative, crying; resistant, need for restraint; a stormy induction)

Emergence
- 1 = Quiet
- 2 = Occasional crying
- 3 = Crying but able to be quieted
- 4 = Thrashing, unable to be quieted

or, if arrhythmias occurred (in two patients), with isoflurane (0.1–2.0%) and N_2O (60%) in oxygen to keep systolic blood pressure within 20% of preoperative values. No opiates, antiemetics, or iv anesthetics were to be used; muscle relaxants were used after tracheal intubation if clinically indicated. Ordinarily, controlled ventilation was maintained until 10–20 min before the end of the operation when halothane was decreased or discontinued and spontaneous ventilation resumed. After termination of all anesthetics, patients' tracheas were extubated when they responded to the tracheal tube, the respiratory rate was >12 breaths/min, and tidal volume was considered to be adequate.

Emergence from anesthesia was evaluated upon arrival in the recovery room and every 15 min thereafter using an emergence score (table 1). Times to awakening (as measured from discontinuation of all inhalation anesthetics until spontaneous eye opening first occurred) and first response to verbal commands (as measured from termination of all inhalation anesthetics until eye opening first occurred upon command) were evaluated every 5 min in the recovery room and recorded. Intravenous opiates (morphine 0.5–1.0 mg or meperidine 5–10 mg) were requested by the recovery room nurses (who were unaware of the premedication used) for control of moderate or severe postoperative pain (as determined by an anesthesiologist uninvolved with the study). Patients were discharged from the recovery room when they achieved a score of 10 using the Aldrete postanesthetic recovery score.[8] Time of fulfillment of discharge criteria was re-

TABLE 2. Demographic Data in 59 Children Receiving Premedication with Oral Transmucosal Fentanyl Citrate (OTFC), an Oral Solution of Meperidine, Diazepam, and Atropine, or No Premedication

	Group 1 No Premedication	Group 2 Oral Premedication	Group 3 OTFC
Gender M/F	12/7	11/9	14/6
Age (yr)	6.3 ± 3.1	6.1 ± 3.6	6.3 ± 3.4
Weight (kg)	22.9 ± 8.2	23.2 ± 9.8	24.6 ± 9.9
Height (cm)	114.0 ± 20.8	118.3 ± 23.5	114.8 ± 22.8
Duration of anesthesia (min)	129.9 ± 79.5	76.0 ± 39.4	98.9 ± 81.5

Values are mean ± SD.

corded. The incidences and times of occurrence of pruritus and nausea (as volunteered by the patient) and vomiting were recorded in the preoperative holding area, operating room, recovery room, and for 3 h postoperatively or until outpatients were discharged.

Data were analyzed for statistical significance using a one-way analysis of variance (ANOVA) for age, weight, height, duration of anesthesia, vital signs, and Sp_{O_2}; individual comparisons were performed by the Duncan multiple range test. Gender, race, type of operation, ASA physical class, and activity scores were compared using chi-square tests. Changes with time for vital signs were evaluated by a repeated measures ANOVA with polynomial contrasts for linear trends. Activity ratings were analyzed at each evaluation period and were grouped as asleep/drowsy (activity scores 1–3) *versus* awake (scores

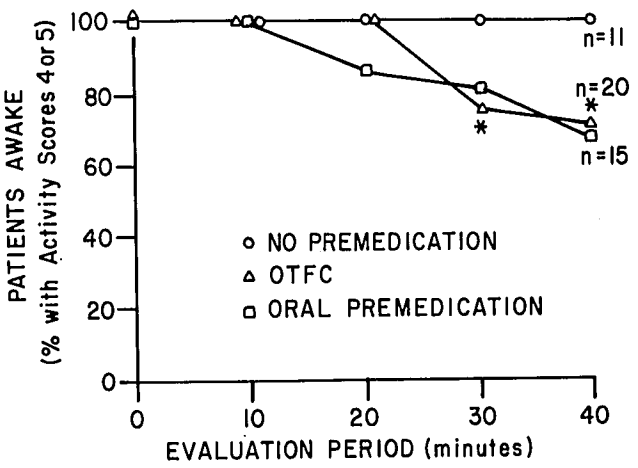

FIG. 1. A graph of children awake (percent with activity scores of 4 or 5) *versus* time. Except at 40 min, there were 19 patients receiving no premedication, 20 receiving an oral solution of atropine, meperidine, and diazepam, and 20 receiving OTFC for premedication. $*P < 0.05$, analysis of change in activity from baseline (Kruskal-Wallis one-way ANOVA with Dunn's multiple comparisons), OTFC compared with no premedication.

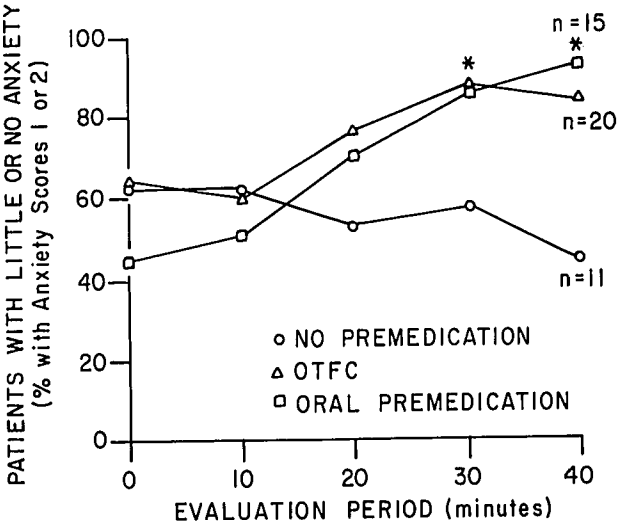

FIG. 2. A graph of children with little or no anxiety (anxiety scores of 1 or 2) *versus* time. Except at 40 min, there were 19 patients receiving no premedication, 20 receiving an oral solution of atropine, meperidine, and diazepam, and 20 receiving OTFC for premedication. $*P < 0.05$, analysis of change in activity from baseline (Kruskal-Wallis one-way ANOVA with Dunn's multiple comparisons) cocktail compared with no premedication.

4 and 5) due to small numbers in most categories and then compared using chi-square tests. Anxiety ratings were analyzed at each evaluation period using a Kruskal-Wallis ANOVA with Dunn's multiple comparisons. Changes in anxiety and activity levels from baseline were analyzed using Kruskal-Wallis ANOVA with Dunn's procedures. Recovery room data (emergence times and side effect incidence) were also analyzed by Kruskal-Wallis ANOVA with Dunn's multiple comparisons. The majority of analyses were performed with the SYSTAT statistical package for the IBM-PC. $P < 0.05$ was considered statistically significant.

Results

Patients in the three groups were similar with respect to gender distribution, the type of operation scheduled, ASA physical status distribution, age, weight, height, baseline vital signs, oxygen saturation, and duration of anesthesia (table 2). Patients receiving OTFC required 19.8 ± 10.3 min (mean ± SD; range 6–40 min) for complete consumption of the lollipop. All oral mucosal observations (before and after premedication) were recorded as normal.

All 59 children had preoperative evaluations for at least 30 min after baseline and until they were brought to the operating room. The number of children evaluated in the three groups decreased with each additional 10-min interval after 30 min as increasing numbers of patients

were called to the operating room. Evaluations at 40 min after baseline were of a total of 46 patients (11, 15, and 20 in groups 1, 2, and 3, respectively).

Figures 1 and 2 depict the percent of patients awake (activity scores of 4 or 5) and calm (little or no anxiety; anxiety scores of 1 or 2) *versus* time. Evaluations past 40 min after baseline are not included in the figures because the number of patients within each group decreased markedly after 40 min. Overall analysis of the proportions of patients that were sleepy or drowsy (activity scores 1, 2, or 3) *versus* awake were comparable among groups at all evaluation periods except at 40 min, when patients in the OTFC group were significantly less active than the group receiving no premedication (group 1; $P < 0.05$). Analysis of change in activity from baseline indicates that patients having OTFC had significantly greater decreases in activity ($P < 0.05$) than those receiving no premedication 30 and 40 min after baseline (fig. 1). There was no difference in activity scores between patients receiving OTFC and oral premedication.

Patients receiving oral premedication (group 2) had significantly ($P < 0.05$) lower anxiety ratings (were less anxious) than those receiving no premedication (group 1) 40 min after baseline recordings.¶ Analysis of change from baseline showed that group 2 (oral premedication) had significantly greater decreases in anxiety than group 1 ($P < 0.05$) after 30 and 40 min. There was no difference in anxiety between groups 2 and 3 or 1 and 3.

There were no significant differences in the three groups in systolic and diastolic arterial blood pressures, heart and respiratory rates, and Sp_{O_2} at any time in the preoperative holding area (fig. 3). Sp_{O_2} values in the OTFC patients tended to decrease with time ($P < 0.01$), but the differences were not significant ($P > 0.05$) when compared with the other two groups. Lowest vital signs and oxygen saturation observed in the holding area are given in table 3. Patients having OTFC had significantly lower minimal Sp_{O_2} ($P < 0.007$) than patients receiving no premedication but were not different than patients having oral premedication (table 3). One patient (5%) having OTFC premedication had a single transient Sp_{O_2} of 89% 30 min after beginning lollipop consumption. He was asked to take a deep breath, which raised his saturation to 95%. He had no further Sp_{O_2} less than 93%. Otherwise, all changes in vital signs and oxygen saturation were of no clinical consequence in any patient at any time during the study.

¶ Similar anxiety analysis demonstrated that groups 2 and 3 had lower anxiety ratings than group 1 at 50 min and that group 3 had lower anxiety ratings than group 1 at 60 min. However, patient counts for groups 1, 2, and 3 were only 5, 10, and 12, respectively, at 50 min and 4, 3, and 8, respectively, at 60 min.

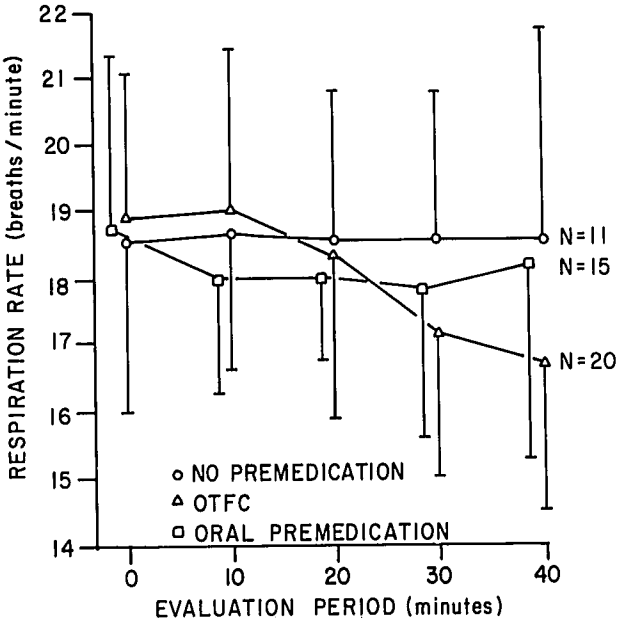

FIG. 3. A graph of the mean respiratory rate (mean ± SD) *versus* time. Except at 40 min, there were 19 patients receiving no premedication, 20 receiving an oral solution of atropine, meperidine, and diazepam, and 20 receiving OTFC for premedication.

The difference in the overall quality of induction of anesthesia in the three groups was not statistically significant. Although patients receiving oral premedication and OTFC had slightly longer mean times to awakening and to first response to verbal command in the recovery room, the differences were not statistically different (table 4). Only four children receiving OTFC required opiates in the recovery room. In contrast, nine of the patients having no premedication and eight having an oral premedication

TABLE 3. Minimal Vital Signs and Hemoglobin Oxygen Saturation Data in the Preoperative Holding Area in 59 Children Receiving Oral Transmucosal Fentanyl Citrate (OTFC), an Oral Solution of Meperidine, Diazepam, and Atropine, or No Premedication

	Group 1 No Premedication	Group 2 Oral Premedication	Group 3 OTFC
Number of patients	19	20	20
Lowest systolic blood pressure (mmHg)	95 ± 11	94 ± 9	95 ± 15
Lowest diastolic blood pressure (mmHg)	63 ± 8	63 ± 8	62 ± 14
Lowest heart rate (beats/min)	91 ± 12	87 ± 13	91 ± 13
Lowest respiratory rate (breaths/min)	18 ± 2	17 ± 2	16 ± 3
Lowest hemoglobin oxygen saturation (mmHg)	96 ± 1	96 ± 1	95 ± 2*

Values are mean ± SD.
* $P < 0.007$ when compared with group 1, one-way ANOVA with Duncan multiple range test.

TABLE 4. Recovery Room Data in 56 Children Receiving Oral Transmucosal Fentanyl Citrate (OTFC), an Oral Solution of Meperidine, Diazepam, and Atropine, or No Premedication

	Time from Last Agent off (min)		
	Group 1 No Premedication	Group 2 Oral Premedication	Group 3 OTFC
Patients (n)	17	20	19
Time to awakening (spontaneous eye opening; min)	17.0 ± 12.6	24.2 ± 14.6	25.6 ± 21.0
Time to first response to verbal command (min)	19.2 ± 14.5	30.3 ± 14.9	30.2 ± 24.1
Time to fulfillment of discharge criteria (min)	67.3 ± 29.4	65.5 ± 20.1	64.5 ± 24.3

Values are mean ± SD.

required opiates in the recovery room. The differences in recovery room narcotic requirements were not statistically different ($P = 0.079$).

Mild facial pruritus occurred preoperatively in 16 of the 20 (80%) patients receiving OTFC and coincided with the onset of sedation. Pruritus did not occur after operation and was not present in any patient in the other two groups. Only two patients (both having OTFC) reported being nauseated at any time during the study (in the recovery room). In contrast, vomiting occurred in patients in all three groups after operation (table 5). Vomiting usually occurred when the patients were asked to sit or stand or were moved from the recovery room. The incidence of vomiting in the preoperative holding area, operating room, recovery room, or after discharge from the recovery room was similar in the three groups (table 5). However, if the incidences of vomiting during all four of these evaluation periods were summed, patients receiving OTFC had a higher overall incidence of vomiting (41%) than those having oral premedication (5%) ($P < 0.05$). The overall incidence of vomiting in patients having no premedication (26%) was not statistically different from those having OTFC or oral premedication. No patient became rigid or required naloxone in the operating or recovery rooms. There was no noticeable decrease in respiratory compliance (as assessed by hand ventilation) in any patient in any of the groups prior to tracheal intubation; however, pulmonary compliance in one child having OTFC seemed to decrease shortly after tracheal intubation. No other side effects were noted in any patient in the study.

TABLE 5. Incidence (percentage) of Side Effects in Children Receiving Oral Transmucosal Fentanyl Citrate (OTFC), an Oral Solution of Meperidine, Diazepam, and Atropine, or No Premedication

		Group 1 No Premedication	Group 2 Oral Premedication	Group 3 OTFC
Preoperative holding	n	19	20	20
Pruritus		0*	0*	80%
Nausea		0	0	0
Vomiting		0	0	5%
Operating room	n	19	20	20
Pruritus		0	0	0
Nausea		0	0	0
Vomiting		16%	0	0
Recovery room	n	17	20	19
Pruritus		0	0	0
Nausea		0	0	11%
Vomiting		12%	5%	26%
After recovery room discharge	n	17	20	19
Pruritis		0	0	0
Nausea		0	0	0
Vomiting		6%	0	11%

* $P < 0.001$ Kruskal-Wallis ANOVA test when compared with group 3.

Discussion

In this study, OTFC was readily accepted by all children and provided significant reductions in preoperative activity (increased sedation) and anxiety starting 30 min after the start of lollipop consumption. We believe that these results demonstrate that OTFC is readily accepted by children, safe, more effective than no premedication, and at least as effective as premedication with an oral solution of meperidine, diazepam, and atropine before elective surgery in children. Although we believe the potential for respiratory depression after 15–20 μg/kg of OTFC mandates that oxygen saturation be monitored during and after its use, only one patient (5%) experienced a single, transient episode of desaturation. No episodes of oxygen desaturation were reported by Streisand *et al.*[6] in 12 patients nor by Leiman *et al.*[9] in 18 patients after 15–20 μg/kg of OTFC; however, both reported small clinically insignificant decreases in respiratory rate after 20 min. Higher doses of OTFC (20–25 μg/kg and above) cause dose-dependent increases in respiratory depression,[5,6] which appear slowly and are best managed by removing the lollipop if it has not been finished, encouraging the patient to breathe, and/or supplying oxygen. OTFC did cause a high incidence of preoperative facial pruritus (80%) and a somewhat higher incidence of postoperative vomiting than did premedication with the oral solution or no premedication. Pruritus heralded the onset of sedation after OTFC and was not disturbing to any of the children or their parents. Postoperative vomiting was also not considered a serious problem.

There are data that suggest that chest wall rigidity and reduced ventilatory compliance after high doses of iv fentanyl and similar opioids are related to the dose and speed with which the drugs are given and thus presumably the

speed and concentration achieved in CNS tissues. Chest wall rigidity was not noted in this study and has not been observed in adult human volunteers receiving up to 78 μg/kg of OTFC and children receiving 25 μg/kg.[5,6] Absence of changes in ventilatory compliance after OTFC is particularly interesting considering the high incidence that was noted by Henderson *et al.*[10] after nasal sufentanil (45%, 57%, and 50% after 1.5, 3.0, and 4.5 μg/kg of sufentanil, respectively). We believe an explanation of these differences could be that Henderson *et al.*[10] used relatively larger doses (especially the 3.0 and 4.5 μg/kg groups) of sufentanil than we used with fentanyl in OTFC and that passage of sufentanil through nasal mucus membranes occurs more rapidly than passage of fentanyl through bucal mucosa. As a result, sufentanil plasma and brain concentrations probably increased more rapidly and to higher levels than fentanyl plasma and brain concentrations. Sufentanil's marked lipid solubility (more than twice that of fentanyl)[11] and its rapid onset of action (4–10 min) after nasal administration[10] *versus* 20–30 min in this study is consistent with this hypothesis.

The effect of oral transmucosal (lollipop) delivery of any drug on the volume and *p*H of gastric contents is a potential concern. Gastric volume and *p*H determinations were not made in this study but have been done in a recent investigation by Leiman *et al.*[9] These authors found that OTFC premedication did not change gastric *p*H, produced only small, <7 ml mean, increases in gastric volume, and had no influence on vomiting when compared with children receiving no premedication or a placebo lollipop.

This study can be criticized for not employing a double-blind approach for evaluation of the children. There were three principal reasons for this decision: 1) limited previous experience with OTFC in children (before this study the total experience in children was 44 patients of whom only 12 had received 15–20 μg/kg of OTFC[6]); 2) the difficulty and potentially increased risk (particularly for gastric aspiration) of giving all patients both a lollipop and an oral solution, which would have been necessary for optimal double blinding; and 3) our institutional review board would not allow children to have an oral solution plus a lollipop, particularly if there was a chance that neither contained an active premedication. Despite the lack of adequate blinding, we believe the data have value because at least some of the measurements (recovery times and emergence scores) were obtained or determined by individuals unaware of the premedication. Furthermore, most of the scoring schedules used reasonably objective end points, and most side effects (pruritus, vomiting) were obviously present or absent.

Patients in this study were scheduled for a variety of surgical procedures of variable duration. Although the distribution of kinds of operations and times of surgery were similar in the three groups, the variation within each group was enormous (*i.e.*, duration of anesthesia ranged from 10 to 370 min). This is the explanation for the large standard deviations in duration of anesthesia (table 2) and may also explain why there were not greater differences in recovery among the three groups. Patients having very short operations did not appear to have longer recovery periods and more postoperative respiratory depression than patients having longer procedures. Nonetheless, it is not clear whether OTFC provides as many benefits to outpatients with little associated postoperative pain as it might for patients to be admitted to the hospital after operations associated with a great deal of postoperative pain. OTFC may be as much or more useful for postoperative pain than it is for preoperative sedation. Obviously, many additional carefully performed studies will be required before the advantages and disadvantages of OTFC are well established.

References

1. Eckenhoff JE: Relationship of anesthesia to post-operative personality changes in children. Am J Dis Child 86:587–591, 1953
2. Jackson K: Psychologic preparation as a method of reducing the emotional trauma of anesthesia in children. ANESTHESIOLOGY 12:293–300, 1951
3. Freeman A, Backman L: Pediatric anesthesia: An evaluation of preoperative medication. Anesth Analg 38:429–437, 1959
4. Desjardins R, Ansara S, Charest J: Pre-anesthetic medication in paediatric day-care surgery. Can Anaesth Soc J 28:141–148, 1981
5. Mock DL, Streisand JB, Hague B, Dzelzkalns R, Bailey PL, Pace NL, Stanley TH: Transmucosal narcotic delivery: An evaluation of fentanyl (Lollipop) premedication in man (abstract). Anesth Analg 65:S102, 1986
6. Streisand JB, Hague B, van Vreeswijk H, Ho GH, Pace NL, Clissold M, Nelson P, East KA, Stanley TO, Stanley TH: Oral transmucosal fentanyl premedication in children (abstract). Anesth Analg 66:S170, 1987
7. Brzustowicz RM, Nelson DA, Betts EK, Rosenberry KR, Swedlow DB: Efficacy of oral premedication for pediatric outpatient surgery. ANESTHESIOLOGY 60:475–477, 1984
8. Aldrete JA, Kroulik D: A postanesthetic recovery score. Anesth Analg 49:924–934, 1970
9. Leiman BC, Walford A, Rawal N, Katz J, Marcus M, van Nieuwenhuyzen M, Cronau L, Stanley TH: The effects of oral transmucosal fentanyl citrate premedication on gastric volume and acidity in children (abstract). ANESTHESIOLOGY 67:A489, 1987
10. Henderson JM, Brodsky DA, Fisher DM, Brett CM, Hertzka RE: Preinduction of anesthesia in pediatric patients with nasally administered sufentanil. ANESTHESIOLOGY 68:671–675, 1988
11. Meuldermans WEG, Hurkmans RMA, Heykants JJ: Plasma protein binding and distribution of fentanyl, sufentanil, and lofentanil in blood. Arch Int Pharmacodyn Ther 257:4–19, 1982