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Oral Transmucosal Fentanyl Citrate for Preanesthetic Medication of Pediatric Day Surgery Patients with and without Droperidol as a Prophylactic Anti-emetic

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The safety and efficacy of oral transmucosal fentanyl citrate (OTFC) as a preanesthetic medication and the efficacy of droperidol as a prophylactic anti-emetic were evaluated in 100 children aged 2–8 yr undergoing general anesthesia for outpatient surgery. Patients were randomly assigned to one of four groups and managed in a double-blinded manner: 1) placebo lozenge 45 min preoperatively and placebo (normal saline) injected intravenously after induction of anesthesia; 2) placebo lozenge 45 min preoperatively and 50 μg/kg droperidol intravenously after induction; 3) 15–20 μg/kg OTFC lozenge 45 min preoperatively and placebo intravenously after induction; and 4) 15–20 μg/kg OTFC lozenge 45 min preoperatively and droperidol 50 μg/kg intravenously after induction. Anesthesia was induced and maintained with halothane and nitrous oxide in oxygen. Heart rate, respiratory rate, blood pressure, and hemoglobin oxygen saturation (Sp_{O_2}) were monitored throughout the study. Scoring systems were used to evaluate sedation, anxiety, cooperation, and ease and quality of anesthetic induction. Emergence, recovery, and discharge times were recorded. Nausea, vomiting, and adverse effects were noted. Preoperatively, children receiving OTFC had significantly greater sedation, slower respiratory rates, lower Sp_{O_2}, and less excitement during induction. Postoperative nausea and vomiting occurred significantly more frequently after OTFC than after placebo. Prophylactic droperidol did not significantly reduce the incidence of nausea and vomiting. The authors conclude that, in pediatric surgical outpatients, OTFC reliably induces preoperative sedation and facilitates inhalation induction of anesthesia, but it is associated with significant decreases in respiratory rate and Sp_{O_2} and a high incidence of postoperative nausea and vomiting that is not significantly reduced by prophylactic droperidol. (Key words: Analgesics: fentanyl. Anesthesia: pediatric. Preanesthetic medication: fentanyl, oral transmucosal.)

IN A SEARCH for a form of preanesthetic medication that is less traumatic and less threatening to children than the traditional intramuscular route of administration, oral transmucosal fentanyl citrate (OTFC), administered in the form of a lozenge on a handle, has been evaluated in recent clinical trials.[1–5] In studies completed thus far, OTFC has been found to be effective in producing sedation but has been associated with a high incidence of postoperative nausea and vomiting. The purpose of this study was to evaluate the safety and efficacy of OTFC in a pediatric outpatient surgical population, and to determine whether postinduction intravenous droperidol affects the incidence of postoperative nausea and vomiting.

Materials and Methods

This study was approved by the Institutional Review Board, and written informed consent was obtained from the parents of the subjects. One hundred children greater than 2 yr of age who were scheduled for a variety of outpatient surgical procedures were studied. Those scheduled for strabismus repair or tonsillectomy were excluded because of the high incidence of postoperative nausea and vomiting already associated with those operations, and those scheduled for myringotomy were excluded because of the brevity of the procedure. Using a table of random numbers, patients were divided into four groups of 25 subjects. A double-blinded study design was used: all study drugs and placebos were selected by the hospital pharmacy and labeled only with the patients' names and hospital numbers. Both OTFC and placebo lozenges were manufactured by the Anesta Corp. (Salt Lake City, UT) as described previously.[6] Group 1 patients received a placebo lozenge 45 min prior to the scheduled time of anesthetic induction. After induction of anesthesia and insertion of an intravenous catheter, patients in this group received a placebo intravenous injection of normal saline. Group 2 patients were also given a placebo lozenge 45 min preinduction but received an intravenous injection of droperidol 50 μg/kg after induction. Group 3 patients received a lozenge containing OTFC 15–20 μg/kg 45 min preinduction and intravenous normal saline postinduction. Group 4 patients received a lozenge containing OTFC 15–20 μg/kg 45 min preinduction and intrave-

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nous droperidol 50 μg/kg postinduction. The lozenges were administered in the day-surgery holding area, where the patients remained with their parents during the preinduction period.

A nurse who was not otherwise involved with the patients' care remained near the patient as an observer throughout the preinduction and postanesthesia recovery periods. Numeric scoring systems used in previous evaluations of OTFC[2,4] were used by the observer to evaluate sedation, anxiety, and cooperation during the preoperative period, and ease and quality of anesthetic induction after separation from parents. Heart rate, blood pressure, and hemoglobin oxygen saturation (Sp_{O_2}) were monitored throughout the study using an automated blood pressure device and a pulse oximeter. Respiratory rate was recorded at 10-min intervals.

Anesthetic induction was carried out by administration *via* mask of halothane in concentrations increasing to 3% in 60% nitrous oxide and 40% oxygen. After induction, the oral mucosa was visually inspected for abnormalities in appearance; the amount of oral secretions was graded by the anesthesiologist as "none," "mild," "moderate," or "excessive"; and any occurrence of airway obstruction, laryngospasm, or abnormality in ventilatory compliance was noted. All patients received atropine 10 μg/kg intravenously after induction. Most patients in each group underwent tracheal intubation (table 1). Muscle relaxants and additional hypnotics, sedatives, or antiemetics were not administered. Anesthesia was maintained with 1.0–1.5% halothane in 60% nitrous oxide and 40% oxygen via a semi-closed circle absorber system.

Postoperatively, time intervals from discontinuance of halothane to extubation, spontaneous opening of the eyes, response to verbal command, orientation to person and place, tolerance of clear oral fluids, and discharge home were noted. Nausea, vomiting, and other adverse effects were recorded.

Statistical analyses were performed with the SYSTAT statistical package for the IBM-PC. Age, height, and weight were compared using one-way analysis of variance (ANOVA). ASA physical status, sex, incidence of tracheal intubation, and operative sites were compared using chi-square tests. Vital signs and Sp_{O_2} were analyzed with one-way ANOVA and Kruskal-Wallis ANOVA; intergroup differences were compared with Dunn's multiple comparisons and the Mann-Whitney rank sum test. Ratings of sedation, anxiety, cooperation, and quality of induction were analyzed using chi-square and Mantel-Haenszel summary chi-square tests. Time intervals of induction, emergence, and recovery variables were compared with Kruskal-Wallis ANOVA; intergroup differences were analyzed with Dunn's multiple comparisons and the Mann-Whitney rank sum test. Adverse effects were analyzed using chi-square and Mantel-Haenszel summary chi-square tests. $P < 0.05$ was considered statistically significant.

Results

The four groups were similar with regard to population characteristics (table 1). Because the droperidol or saline was injected after anesthetic induction, results from data collected during the preoperative period are presented as if there were only two groups: placebo lozenge (groups 1 and 2) *versus* OTFC (groups 3 and 4).

Preoperative Period

The lozenges were readily accepted by all of the children. By 30 min after administration of the lozenges, significantly greater sedation was observed in the children

TABLE 1. Population Characteristics

	Group 1	Group 2	Group 3	Group 4
Age (yr)	3.8 ± 1.9	3.8 ± 1.8	4.6 ± 1.8	4.4 ± 1.9
Weight (kg)	17 ± 5	16 ± 4	19 ± 7	18 ± 5
Height (cm)	102 ± 13	102 ± 15	109 ± 13	107 ± 13
Male	20	16	16	14
ASA physical status 1	23	21	24	22
Tracheal intubation	17	19	21	18
Surgical site				
Inguinal	12	16	7	7
Dental	7	4	9	8
Penis	4	2	2	3
Skin	1	2	3	4
Lip	0	0	3	1
Neck	0	0	1	1
Extremity	1	1	0	1

Data are means ± SD or number of patients (n = 25 in each group). There are no significant differences in this table.

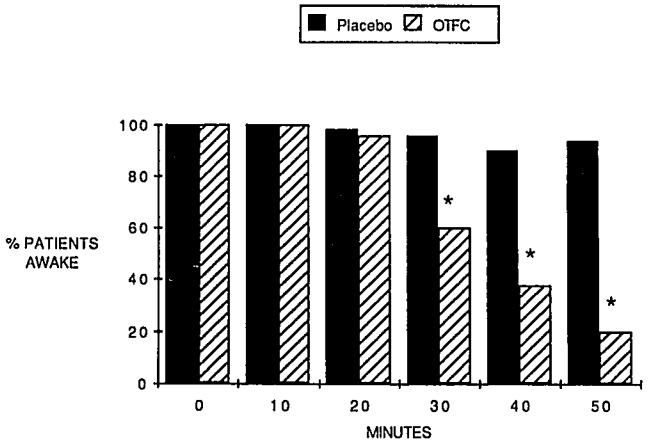

FIG. 1. Percentage of children awake (sedation score of 4 or 5) as a function of time following preanesthetic medication with either oral transmucosal fentanyl citrate (OTFC) or placebo. n = 50 in each group through 30 min. At 40 min, n = 27 (placebo), 29 (OTFC). At 50 min, n = 12 (placebo), 17 (OTFC). *$P < 0.01$ by Mantel-Haenszel summary chi-square analysis.

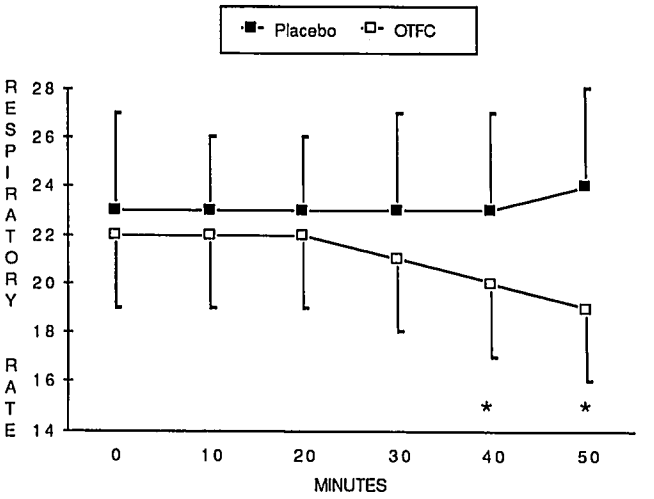

FIG. 3. Respiratory rate (breaths per min, mean ± SD) as a function of time following preanesthetic medication of children with either oral transmucosal fentanyl citrate (OTFC) or placebo. n = 50 in each group through 30 min. At 40 min, n = 27 (placebo), 29 (OTFC). AT 50 min, n = 12 (placebo), 17 (OTFC). *$P < 0.02$ by one-way ANOVA.

who received OTFC than in those who received a placebo (fig. 1). Lack of cooperation and displays of anxiety were rare during the preoperative period, and no significant differences in those scores existed between the OTFC and placebo lozenge groups.

By 20 min after lozenge administration and during the remaining preoperative period, Spo_2 was significantly less in patients who had received OTFC than in those who had received a placebo (fig. 2). At 30 and 40 min, Spo_2 (mean ± standard deviation) was 95 ± 2% in OTFC patients and 97 ± 1% in placebo patients. Six patients in the OTFC group were observed to have Spo_2 less than 90% during the preoperative period. The lowest Spo_2 observed in an individual patient was 85% in the OTFC group and 90% in the placebo group. In each instance of Spo_2 less than 90%, improvement occurred in response to gentle verbal or tactile stimulation.

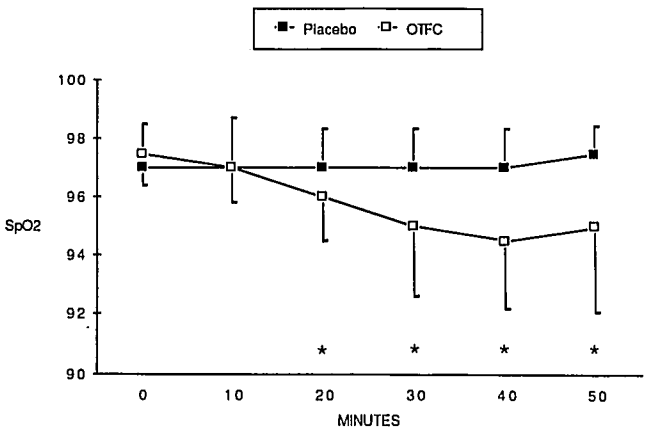

FIG. 2. Hemoglobin oxygen saturation (Spo_2, mean ± SD) as a function of time following preanesthetic medication of children with either oral transmucosal fentanyl citrate (OTFC) or placebo. n = 50 in each group through 30 min. At 40 min, n = 27 (placebo), 29 (OTFC). At 50 min, n = 12 (placebo), 17 (OTFC). *$P < 0.02$ by one-way ANOVA.

By 40 min after lozenge administration and during the remaining preoperative period, respiratory rate was significantly less in patients who had received OTFC than in those who had received placebo (fig. 3). At this time, respiratory rate (mean ± standard deviation) was 20 ± 3 breaths/min in OTFC patients and 23 ± 4 breaths/min in placebo lozenge patients. The lowest respiratory rate observed in an individual patient during the preoperative period was 16 breaths/min in each group.

Other observed differences between OTFC and placebo groups during the preoperative period are listed in

TABLE 2. Adverse Effects during the Preoperative Period

	Placebo	OTFC	P*
Facial pruritis	6	70	0.001
Dizziness	0	12	0.04
Spo_2 < 90%	0	12	0.04
Sweating	0	8	0.13
Nausea	2	10	0.21

Data are percentage of patients (n = 50 in each group).
OTFC = oral transmucosal fentanyl citrate.
* By chi-square analysis.

TABLE 3. Anesthetic Induction Scores

	Placebo	OTFC
Excellent	44	70
Good	28	16
Fair	16	12
Poor	12	2

Data are percentage of patients (n = 50 in each group).
OTFC = oral transmucosal fentanyl citrate.
The groups are significantly different ($P = 0.014$ by chi-square analysis).

table 2. No differences in heart rate or blood pressure were noted at any time during the study.

After separation from parents, significantly more patients in the OTFC group were judged to have an "excellent" anesthetic induction score (table 3). Induction times (from application of mask to loss of eyelid reflex) were 2.1 ± 0.8 min in OTFC patients and 2.5 ± 0.8 min in placebo lozenge patients ($P = 0.013$). During induction, no significant differences between the groups in ventilatory compliance, secretions, airway obstruction, or laryngospasm were noted. No abnormalities of the oral mucosa were seen.

POSTOPERATIVE PERIOD

Emergence and recovery times were affected by both OTFC and droperidol and varied among the groups (table 4). OTFC delayed extubation in the operating room. One patient in Group 3 required intravenous naloxone prior to extubation. Droperidol delayed spontaneous eye opening and response to verbal commands in patients who had received OTFC, and it delayed orientation to time and place in patients who had received either OTFC or placebo lozenges. Both OTFC and droperidol delayed discharge to home.

The incidence of postoperative nausea and vomiting was significantly greater in the OTFC groups than in the placebo lozenge groups ($P = 0.007$, Mantel-Haenszel chi-square analysis) (table 5). Intravenous droperidol did not have a statistically significant effect on the incidence of nausea and vomiting. Fewer patients who had received OTFC cried in the postanesthesia care unit.

Discussion

Preanesthetic medication to achieve sedation and anxiolysis has long been believed to benefit children by reducing perioperative emotional trauma.[7–9] Despite the use of preoperative tours of the surgical suite[10] and of parental presence during induction,[11] many anesthesiologists believe that premedication will more successfully allay anxiety. The traditional route of administration—intramuscular injection—has, however, curbed the use of preanesthetic medication in children because of its associated pain and fear.[12] Accordingly, alternative routes of drug administration are being examined in an effort to find an effective, atraumatic method of preanesthetic medication. OTFC is currently undergoing such clinical trials.

The results of this study demonstrate that administration of 15–20 μg/kg OTFC to children scheduled to undergo elective outpatient surgery causes most patients to become drowsy or asleep during the preoperative period. This success at achieving sedation is consistent with prior studies of OTFC in pediatric patients.[1–4]

While other studies have shown OTFC to be associated with a reduction in anxiety during the preoperative period,[2–4] we were not able to make that association because significant anxiety was not detected by our methods dur-

TABLE 4. Emergence and Recovery from Anesthesia

	Group 1	Group 2	Group 3	Group 4
Preoperative lozenge	Placebo	Placebo	OTFC	OTFC
Postinduction drug	Placebo	Droperidol	Placebo	Droperidol
Duration of anesthesia (min)	64 ± 39	71 ± 26	80 ± 45	63 ± 31
Minutes from halothane off until:				
Extubation*	6.0 ± 5.0	7.1 ± 3.6	12.0 ± 7.4	12.4 ± 6.9
Spontaneous eye-opening†	29 ± 12	33 ± 15	34 ± 22	50 ± 26
Response to verbal command†	31 ± 14	37 ± 16	35 ± 22	57 ± 22
Oriented to name and place‡	43 ± 16	60 ± 38	54 ± 36	74 ± 34
Tolerate oral clear fluids	116 ± 48	125 ± 57	149 ± 87	124 ± 55
Discharge home§	152 ± 39	181 ± 63	207 ± 65	189 ± 48

Data are means ± SD (n = 25 in each group).
OTFC = oral transmucosal fentanyl citrate.
* Groups 3 and 4 differ from others ($P = 0.001$, Kruskal-Wallis ANOVA and Mann-Whitney rank sum test).
† Group 4 differ from others ($P = 0.011$, Kruskal-Wallis ANOVA).
‡ Groups 2 and 4 differ from others ($P = 0.05$, Kruskal-Wallis ANOVA and Dunn's rank sum test).
§ Group 1 different from others ($P = 0.001$, Kruskal-Wallis ANOVA).

TABLE 5. Analgesia, Nausea, and Vomiting during the Postoperative Period

	Group 1	Group 2	Group 3	Group 4
Preoperative lozenge	Placebo	Placebo	OTFC	OTFC
Postinduction drug	Placebo	Droperidol	Placebo	Droperidol
Crying in PACU*	60	76	40	32
Nonopioid analgesics administered in PACU	32	48	36	40
Opioid analgesics administered in PACU	24	28	16	24
Opioid administration preceding nausea and vomiting	4	4	4	8
Postoperative nausea and vomiting†	32	16	64	40

Data are percentage of patients (n = 25 in each group).
OTFC = oral transmucosal fentanyl citrate; PACU = postanesthesia care unit.
* Groups 3 and 4 differ from others ($P = 0.003$, chi-square analysis).
† Groups 3 and 4 differ from others ($P = 0.007$); group 1 *versus* group 2, $P = 0.325$; group 3 *versus* group 4, $P = 0.161$ (Mantel-Haenszel chi-square analysis).

ing this time in any group. This lack of anxiety may be attributable to the children's young ages and their slight understanding of what was about to happen to them, or to the nonthreatening environment of the preoperative holding area of the outpatient surgical unit. The perioperative event traditionally associated with the greatest anxiety is the anesthetic induction itself,[7,8] and at that time the children who had received OTFC were judged to have better induction scores than those who had received placebo (table 3). Thus, both sedation and anxiolysis were achieved by OTFC.

These benefits of OTFC, however, were accompanied by some adverse effects. Significant decreases in both respiratory rate and Sp_{O_2} are the most important of these. Previous reports have documented decreases in respiratory rate associated with 15–20 μg/kg OTFC,[3,4] but none has reported significant decreases in oxygen saturation in healthy children receiving this dose. Although the statistically significant difference in mean Sp_{O_2} between placebo lozenge and OTFC patients (97% *vs.* 95%) is of minimal clinical significance, the decrease in Sp_{O_2} to below 90% in six OTFC patients is important. No patient in this study experienced morbidity associated with ventilation. Patients were well monitored, and those with decreased Sp_{O_2} or respiratory rates responded satisfactorily to mild stimulation. Nonetheless, the potential for respiratory depression dictates that OTFC should be used in a controlled setting that includes appropriate monitors and personnel.

Postoperative nausea and vomiting are side effects of OTFC that have been reported consistently,[1–4] and they were frequent adverse effects in the present study. The 64% incidence of postoperative nausea and vomiting that we observed after OTFC affected both the quality and duration of postanesthetic recovery. Postoperative nausea and vomiting in patients receiving OTFC was not significantly reduced by intravenous droperidol 50 μg/kg. Droperidol, in a range of doses, has been shown to be effective in reducing the incidence of postoperative nausea and vomiting in other clinical situations.[13–16] Perhaps further clinical investigation will define a more successful method of controlling this problem.

Various emergence and recovery times were prolonged by both OTFC and droperidol, and OTFC delayed discharge home (table 4). Although the discharge delay was less than 1 h, such a delay could affect the efficiency of a busy outpatient surgical unit. On the other hand, three previous studies of OTFC in children found that OTFC did not prolong emergence or discharge from the postanesthesia care unit.[2–4]

We conclude that OTFC has both favorable and unfavorable characteristics as a preanesthetic medication for children undergoing outpatient surgery. It is readily accepted by patients; it reliably produces preoperative sedation; and it facilitates induction of anesthesia. The adverse effects of decreases in respiratory rate and Sp_{O_2} and of postoperative nausea and vomiting, however, are problems that may limit the applicability of OTFC in pediatric surgical outpatients.

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