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Respiratory Depression Following Orally Administered Flunitrazepam for Preanesthetic Medication in Children

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Because children fear needles, we advocate preanesthetic sedation by oral or rectal route.[1,2] Benzodiazepines can cause respiratory depression[3,4] although contradictory data have been published.[5,6] These conflicting results probably are due to the varying conditions of investigation, such as dosage and route of administration of different drugs, age of subjects, and measuring methods utilized. In adults the apparatus used for respiratory measurements may itself alter breathing pattern. Face mask, mouth piece, and nose clips produce an increase in tidal volume (V_T) and a decrease in respiratory rate.[7,8] Thus, respiratory measurement with standard methods in awake children are likely to be altered by measuring devices even more than in adults.

Oral administration of a long-acting benzodiazepine, flunitrazepam (FNZP),[9,10] 30–45 min before induction of anesthesia provides satisfactory premedication in children. The purpose of this study was to evaluate, with a noninvasive method, the respiratory effects of FNZP, administered orally as premedication in children undergoing elective minor ENT surgery.

PATIENTS AND METHODS

Ten children, aged 7.1 ± 1.5 years ($\bar{x}$ ± SD), weighing 24.7 ± 7.7 kg, participated in the study, which was

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approved by the Committee for Ethics in Human Research of our Institution, after informed consent from the child and at least one parent had been obtained.

Tidal volume (V_T), respiratory rate (f), minute ventilation (V_{min}), the ratio of the rib cage (RC) contribution to V_T (RC/V_T), and the changes in respiratory end-expiratory level, which is defined as end-tidal volume (ETV), were measured continuously with a noninvasive method recently described.[12] Two air-filled bellow pneumographs (Hewlett-Packard [HP] model 108 pneumograph) were attached circumferentially around the RC and the abdomen (ABD). Any change in circumference of the RC and ABD produces a linear variation of air pressure within the bellow pneumographs, which is detected through an airfilled polyethylene tubing by two differential pressure transducers (HP 267 BC). The electrical signals of changes in air pressure given by the transducers of the RC and ABD as well as their electrical sum were amplified and recorded on a polygraph (HP 7754 B) and simultaneously analyzed by a microcomputer (Apple II Plus®). Mean inspiratory flow (V_T/T_I), which is equal to the V_T over inspiratory time (T_I) and is an index of central inspiratory drive, and respiratory duty cycle (T_I/T_{tot}), which is the timing mechanism of the respiratory center,[13] were computed. The system is calibrated with the least-squares method, using a computer-aided procedure as previously described.[11] The sum of the signals of ABD and RC bellow pneumographs were matched with the exhaled volumes and measured with a pneumotachograph (Godard 17212), while the subjects breathed through an adapted face mask.

The study was performed with the children in the supine position. Once the calibration had been performed, the pneumotachograph was removed and the patients were supine in a quiet semidark room for 15 min, after which they were given orally a solution of FNZP 0.25%, 0.10 mg/kg to 10 kg and 0.05 mg/kg for each additional kg. Respiratory variables were measured continuously during 10 min before administration of FNZP and during at least 30 min after the child had fallen asleep. The onset of sleep was determined at the time when the child did not respond when called three times by his or her name. Respiratory variables are presented as the mean ± SD ($\bar{x} \pm SD$) of 5-min periods: 1) 5 min before FNZP; 2) the last 5 min before sleep after administration of FNZP; 3) 0–5 min after onset of sleep; 4) 10–15 min after onset of sleep; 5) 25–30 min after onset of sleep.

At the end of the respiratory measurements, the patients were transferred to the operating room where a N_2O/O_2-halothane inhalation anesthesia was induced via a mask.

The quality of the premedication was assessed on arrival in the operating room and graded as follows: asleep, awake and calm, restless; and it was noted whether the patient reacted by moving or waking upon insertion of 23-gauge needle iv. At the end of the surgical procedure, it also was noted if the child woke up easily and was calm.

To assess the regularity of the breathing pattern, the variation coefficient (SD/mean) of V_T was calculated for each patient at the different times of measurement. Because of the wide range of body weight of the subjects (16–37 kg), changes in respiratory volume are expressed in percentage changes from control values instead of milliliters. All data are presented as mean ± SD. Respiratory data of different periods were compared using a one-way analysis of variance, with differences being detected with a Scheffé test.

Results

After calibration, respiratory volumes obtained with the bellows pneumographs system and the pneumotachograph at different thoracoabdominal contributions to V_T differed by 3.7 ± 2.6%; the linear correlation between the volumes measured with the two systems at 15 different V_T, from small V_T to large V_T, was highly significant ($\bar{r} = 0.985 \pm 0.002$, $\bar{s} = 0.90 \pm 0.08$).

All 10 children fell asleep 15.7 ± 5.4 min after the administration of FNZP. Apnea, defined as an absence of respiratory movement of more than 10 s, never occurred, whereas minor upper airway obstruction was observed in two patients and treated easily by supporting the chin.

Changes in respiratory variables are summarized in tables 1 and 2. Individual data are illustrated in figures 1 and 2. While respiratory frequency did not change significantly, FNZP produced a significant decrease in V_T (−29 ± 12%) ($P < 0.001$), even before the subjects fell asleep. The subsequent decrease in V_T when sleep was induced was not significant. These changes resulted in a significant decrease in minute ventilation (−17 ± 15%) ($P < 0.001$).

Analysis of individual changes shows that 9 out of the 10 patients decreased their V_T after FNZP before falling asleep and that once asleep a further decrease in V_T occurred only in four subjects (fig. 1).

Mean inspiratory flow (V_T/T_I) decreased significantly ($P < 0.05$) after the administration of the drug but before the patients fell asleep, while respiratory duty cycle (T_I/T_{tot}) increased significantly only once the patients were asleep.

Changes in relative rib cage contribution to V_T (RC/V_T) are illustrated in figure 2. Although this ratio did not increase significantly before sleep was induced, it was increased significantly after 5 min of sleep, the mean values going from 0.30 ± 0.11 to 0.46 ± 0.11 (P

TABLE 1. Tidal Volume (V_T), Variation Coefficient for V_T, Respiratory Frequency (f), and Minute Volume ($\dot{V}_{min}$) Before and at Four Different Periods after Administration of Flunitrazepam, and Per cent Changes of all these Variables from Control (n = 10) ($\bar{x} \pm SD$)

	Before FNZP (Control)	5 Min before Falling Asleep	5 Min into Sleep	15 Min into Sleep	30 Min into Sleep
V_T (ml)	211 ± 100	144 ± 54	131 ± 31	134 ± 30	127 ± 36
Per cent change	0	−29 ± 12*	−32 ± 11*	−36 ± 14*	−35 ± 13*
Variation coefficient for V_T	0.48 ± 0.23	0.42 ± 0.45	0.21 ± 0.15†	0.17 ± 0.15*	0.19 ± 0.14*
f (breath/min)	18 ± 5.4	21.1 ± 2.8	22.1 ± 2.8	21.0 ± 2.6	21.5 ± 2.7
$\dot{V}_{min}$ (ml)	3,600 ± 900	2,950 ± 820	2,870 ± 600	2,790 ± 470	2,680 ± 570
Per cent change	0	−17 ± 15*	−19 ± 15*	−23 ± 14*	−23 ± 12*

Because of the wide range of body weight, per cent changes only were used to compare statistically V_T, V_{min}, and f between periods (one-way analysis of variance—Scheffé-test).

* $P < 0.001$.
† $P < 0.01$.

< 0.05). Since V_T decreased by 30% and RC/V_T increased by 50%, the reduction in V_T after FNZP is due exclusively to the decreased relative abdominal contribution to V_T. No significant change in ETV was observed.

After FNZP, variation coefficient of V_T decreased significantly (table 1), indicating a more regular respiratory pattern than observed before the drug.

The children arrived in the operating room 71 ± 22 min after the administration of FNZP. Six of them were asleep, while the other four were awake and calm. Only one patient reacted to the insertion of a 23-gauge catheter. Induction of anesthesia was performed in all cases via a mask without any difficulty. At the end of the anesthesia (halothane O_2/N_2O), which lasted a mean of 37 min, seven patients woke up readily, while the others had a delayed recovery, lasting more than 20 min after extubation of the trachea.

DISCUSSION

FNZP administered orally is a reliable drug for preanesthetic sedation; it induced sleep in all the subjects in less than 30 min without clinically undesirable side effects. However, FNZP produced significant respiratory changes, which were different before and after sleep was induced. After FNZP, during the last 5 min before sleep, V_T, $\dot{V}_{min}$ and V_T/T_I decreased significantly, indicating a depression of the respiratory drive,[13] which can be attributed to the effects of FNZP itself, since the subjects were not yet asleep. While V_T, $\dot{V}_{min}$, and V_T/T_I did not further decrease with the induction of sleep, T_I/T_{tot}, variation coefficient for V_T and RC/V_T increased significantly at that time, indicating a change in breathing pattern that could be due to the peak effect of FNZP or to the state of sleep[19] induced by the drug or to a combination of both. The increase in T_I/T_{tot} is attributed to an increase in T_I, since T_{tot} did not change between the pre- and post-sleep period. The significant decrease in the variation coefficient for V_T demonstrates a more regular breathing pattern after FNZP.

The significant increase in RC/V_T occurring only after induction of sleep indicates a dramatic change in breathing pattern that is not related to changes in V_T or V_T/T_I, since these two variables had been influenced by FNZP before sleep was induced and then remained stable. There was no correlation between changes in T_I and RC/V_T.

During sleep, since the relative rib cage contribution to tidal volume increased significantly after FNZP, the decrease in V_T can be attributed to the decrease of the abdominal contribution: This respiratory effect of FNZP contrasts with the volatile anesthetic agents that have been shown to decrease RC/V_T.[14,15] Our findings, however, are supported by animal investigations in which two other benzodiazepines, diazepam and midazolam, have been shown to reduce the phrenic nerve activity by 80%.[16,17] If this phenomenon could be extended to

TABLE 2. Mean Inspiratory Flow (V_T/T_I), Respiratory Duty Cycle (T_I/T_{tot}), and Thoracic Contribution to V_T (RC/V_T) Before and at Four Different Periods after Administration of Flunitrazepam and Per cent Changes from Control (n = 10) ($\bar{x} \pm SD$)

	Before FNZP (Control)	5 Min before Falling Asleep	5 Min into Sleep	15 Min into Sleep	30 Min into Sleep
V_T/T_I (ml/min)	163 ± 45	130 ± 46	113 ± 43	119 ± 32	120 ± 21
Per cent change	0	−16 ± 17*	−18 ± 22*	−16 ± 20*	−15 ± 23*
T_I/T_{tot}	0.37 ± 0.02	0.38 ± 0.05	0.46 ± 0.14	0.41 ± 0.12	0.39 ± 0.11
Per cent change	0	+3 ± 11	+26 ± 34†	+12 ± 30*	+6 ± 29
RC/V_T	0.30 ± 0.11	0.36 ± 0.13	0.46 ± 0.11*	0.46 ± 0.19*	0.47 ± 0.18
Per cent change	0	+30 ± 56	+64 ± 77*	+63 ± 79*	+65 ± 77*

* $P < 0.05$.
† $P < 0.01$.

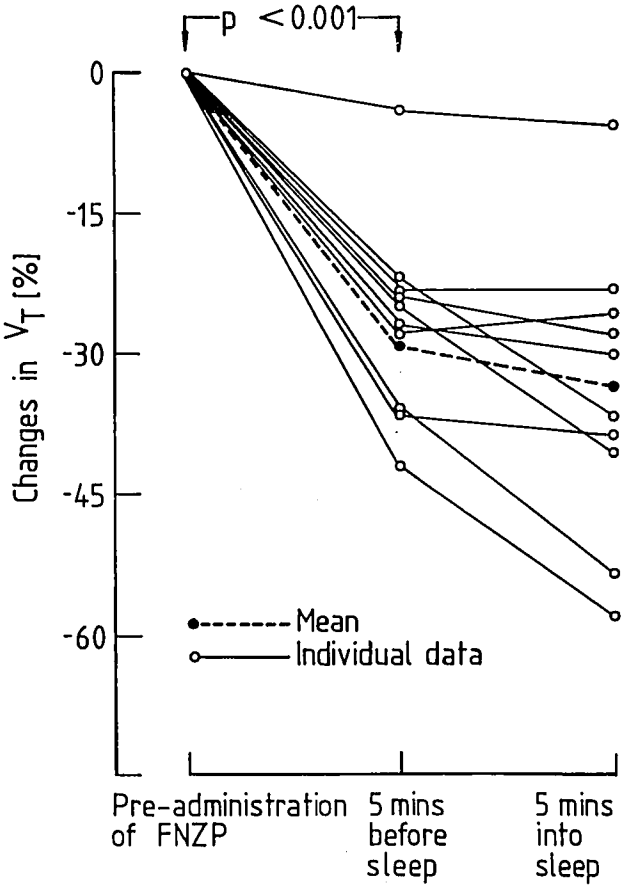

FIG. 1. Individual and mean percentage changes in V_T before administration of flunitrazepam (FNZP), 5 min before and 5 min after the beginning of sleep.

humans, a more profound respiratory depression would be expected after benzodiazepines in patients with impaired thoracic muscle strength, such as high epidural anesthesia or quadriplegia.

The respiratory depression after FNZP administered orally in children closely resembles that observed after an intravenous injection of midazolam in adults,[18] except that the significant increase in respiratory rate with iv midazolam did not occur in our study.

This study validates the use of a noninvasive method to measure respiratory variables in spontaneously breathing children and will provide more precise detection of ventilatory effects of drugs than can be achieved with the intrusive methods commonly utilized.[7,8] Calibration of this relatively simple respiratory monitoring device was accurate and not difficult in children in this age range (5.5–9 years old). Our study also demonstrates significant changes in respiratory variables occurring after oral administration of a commonly prescribed drug in healthy subjects who usually are left unattended while being under the effect of the drug. This contrasts with the opinion that orally administered benzodiazepines are generally devoid of respiratory effects.[19]

The absence of a control group in order to compare our results after FNZP with similar respiratory data under natural sleep could appear as a deficit to our study. However, the respiratory changes induced by FNZP are different than those observed during sleep where V_T remains stable and the increase in RC/V_T is not related to a decreased abdominal contribution to V_T.[20]

Our results confirm the data of a recent controlled study on the influence of another benzodiazepine, midazolam.[18] Perhaps a smaller dose of FNZP would have produced comparable respiratory effects because it has been demonstrated that the ventilatory effects of benzodiazepine are not directly related to dose.[21] Because the respiratory effects of other premedication agents have not been studied with a noninvasive method, our data cannot be compared with others in the literature. Nevertheless, opiates administered alone or in combi-

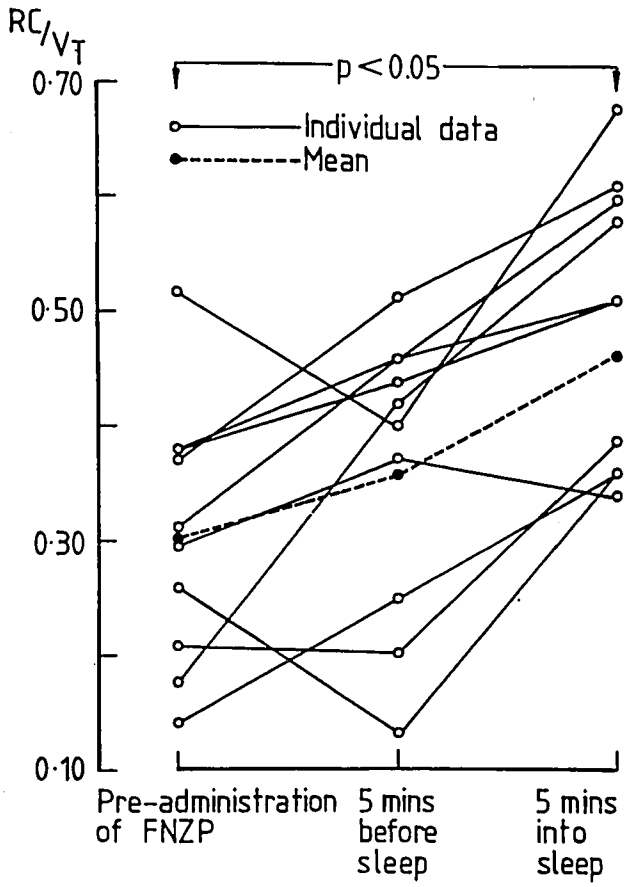

FIG. 2. Individual and mean changes in RC/V_T before administration of flunitrazepam (FNZP), 5 min before and 5 min after the beginning of sleep.

nation with some barbiturates may have even more dramatic effects on respiration and could be dangerous when prescribed to sedate patients who are not watched closely after administration of the drug.

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Emergency Coronary Artery Bypass Surgery Following Intracoronary Streptokinase

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Acute myocardial infarction is associated with coronary artery (CA) thrombosis in 80–90% of patients.[1–4] Thrombi can be lysed with intracoronary streptokinase, thus relieving angina, reverting ECG signs of ischemia, and improving left ventricular function.[1,2,5,6] Clot lysis, or percutaneous transluminal coronary recanalization (PCTR) with streptokinase is most effective when performed within 4–6 h after onset of angina.[1,6] Fixed atherosclerotic lesions predispose to CA thrombosis; following acute clot lysis, significant CA occlusion may remain. Combined PCTR and percutaneous transluminal coronary angioplasty (PCTA) has been attempted in several centers.[7–9] Emergency coronary artery bypass grafting (CABG) following PCTA and intracoronary streptokinase may be necessary, but experience with such cases is limited. We describe one such case in which a severe coagulopathy resulted.

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