Respiratory Depression Following Orally Administered Flunitrazepam for Preanesthetic Medication in Children

A. FORSTER, M.D.,* Z. GAMULIN, M.D.,† D. MOREL, M.D.,‡ V. WEISS, M.D.,† J.-CL. ROUGE, M.D.†

Because children fear needles, we advocated preanesthetic sedation by oral or rectal route.1,2 Benzodiazepines can cause respiratory depression3,4 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 (VT) 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 (x ± SD), weighing 24.7 ± 7.7 kg, participated in the study, which was...
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 ($r = 0.985 ± 0.002$, $s = 0.90 ± 0.08$).

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 ($T_i/T_{in}$) 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 (Vₜ), Variation Coefficient for Vₜ, Respiratory Frequency (f), and Minute Volume (Vₐᵥ) Before and at Four Different Periods after Administration of Flunitrazepam, and Per cent Changes of all these Variables from Control (n = 10) (± SD)

<table>
<thead>
<tr>
<th></th>
<th>Before FNZP</th>
<th>5 Min before Falling Asleep</th>
<th>5 Min into Sleep</th>
<th>15 Min into Sleep</th>
<th>30 Min into Sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vₜ (ml)</td>
<td>211 ± 100</td>
<td>144 ± 54</td>
<td>131 ± 31</td>
<td>134 ± 30</td>
<td>127 ± 36</td>
</tr>
<tr>
<td>Per cent change</td>
<td>0</td>
<td>−29 ± 12*</td>
<td>−32 ± 11*</td>
<td>−36 ± 14*</td>
<td>−35 ± 13*</td>
</tr>
<tr>
<td>Variation coefficient for Vₜ</td>
<td>0.48 ± 0.23</td>
<td>0.42 ± 0.45</td>
<td>0.21 ± 0.15†</td>
<td>0.17 ± 0.15*</td>
<td>0.19 ± 0.14*</td>
</tr>
<tr>
<td>f (breath/min)</td>
<td>18 ± 5.4</td>
<td>21.1 ± 2.8</td>
<td>21.1 ± 2.8</td>
<td>21.0 ± 2.6</td>
<td>21.5 ± 2.7</td>
</tr>
<tr>
<td>Vₐᵥ (ml)</td>
<td>3,600 ± 900</td>
<td>2,950 ± 820</td>
<td>2,870 ± 600</td>
<td>2,790 ± 470</td>
<td>2,680 ± 570</td>
</tr>
<tr>
<td>Per cent change</td>
<td>0</td>
<td>−17 ± 15*</td>
<td>−19 ± 15*</td>
<td>−23 ± 14*</td>
<td>−23 ± 12*</td>
</tr>
</tbody>
</table>

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

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

After FNZP, variation coefficient of Vₜ 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 O₂/N₂O), 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 pre-anesthetic 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, Vₜ, Vₐᵥ, and Vₜ/Tₚ did not further decrease with the induction of sleep, T₁/Tₚ, variation coefficient for Vₜ and RC/Vₜ 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 induced by the drug or to a combination of both. The increase in T₁/Tₚ is attributed to an increase in T₁, since Tₚ did not change between the pre- and post-sleep period. The significant decrease in the variation coefficient for Vₜ demonstrates a more regular breathing pattern after FNZP.

The significant increase in RC/Vₜ occurring only after induction of sleep indicates a dramatic change in breathing pattern that is not related to changes in Vₜ or Vₜ/Tₚ, since these two variables had been influenced by FNZP before sleep was induced and then remained stable. There was no correlation between changes in T₁ and RC/Vₜ.

During sleep, since the relative rib cage contribution to tidal volume increased significantly after FNZP, the decrease in Vₜ 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/Vₜ.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 (Vₜ/Tₚ), Respiratory Duty Cycle (T₁/Tₚ), and Thoracic Contribution to Vₜ (RC/Vₜ) Before and at Four Different Periods after Administration of Flunitrazepam and Per cent Changes from Control (n = 10) (± SD)**

<table>
<thead>
<tr>
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<th>30 Min into Sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vₜ/Tₚ (ml/min)</td>
<td>163 ± 45</td>
<td>130 ± 46</td>
<td>113 ± 43</td>
<td>119 ± 32</td>
<td>120 ± 21</td>
</tr>
<tr>
<td>Per cent change</td>
<td>0</td>
<td>−16 ± 17*</td>
<td>−18 ± 22*</td>
<td>−16 ± 20*</td>
<td>−15 ± 23*</td>
</tr>
<tr>
<td>T₁/Tₚ</td>
<td>0.57 ± 0.02</td>
<td>0.38 ± 0.05</td>
<td>0.46 ± 0.14</td>
<td>0.41 ± 0.12</td>
<td>0.39 ± 0.11</td>
</tr>
<tr>
<td>Per cent change</td>
<td>0</td>
<td>+9 ± 11</td>
<td>+26 ± 34*</td>
<td>+12 ± 30*</td>
<td>+66 ± 29</td>
</tr>
<tr>
<td>RC/Vₜ</td>
<td>0.50 ± 0.11</td>
<td>0.36 ± 0.13</td>
<td>0.46 ± 0.11*</td>
<td>0.46 ± 0.19*</td>
<td>0.47 ± 0.18</td>
</tr>
<tr>
<td>Per cent change</td>
<td>0</td>
<td>+30 ± 56</td>
<td>+64 ± 77*</td>
<td>+63 ± 79*</td>
<td>+65 ± 77*</td>
</tr>
</tbody>
</table>

* P < 0.05.  † P < 0.01.
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 𝑉ₜ remains stable and the increase in 𝑅𝐶/𝑉ₜ is
not related to a decreased abdominal contribution
to 𝑉ₜ.²⁰
Our results confirm the data of a recent controlled
study on the influence of another benzodiazepine, mid-
azolam.¹⁸ Perhaps a smaller dose of FNZP would have
produced comparable respiratory effects because it has
been demonstrated that the ventilatory effects of ben-
zodiazepine 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. 1. Individual and mean percentage changes in 𝑉ₜ 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 im-
paired 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 detec-
tion of ventilatory effects of drugs than can be achieved
with the intrusive methods commonly utilized.⁷,⁸ Calib-
ration 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

Fig. 2. Individual and mean changes in 𝑅𝐶/𝑉ₜ before adminis-
tration 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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REFERENCES

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.1–9 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.