

Title : COMPARATIVE RESPIRATORY EFFECTS OF MIDAZOLAM AND DIAZEPAM

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Introduction. Midazolam is a short acting, water soluble benzodiazepine with a brief half-life. Its efficacy for induction of anesthesia has been demonstrated (1). The respiratory effects of this drug have not been studied so far. The purpose of this investigation was to examine if midazolam induces respiratory depression in healthy subjects. Comparison of the respiratory effects of this new compound was obtained with diazepam.

Methods. Eight volunteers, four males and four females, were studied. Their mean age was 30 years, mean weight 61.5 kg. Informed consent was obtained and the committee for ethics in clinical research of our institution approved this study. Each subject was studied twice : once under midazolam (0.15 mg/kg), once under diazepam (0.3 mg/kg). Each experiment was done at least ten days apart. Electrocardiogram, blood pressure measured through a radial catheter, end-tidal PCO_2 ($P_A CO_2$), tidal volume and respiratory frequency were continuously recorded on a polygraph. After a thirty minutes rest period in supine position, a control ventilatory response to carbon dioxide using Read's rebreathing method was measured (2). Simultaneously, the airway was occluded for 0.1 sec at end-expiration, at several $P_A CO_2$ levels (3), in order to measure mouth occlusion pressure ($P_{0.1}$). The same measurements of the respiratory response were done 4 minutes after the intravenous injection over 15 seconds of one of the two drugs tested. The ventilatory and the mouth occlusion pressure responses to CO_2 were expressed as the slope of the linear correlation between ventilation or occlusion pressure against $P_A CO_2$ during rebreathing. The paired Students t-test was used for statistical comparison of the control slope and the slope after injection of the drug for the same subject.

Results. The results are summarized in table 1. The control slopes for the ventilatory response as well as for the mouth occlusion pressure response to CO_2 are steeper than the slopes after injection of midazolam or diazepam, with the exception of subject No 4 for midazolam. The difference between the control slopes and the slopes after injection of the drugs is significant ($p < 0.05$). However, there is no statistical difference between the midazolam and the

diazepam slopes. We were not able to obtain all the data for subjects No 1, 2 and 7 for technical reasons or because hypercapnia was not well tolerated.

Table 1 : ventilatory and mouth occlusion pressure responses to CO_2 .

| Subject no | Slope $\Delta V_E / \Delta P_A CO_2$ L.min ⁻¹ /mmHg | | | | Slope $\Delta P_{0.1} / \Delta P_A CO_2$ cmH ₂ O/mmHg | | | |
|------------|---|------|------|------|---|------|------|------|
| | C | M | C | D | C | M | C | D |
| 1 | 2.39 | 1.28 | 2.25 | 1.72 | - | - | 0.52 | 0.08 |
| 2 | 3.23 | 1.50 | 1.87 | 1.32 | - | - | - | - |
| 3 | 2.63 | 1.40 | 2.40 | 1.70 | 0.75 | 0.25 | 0.44 | 0.50 |
| 4 | 1.80 | 1.84 | 1.87 | 1.84 | 0.54 | 0.40 | 0.40 | 0.27 |
| 5 | 1.92 | 1.30 | 2.83 | 0.76 | 0.38 | 0.18 | 0.59 | 0.18 |
| 6 | 1.13 | 1.04 | 1.13 | 0.75 | 0.56 | 0.29 | 0.29 | 0.21 |
| 7 | - | - | 1.49 | 0.98 | 0.59 | 0.42 | 1.12 | 0.59 |
| 8 | 1.88 | 1.20 | 1.87 | 1.27 | 0.44 | 0.23 | 0.98 | 0.18 |
| n | 7 | 7 | 8 | 8 | 6 | 6 | 7 | 7 |
| Mean | 2.14 | 1.45 | 1.95 | 1.28 | 0.54 | 0.30 | 0.87 | 0.28 |
| SEM | 0.28 | 0.13 | 0.21 | 0.14 | 0.05 | 0.04 | 0.12 | 0.07 |
| p | < 0.05 | | | | < 0.05 | | | |

C : control slope
slope after injection of the drug : M : Midazolam
D : Diazepam

Discussion. The results of the present study demonstrate that an intravenous injection of 0.15 mg/kg of midazolam or 0.3 mg/kg of diazepam produces a comparable and significant respiratory depression in healthy volunteers, as measured by two different methods. Whereas the decrease of the ventilatory response to CO_2 after drug injection does not necessarily imply a depression of respiratory centers (4), the parallel decrease of mouth occlusion pressure observed in our study during CO_2 rebreathing indicates that midazolam and diazepam depress the respiratory center output directly (4).

References.

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