

Anesthesiology  
65:348, 1986

## Diazepam Depresses the Ventilatory Response to Carbon Dioxide

*To the Editor:*—In their recent article,<sup>1</sup> Bailey *et al.* once again raise the question of whether diazepam causes significant depression of the hypercarbic ventilatory response. In 1982, we used the dual isohypercapnic method to measure the time course of ventilatory depression after diazepam, 0.4 mg/kg iv, and found that the slope of the ventilatory response to hypercarbia was significantly depressed for at least 25 min.<sup>2</sup> In a second study,<sup>3</sup> we used Read's rebreathing method and found that diazepam, 0.4 mg/kg, reduces the slope of the ventilatory response to carbon dioxide from 2.41 to 1.30 l·min<sup>-1</sup>·mmHg<sup>-1</sup> ( $P < 0.001$ ) within 5 min.

Why, then, were Bailey and his colleagues unable to demonstrate this statistically and clinically significant depression of ventilatory drive? First, their diazepam dose (0.1 mg/kg) is relatively low for young, healthy volunteers. In fact, recommended doses for endoscopic procedures range from 0.15 to 0.3 mg/kg. Clearly, larger doses should be used in fit, young volunteers to predict the effect of clinical doses in elderly or frail patients, who may be more susceptible to diazepam's adverse effects.<sup>4</sup> A second consideration is the statistical analysis of the results. While the authors are to be commended for avoiding the "multiple *t*-test trap," their use of Bonferroni adjusted *t* tests may have been overly conservative. Indeed, had the authors used a more appropriate test, such as the Newman-Keuls or Dunnett's test, the *P* value for ventilatory depression at 5 min would almost certainly have decreased from 0.0508 to less than 0.05. Then, of course, the authors would have written a different paper: "Diazepam decreases the ventilatory response to carbon dioxide." This is but another example of "absence of evidence is not evidence of absence."<sup>5</sup>

Before the authors may state, "The results of this study demonstrate that diazepam, as a 0.1 mg/kg iv bolus, did not depress the ventilatory response to CO<sub>2</sub> . . .,"<sup>1</sup> they must perform a power analysis to determine the probability of a type II error. Because such an analysis would certainly show that this probability is high (in view of the *P* value of 0.0508), I believe that Bailey's study is best interpreted as confirming our earlier findings of ventilatory depression after iv diazepam.

JEFFREY B. GROSS, M.D.

Department of Anesthesia (112)

Philadelphia Veterans Administration Medical Center

University and Woodland Avenues

Philadelphia, Pennsylvania 19104

## REFERENCES

1. Bailey PL, Andriano KP, Goldman M, Stanley TH, Pace NL: Variability of the respiratory response to diazepam. *ANESTHESIOLOGY* 64:460-465, 1986
2. Gross JB, Smith L, Smith TC: Time course of ventilatory response to carbon dioxide after intravenous diazepam. *ANESTHESIOLOGY* 57:18-21, 1982
3. Spaulding BC, Choi SD, Gross JB, Apfelbaum JL, Broderson H: The effect of physostigmine on diazepam-induced ventilatory depression: A double-blind study. *ANESTHESIOLOGY* 61:551-554, 1984
4. Kanto J, Maenpaa M, Mantyla R, Sellman R, Valovirta E: Effect of age on the pharmacokinetics of diazepam given in conjunction with spinal anesthesia. *ANESTHESIOLOGY* 51:154-159, 1979
5. Hartung J, Cottrell JE, Giffin JP: Absence of evidence is not evidence of absence. *ANESTHESIOLOGY* 58:298-300, 1983

(Accepted for publication June 9, 1986.)

Anesthesiology  
65:348-349, 1986

*In reply:*—Dr. Gross questions our findings and interpretation in the article, "Variability of the respiratory response to diazepam." He makes two suggestions in support of his contention that diazepam does depress the ventilatory response to carbon dioxide.

First, Dr. Gross suggests our dose (0.1 mg/kg) was too low and that larger doses (0.4 mg/kg) should be used. Our intention was not to study anesthetic induction doses of diazepam, but rather the sedative doses frequently used for local standby or regional anesthesia or as supplements

in general anesthesia. We, therefore, thought a study of the effects of 0.1 mg/kg to be clinically relevant. Nevertheless, others have also found that higher doses of diazepam (0.15 and 0.29 mg/kg iv) do not produce significant depression of the ventilatory response to CO<sub>2</sub>.<sup>1,2</sup> Interestingly, variability of response is also seen in some subjects in those studies.

Dr. Gross also questions our statistical approach. He is incorrect in his assumption that we used Bonferroni adjusted paired *t* tests as the basis for our statement that at