

## CORRESPONDENCE

Anesthesiology  
55:82, 1981

### The Effective Dose of Midazolam

*To the Editor:* Midazolam maleate is a water-soluble benzodiazepine used for intravenous anesthesia induction. In reviewing the initial paper by Fragen and co-workers,<sup>1</sup> a problem emerges which has plagued midazolam research, *i.e.*, what is the effective dose? Fragen stated, "based upon unpublished studies, 0.15 mg/kg is the suggested induction dose" of midazolam; however, his results revealed that the actual induction dose was 0.177 mg/kg (mean weight = 68.4 kg and mean induction dose 12.1 mg).<sup>1</sup> We subsequently used as an induction dose 0.2 mg/kg.<sup>2</sup> Dundee stated that the variation in individual response to midazolam "places limits on its use as an induction agent."<sup>3</sup> It is presently our feeling that at least part of the observed midazolam induction failures and clinical impressions of great variability are because of inadequate dosing. For this reason, we have examined with probit analysis our earlier published data<sup>2</sup> to predict an ED<sub>50</sub> and ED<sub>99</sub> for midazolam.

The data base comes from 30 unpremedicated healthy (ASA I-II) patients. Three groups of ten patients were given induction dosages of 0.1, 0.15, and 0.2 mg/kg of midazolam maleate administered over 15 s. Induction was defined as loss of lid reflex and failure to respond to oral command. In the three groups induction occurred in three, five, and ten patients of the 0.1, 0.15, and 0.2 mg/kg groups, respectively. Probit analysis, based on methodology by Finney,<sup>4</sup> was performed and table 1 was generated predicting the effective dosages for midazolam along with 95 per cent fiducial limits. Note that the ED<sub>50</sub> is 0.13 mg/kg, ED<sub>95</sub> is 0.20 mg/kg, and ED<sub>99</sub> 0.23 mg/kg. It would appear from these data that to be certain of induction in all patients, >0.23 mg/kg of midazolam should be administered. That dosages this high may be safely administered has recently been shown by Melvin and co-workers who infused dosages of midazolam up to 0.6 mg/kg.<sup>5</sup> Because of the narrow range of dosages and because all patients in the 0.2 mg/kg group were successfully induced, the probit analysis is subject to some error and has wide fiducial limits. Nevertheless, these

Anesthesiology  
55:82-83, 1981

TABLE 1. Probit Analysis of Midazolam Induction Dosages in Healthy Unpremedicated Patients

| ED | Dose (mg/kg) | 95 Per Cent Fiducial Limits (mg/kg) |
|----|--------------|-------------------------------------|
| 1  | 0.03         | 0-0.08                              |
| 5  | 0.06         | 0-0.10                              |
| 25 | 0.10         | 0.03-0.13                           |
| 50 | 0.13         | 0.10-0.16                           |
| 75 | 0.16         | 0.14-0.22                           |
| 95 | 0.20         | 0.17-0.33                           |
| 99 | 0.23         | 0.19-0.42                           |

data may explain the failure of induction seen with lower dosages of midazolam<sup>1-3</sup> and could account for the clinical impression that there is great individual variation to the drug.

J. G. REVES, M.D.  
*Professor*

IGOR KISSIN, M.D.  
*Associate Professor*  
*Department of Anesthesiology*

L. R. SMITH, M.A.  
*Research Support Service*  
*University of Alabama*  
*School of Medicine*  
*Birmingham, Alabama 35294*

#### REFERENCES

1. Fragen RJ, Gahl F, Caldwell N: A water-soluble benzodiazepine, Ro-21 3981, for induction of anesthesia. *ANESTHESIOLOGY* 49:41-43, 1978
2. Reves JG, Corsen G, Holcomb C: Comparison of two benzodiazepines for anaesthesia induction: Midazolam and diazepam. *Can Anaesth Soc J* 25:211-214, 1978
3. Dundee JW: New I.V. Anaesthetics. *Br J Anaesth* 51:641-648, 1979
4. Finney DJ: *Statistical Method in Biological Assay*. London. Hefner, 1964, pp 437-467
5. Melvin MA, Johnson BM, Quasha AL, et al: Induction of anesthesia with midazolam decreases MAC in man. *ANESTHESIOLOGY* 53:S10, 1980

(Accepted for publication December 30, 1980.)

### Uvular Edema without Endotracheal Intubation

*To the Editor:*—Recently, two cases of uvular edema following general endotracheal anesthesia have been

reported.<sup>1,2</sup> In each, the proposed mechanism of this complication was trapping of the uvula between an