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A Really Long Sufentanil Infusion

To the Editor:—We were reading the September issue of ANES-THESIOLOGY when, by a cruel quirk of fate, Hurricane Emily suddenly snatched it from our white-knuckled grip. After a titanic struggle against the forces of nature and many near-death experiences, we, regrettably, were able to salvage only a single page (13A), containing part of the table of contents. While awaiting fresh ANESTHESIOLOGY copies to restock our soggy libraries, we wonder whether Albanese and colleagues had any unusual or unique complications when "sufentanil in a dose of 1 mg/kg administered over 6 months" was given to their unique subset of head trauma patients requiring long-term intracranial pressure monitoring.

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Editor's Note

No, Albanese and colleagues were not breaking new therapeutic ground, and an erratum in this issue of the Journal (page 250) correctly identifies this dose as 1 μg/kg over 6 min.

Does Flumazenil Antagonize Midazolam-induced Depression of Ventilatory Response to Hypoxia?

To the Editor:—In their investigation of the effects of flumazenil on hypoxic respiratory drive following midazolam, Blouin et al.[1] conclude that "flumazenil increases ventilation throughout a wide range of conditions . . . [and] may be useful in the treatment of benzodiazepine-induced ventilatory depression." The authors normalized the hypoxic drive slope data to the baseline premidazolam administration before data analysis, presumably to minimize the effect of day-to-day variability in the slope. We question whether this manipulation of the data was appropriate, because (as stated in the results) there was no significant difference between the baseline slopes, and these slopes were within the expected ranges reported in the literature.

The authors analyzed the slope data using analysis of variance with repeated measures and stated: "When all post-study drug determinations were considered, slopes were significantly greater after flumazenil than after placebo ($P < 0.05$); however, *post hoc* testing could not attribute this difference to any particular observation times." The latter statement suggested that only marginal overall differences were found between the two treatment groups. We, therefore, calculated the *actual* mean slope data using the baseline slopes (1.04 and 1.45 $l \cdot min^{-1} \cdot \%Sp_{O_2}^{-1}$) and the fractions of baseline

from their figure 2. These data are presented in table 1 and suggest that the difference between the groups might not have been statistically significant had the authors analyzed the actual (rather than the normalized) data. In fact, the mean respiratory slopes of placebo patients returned to above their baseline values. Given the small sample size (n = 12), presentation of the actual data would have been more useful than the illustration showing fractions of baseline values. Examination of the real data of drug effect over time in each patient would have allowed more substantive comparison with other studies,[2,3] reporting the effects of flumazenil on respiratory drive.

Blouin et al. also commented that, in contrast to their present study, the methods used in our previous work[2] may not have controlled for the level of hypercarbic stimulation during the hypoxic challenge. We wish to clarify the authors' misunderstanding of our methodology. Our methods clearly ensured against a hypercarbic state, because the patient's $P_{ET_{CO_2}}$ was kept in the normocarbic range (± 1 mmHg). In contrast, hypercarbic and hypoxic stimulation are likely to have additive effects on the measured tidal volume and/or respiratory rate with the methods used by Blouin et al. We described the methodologic differences between the two studies in a letter to the editor[4] published in 1990.

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Table 1. Mean Slope ($1 \cdot min^{-1} \cdot \% \, Sp_{O_2}^{-1}$) of the Hypoxic Ventilatory Response

	Baseline	After Midazolam	Minutes after Study Drug				
			3	30	60	120	180
Saline	1.45	0.94	1.17	1.05	1.05	1.30	1.60
Flumazenil	1.04	0.55	1.20	1.05	0.93	1.20	1.15

Values calculated using the actual baseline times the fraction of baseline taken from Blouin *et al.*'s figure 2.

Flumazenil may have a transient benefit in the reversal of benzodiazepine-induced respiratory depression; however, these changes may not be attributable simply to the specific respiratory antagonistic effects of flumazenil. The mechanisms responsible for the respiratory changes reported by Blouin *et al.* may be influenced by other physiologic factors (*e.g.*, enhanced wakefulness) that have been shown to increase central respiratory drive.[5] If so, it would explain both why the increase in respiratory drive seen in the flumazenil group was observed only for a brief period (≤ 30 min) and why repeated-measures analysis of variance, designed to examine changes over time, was unable to assign the statistical significance between the groups to a particular time.

Given the fact that other studies have reported varying effects of flumazenil on respiratory drive after benzodiazepine-induced sedation, we believe further investigation is required to substantiate the authors' conclusion that "flumazenil increases ventilation throughout a wide range of conditions of chemical drive."

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In Reply:—In their critique of our investigation of the effects of flumazenil on the hypoxic ventilatory response following midazolam,[1] Torjman *et al.* raise several issues that we believe deserve clarification. First, the hypoxic ventilatory response slope data were normalized to allow meaningful conclusions to be drawn despite the known day-to-day variability in baseline ventilatory drive[2]; in some subjects, this exceeded $2 \, 1 \cdot min^{-1} \cdot \% Sp_{O_2}^{-1}$. Without normalization, this variability would have rendered between-treatment comparisons meaningless. In addition, insignificant differences between *mean* flumazenil and placebo baseline slopes should not be interpreted as an indication that values did not differ from day to day.

Second, in questioning our conclusion that "flumazenil was associated with a greater increase in hypoxic ventilatory response than was a placebo," Torjman *et al.* "back-calculated" the "actual" mean slope data, multiplying baseline values by the normalized values shown in the figures. This fails to recognize an important mathematical principle: The arithmetic mean of a series of ratios (*i.e.*, normalized values) may differ appreciably from the ratio of the arithmetic means. For example, the actual mean data, presented in table 1, show that the slope of the hypoxic ventilatory response 180 min after placebo was 1.27 rather than $1.60 \, 1 \cdot min^{-1} \cdot \% Sp_{O_2}^{-1}$, as indicated by Torjman *et al.* Furthermore, as shown in table 1, the mean (non-normalized)