Anesthesiology
60:264–265, 1984

Effect of Brain Levels of Drugs on the Validity of Techniques Measuring Ventilatory Depression

To the Editor:—Gross *et al.* utilized "a dual isohypercapnic technique" for measuring the ventilatory response to CO_2 of intravenous agents used for sedation and induction of anesthesia.[1,2] These authors criticized the use of a rebreathing technique to measure the slope of the CO_2 response curve because it ". . . systematically overestimated the slope due to a waning drug effect. . . ."[2] Ideally, the brain concentration of an agent parallels respiratory depression it produces and should not be a variable when comparing the ventilatory response at two different CO_2 levels. In the case of fentanyl, the brain concentration, as reflected by the cisternal cerebrospinal fluid concentration, does parallel the degree of ventilatory depression in the dog.[3]

The dual isohypercapnic technique is also open to criticism in that the brain concentrations of the study drugs are different at the times compared because of the effect of CO_2 both on cerebral blood flow (CBF) and on the relative concentrations of the active unionized forms of acidic and basic drugs (Henderson–Hasselbalch equation). Finck *et al.*[4] and Ainslie *et al.*[5] have shown that the time to peak effect, the brain half-life, and the absolute brain levels of morphine and fentanyl, respectively, are markedly affected by the CO_2 tension.

Thiopental is a weak acid. Respiratory acidosis will increase the percentage of the unionized fraction so that more of the active form of the drug is available. Hypercarbia will increase CBF and provide for faster delivery of the thiopental to the brain. The brain thiopental concentration 1 min after a rapid iv injection will be greater at a CO_2 = 60 mmHg than the brain thiopental concentration 1 min after iv injection at a CO_2 = 49 mmHg. The $\dot{V}_E$ at CO_2 = 60 will be more depressed by thiopental than the $\dot{V}_E$ at a CO_2 = 49 at any given time during induction. $\Delta\dot{V}_E = \dot{V}_E\ (CO_2 = 60) - \dot{V}_E\ (CO_2 = 49)$ will be smaller in this study than if the brain concentrations were equal at both CO_2 tensions. The slope of the CO_2 response curve $\Delta\dot{V}_E/\Delta P_{CO_2}$ will be less. Thus, the dual isohypercapnic technique *overestimates* the degree of ventilatory depression during induction.

Similarly, emergence from anesthesia will be faster at a CO_2 = 60 than at a CO_2 = 49 because cardiac output and CBF will be greater. The brain levels at CO_2 = 60 on emergence will be less than the brain levels at CO_2 = 49 at that same time. $\dot{V}_E$ at CO_2 = 60 will reflect less anesthetic depression than if the brain levels were equal at the two end-tidal CO_2 concentrations. Thus, on emergence the dual isohypercapnic technique *underestimates* the degree of ventilatory depression. The time-dependent awareness scores reflect a faster induction and a faster emergence at a CO_2 = 60 than at CO_2 = 49 and support this line of reasoning.[1]

With midazolam and diazepam, CBF will be the primary determinant of differences in brain levels at any particular time after injection. Even with fentanyl, where the *p*H changes should oppose the CBF effect, there are markedly different brain levels of drug at different CO_2 tensions.[5]

What is the clinical significance of the slope of the CO_2 response curve when in fact most patients who are induced with a $CO_2 \leq 40$ mmHg become apneic from thiopental 3.5 mg · kg^{-1} or midazolam 0.2 mg · kg^{-1}?[6] Does the apnea persist until the brain level of the drug falls or does the drug shift the CO_2 response curve so that apnea persists until CO_2 exceeds a particular threshold tension? Because no apnea was observed by Gross *et al.* at end-tidal CO_2 tensions greater than 43 mmHg,[1] the most significant factor governing a return of spontaneous ventilation appears to be CO_2 accumulation to a particular threshold tension.

This conclusion influences airway management during mask spontaneous breathing techniques and is an arguement for preoxygenation. Sufficient oxygen ought to be present in the functional residual capacity to permit CO_2 accumulation during an apneic period without interposing controlled ventilation.

In summary, while the dual isohypercapnic technique is an improvement over rebreathing methods, it too has its limitations. However, the conclusions drawn by Gross *et al.* are not invalid, just understated, because on emergence their technique underestimates the degree of ventilatory depression.

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(Accepted for publication August 26, 1983.)

Anesthesiology
60:265, 1984

Malignant Hyperthermia: Platelet Bioassay

To the Editor:—Giger and Kaplan have concluded that our platelet bioassay is not a reliable test for identifying malignant-hyperthermia–susceptible individuals.[1] We wish to refute the statement and to challenge the methods by which they reached their negative conclusions. In passing, we should add that while we have had the pleasure of supplying Dr. Kaplan with bioassay results and personal information about our technique, we had no prior knowledge that Dr. Kaplan planned to publish a rebuttal of our method.

Platelets are a muscle analogue with similarities of metabolism and contractile apparatus. Few workers in the field seem to be aware of the obsessive technical care that is necessary throughout every stage between collection of the blood and extraction of the nucleotides. Platelets are tender morsels that must be treated with every physical consideration at all times if their contractile apparatus are to remain undamaged. Giger and Kaplans' work is flawed because:

1. Freezing the platelet pellet directly after incubation results in variable amounts of cold stress. This stress is expressed in nucleotide metabolism and in deterioration of the internal contractile system and confounds interpretation of the data. The stress appears to be time related, but no provision was made for strict control of the time of exposure to cold.

2. They deviated from accepted standards of laboratory technique by omission of a nonmetabolizable internal standard to alert them to the presence of technical errors. Errors of this type occurred at the sonication step and were observed when 2-deoxyuridine was added as internal standard to their methods. Such a result would fail our quality control criteria by a wide margin. However, in our technique, the internal standard indicated the absence of comparable errors.

3. We have also checked the individual steps of washing with EDTA, sonication, freezing, and centrifugation as described by Giger and Kaplan and found that they produced large artifactual decreases in ATP in normal platelets to render them indistinguishable from MH platelets.

4. We carefully replicated Giger and Kaplans' methods in our laboratory and found a decrease in ATP, which was twice as large as that reported in their article.

We therefore conclude that their method for managing the platelets is too harsh to be able to distinguish between the metabolic behavior of normal and MH platelets.

In view of these criticisms, we find that the method of Giger and Kaplan is not a reliable evaluation of the platelet as a model for studying malignant hyperthermia and that their negative conclusions in this regard are unwarranted. A description of a large series of commonly committed errors in various laboratories in the United States and overseas is included in our forthcoming paper already accepted for publication to *Acta Anaesthesiologica Scandinavica.*

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(Accepted for publication August 26, 1983.)