Sevoflurane MAC and Cerebellar Cyclic GMP

To the Editor.—The article by Ichinose et al.1 was interesting and enlightening. The sevoflurane minimum alveolar concentration (MAC) reduction effect, in a dose-dependent manner, by acute administration of the neuronal nitric oxide synthase (NOS) inhibitor, 7-nitroindazole (7-NI), is consistent with our previous findings.1,3 This suggests a role for the nitric oxide signaling pathway in MAC reduction and in the mechanisms mediating consciousness. The additional observation by the authors that MAC of sevoflurane was not reduced in mice after long-term administration of 7-NI is in agreement with other studies.1,3 However, we would like to address some concerns regarding the interpretation of their data. In their conclusion and implied by their title, Ichinose et al.1 state the possibility that sevoflurane MAC reduction, during long-term administration of 7-NI (= 3 days), was not mediated through the nitric oxide/soluble guanylate cyclase-cyclic guanosine monophosphate (cGMP) pathway. This was based on the fact that long-term administration of 7-NI did not reduce sevoflurane MAC, despite a reduction in cGMP production. The authors cannot speculate on the role of cGMP in the mechanism of sevoflurane MAC reduction when they did not show any MAC reduction during long-term administration of 7-NI. In contrast, the sevoflurane MAC reduction obtained after acute administration of 7-NI suggests a correlation between sevoflurane MAC reduction and decrease in cGMP production. The fact that long-term administration of 7-NI failed to reduce sevoflurane MAC could be related to cGMP-independent compensatory mechanisms that mediate nociception (as suggested by the authors) or excitatory cGMP-independent compensatory mechanisms that stimulate consciousness centers, or both. Indeed, there is a precedent for heterologous compensation of nitric oxide inhibitor-induced MAC reduction when the inhibitor is administered for prolonged periods and in studies performed in neuronal nitric oxide synthase knockout mice.4,6

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In Reply.—I thank Drs. Haddad, Johns, and Pajewski for their interest and valuable comments regarding our recent article.2 I have to admit that our speculation regarding the role of cyclic guanosine monophosphate (cGMP) in the mechanism of sevoflurane minimum alveolar concentration (MAC) reduction is based on rather weak evidence. I also agree with Haddad et al. regarding the possible development of compensatory mechanisms as we described in our discussion. However, we would like to point out that, although we found a correlation between the reduction of cGMP and sevoflurane MAC after acute 7-NI, there was a marked difference in the magnitude of reduction of the two parameters. Together with the dissociation of the two parameters after long-term 7-NI administration, these observations may suggest that the relation between cGMP and MAC is not linear. It is conceivable that only a small amount of nitric oxide or cGMP, or both, is necessary to maintain normal nociception. If this is the case, variation of nitric oxide synthase (NOS) activity or cGMP concentrations, or both, in the brain may not closely correlate with MAC of volatile anesthetics. I would also like to point out the limitation of the studies of our own1 and others4 that tested the effects of NOS inhibitors on anesthetic potencies and NOS activities. In two studies in which cGMP

References

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INTERRGENT CPAP during General Anesthesia

To the Editor.—The interesting article by Bratzke et al. uses an unusual measure of ventilatory efficiency: partial pressure of arterial carbon dioxide (P_a CO_2) /minute ventilation. This measure is adequate only during very restricted circumstances. As the authors point out, when comparing two modes of ventilation in rapid succession, an increase in the ratio equates with more efficient ventilation. However, the comparison assumes that carbon dioxide output (V CO_2) and P_a CO_2 are “clamped.” If cellular carbon dioxide production were to increase, say by 10%, unchanged ventilation would cause P_a CO_2 to increase by 10%. The ratio would then also increase by 10%, but this would not signify greater efficiency. In order not to be misleading, this index can only apply to changes in minute ventilation at constant P_a CO_2.

For all-around applicability, an index of ventilatory efficiency must always compare expired and blood gas partial pressure of carbon dioxide (P CO_2), the basis of the dead space concept. The nearest index to the one the authors have used here, i.e., one that increases with increasing efficiency, would be (1 - V D / V L), which is obtained from mixed expired P CO_2 divided by P a CO_2. It is the same thing as alveolar ventilation divided by total ventilation.

A second point about the article is that the assumption that anatomic dead space was constant may not be correct. Increases in end-inspiratory pause of a fraction of a second can reduce anatomic dead space significantly (L. Nordstrom, personal communication, November, 1998), and, therefore, the long continuous positive airway pressure (CPAP) periods used by Bratzke et al. may markedly reduce this dead space, contributing considerably to the increase in alveolar ventilation noted.

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