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## Multiples of Minimal Alveolar Concentration of Volatile Agents Are Not Necessarily Equipotent

To the Editor:

I read with interest the article titled, "Isoflurane Causes Greater Neurodegeneration Than an Equivalent Exposure of Sevoflurane in the Developing Brain of Neonatal Mice," in the June 2010 issue of *ANESTHESIOLOGY* by Liang *et al.*<sup>1</sup> The entire premise of the article is based on the assumption that 0.5 MAC of isoflurane is equipotent to 0.5 MAC of sevoflurane. Furthermore, the authors not only assume that these partial MAC values are equipotent for motion on surgical stimulation (the original comparative endpoint for MAC in humans), but that they are also equipotent for neurodegeneration in the developing mouse brain. I would submit that neither assumption is valid.

As early as 1970, Waud and Waud<sup>2</sup> published an editorial in *ANESTHESIOLOGY* explaining that MAC is only one point on an entire dose-response curve. This editorial inspired follow-up letters to the editor in support.<sup>3-5</sup> I can find no evidence in the literature that, to date, the shape of the entire dose-response curve for percentages of patients showing motion on stimulation *versus* end-tidal concentration for any volatile agent has been established. For example, the percentage of patients who will move on surgical stimulation under 0.5 MAC *versus* 1.5 MAC, etc., remains unknown. There is certainly no assurance that the dose-response curve for any volatile agent will parallel any other dose-response curve for the volatile agents. Moreover, MAC is really a median minimal alveolar concentration, and there is no assurance that any specific MAC value holds true for any given patient or mouse.

In addition to the unverified assumption that partial MAC values are equipotent, even for percentages of patients moving with surgical stimulation, the authors go on to make the assumption that partial MAC values are also equipotent for an entirely different dose-response curve (neurodegeneration in the developing mouse brain *vs.* alveolar concentration). Even full MAC values for motion cannot be assumed to be equipotent between agents for a totally different dose-response curve. Likewise, if the equipotency of partial MAC values cannot be assumed for the original dose-response

curve, it is at least equally invalid to assume equipotency of those partial MAC values when they are transferred to a totally different dose-response curve. The authors have not yet established a valid full MAC value for neurodegeneration in their study population. However, even if they did, there is no validity in assuming that partial MAC values for that dose-response curve would be equipotent, unless the authors determined the shape of the entire dose-response curve for each agent tested.

The authors only can assert with validity that, when given 0.5 MAC of isoflurane and 0.5 MAC of sevoflurane, there seems to be greater neurodegeneration in the developing mouse brain with isoflurane. The assertion that the mice have been administered equipotent doses of the two volatile agents can be supported by neither the definition of MAC nor the medical literature to date.

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In Reply:

We thank Dr. Cross for his insightful comments concerning our recent article.<sup>1</sup> Dr. Cross makes several excellent points in regard to the nonlinear dose-response curves and the validity of partial minimum alveolar concentration (MAC) values.

In 1963, Merkel and Eger<sup>2</sup> originated the term MAC, describing it as an "index of comparison" for different anesthetic agents. They defined 1 MAC as the end-tidal concentration of anesthetic that prevents movement in 50% of animals in response to a supramaximal painful stimulus.<sup>2</sup> Subsequently, the use of MAC, to represent "a unifying concept of inhaled anesthetic potency" has grown to incorporate other clinical endpoints, such as MAC awake, MAC intubation, and MAC-BAR (blunt autonomic reflexes).<sup>3,4</sup>

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