Can Minimum Alveolar Concentrations in Immature Rodents Be a Single Number?

To the Editor:

In the March issue of ANESTHESIOLOGY, Istaphanous *et al.*[1] compared the neurotoxic properties of isoflurane, sevoflurane, and desflurane in 7- to 8-day-old mice and found that all three agents cause a similar degree of neuronal cell death in the immature brain. This is at odds with other investigations reporting that sevoflurane has a more favorable neurotoxicity profile than, for example, isoflurane[2–4] or propofol.[5] However, Istaphanous *et al.*[1] recognized that comparative studies require equianalgesic dosing and attempted to establish such a dosing regimen. They administered 0.6 minimum alveolar concentrations (MAC), of each agent for 6 h. MAC was determined by tail clamping after an equilibration period of 15 min, after which the anesthetic concentration was adjusted according to prospectively defined criteria, and the response to tail clamping was reassessed after another 15-min equilibration period. A total of four tail clampings were performed per mouse. Using this methodology, the inspired anesthetic concentration, determined to be MAC for isoflurane, sevoflurane, and desflurane, was 2.7, 5.4, and 12.2, respectively.[1] As the authors pointed out, MAC is age-dependent, so it would have been inappropriate to simply use the published MAC for adult animals.

The authors[1] stated that MAC of isoflurane in 7- to 8-day-old mice agreed well with MAC of isoflurane in 7-day old rats, which had been found previously to be 2.75% atm (atmosphere).[6] We would like to point out that this is only a small part of the story, in that MAC was 2.75% atm only after 1 h of isoflurane anesthesia.[6] After 4 h of anesthesia, the inspired MAC of isoflurane had decreased to 1.21% atm, a 56% decrease.[6] In the same study,[6] the brain concentration of isoflurane after 1 h of isoflurane anesthesia was only 1.9%, indicating that equilibration between inspired and brain partial pressures of isoflurane had not yet occurred.[6] The same is true for the rather insoluble agent desflurane (data not shown), which may come as a surprise. Although we have not done the same experiment using sevoflurane, a central assumption underlying the methodology used by Istaphanous *et al.*, that equilibration between inspired and brain concen-

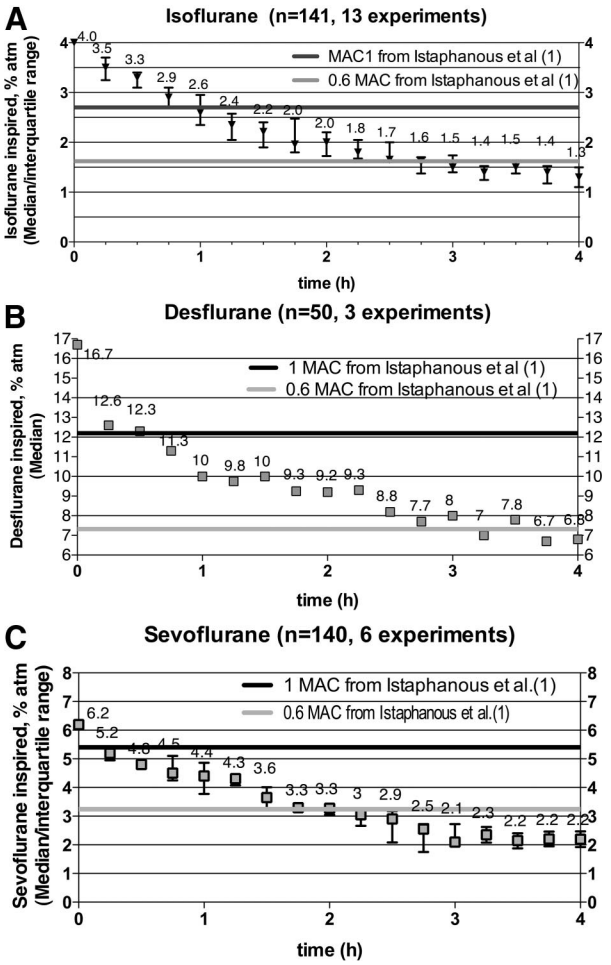

Fig. 1. Seven-day-old rats were anesthetized in groups of at least 10. Tail clamping was performed, and the anesthetic concentration was adjusted, as shown here in table 1. Minimum alveolar concentration (MAC) of isoflurane decreases with increasing duration of anesthesia (*A*). MAC of desflurane decreases with increasing duration of anesthesia (*B*). MAC of sevoflurane decreases with increasing duration of anesthesia (*C*). atm = atmosphere.

Table 1. Protocol for Adjusting Isoflurane, Sevoflurane, and Desflurane to 1 MAC in Postnatal Day 7 Rats

Rats Moving in Response to Tail Clamping (%)	Change in Anesthetic Concentration (%)		
	Isoflurane Start P7: 5%	Sevoflurane Start P7: 7%	Desflurane Start P7: 16%
0	−1.0	−1.4	−2.2
10	−0.8	−1.15	−1.7
20	−0.6	−0.9	−1.0
30	−0.4	−0.6	−0.7
40	−0.2	−0.3	−0.35
50	No change	No change	No change
60	No change	No change	No change
70	+0.1	+0.15	+0.35
80	+0.2	+0.3	+0.70
90	+0.3	+0.5	+1.40
100	+0.5	+0.7	+2.0

MAC = minimum alveolar concentration.

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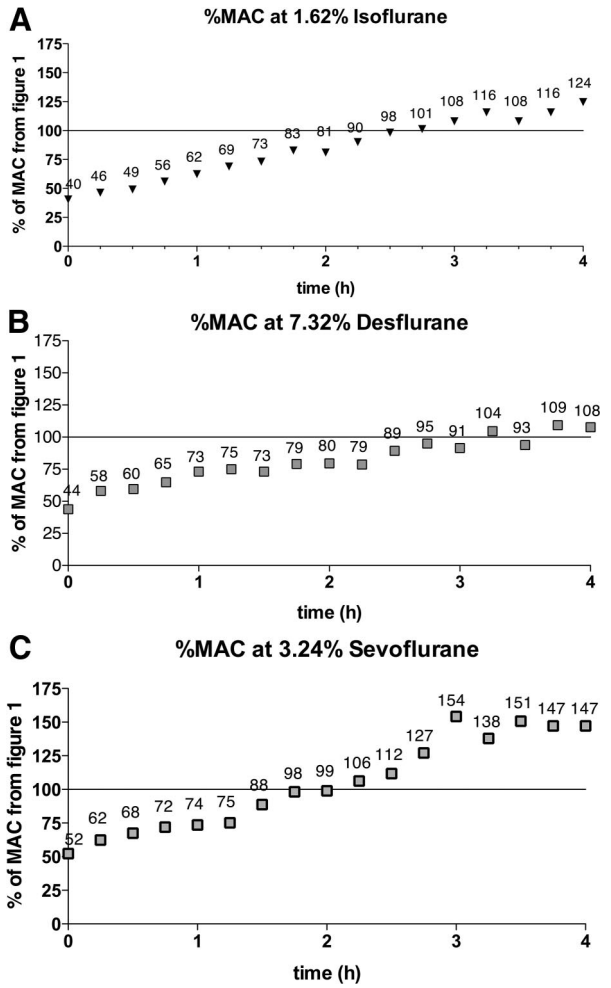

Fig. 2. Percentages of minimum alveolar concentrations (MAC) were calculated using the formula: (0.6 MAC from Istaphanous *et al.*[1]/MAC from figure 1C × 100). The 0.6 MAC of Istaphanous *et al.*[1] expressed as percent of MAC at 1.62% isoflurane from figure 1A (*A*). The 0.6 MAC of Istaphanous *et al.*[1] expressed as percent of MAC at 7.32% desflurane from figure 1B (*B*). The 0.6 MAC of Istaphanous *et al.*[1] expressed as percent of MAC at 3.24% sevoflurane from figure 1C (*C*).

trations of volatile agents in immature rodents is complete within 15 min,[1] may not be correct.

After 4 h of anesthesia, the inspired and brain partial pressures of isoflurane had equilibrated and the brain isoflurane concentration at MAC was 1.27%, which is 33% less than at 1 h of anesthesia.[6] Therefore, both the inspired and the brain partial pressures that constitute MAC are moving targets in immature rats but not adult ones.[6] Administration of 1 MAC of a volatile agent to immature rats, and possibly also to mice, requires a continuous adjustment of the anesthetic concentration.[6] Figure 1A shows the anesthetic depth of a 7-day-old rat anesthetized for 4 h with the isoflurane concentration determined to be MAC. Using this steady anesthetic concentration, the anesthetic depth initially would be less than 1 MAC, then exactly 1 MAC for a very brief period of time, followed by greater than 1 MAC for the remainder of the anesthetic period. Figure 1, B and C, show that a similar decrease of MAC occurs with increasing duration of sevoflurane and desflurane anesthesia in 7-day-old rats. Figure 1 also suggests that the anesthetic concentrations used by Istaphanous *et al.*[1] may or may not have been equipotent. Using isoflurane at a steady concentration of 0.6 MAC would result in an anesthetic depth of 1 MAC at approximately 2:30 h and exceed 1 MAC presumably for the remainder of the 6-h anesthetic period, although we cannot exclude the possibility that MAC increases between 4 and 6 h of anesthesia, however unlikely that seems. With sevoflurane, MAC is reached at approximately 1:45 h, and with desflurane, MAC is not reached until 3:15 h. Figure 2 shows that the impression of lack of equipotency is confirmed when expressing the data as percentage of MAC given in figure 1. Using Simpson's method, we calculated the areas under the curves shown in figure 2, which are 328, 336, and 416 for isoflurane, desflurane, and sevoflurane, respectively. If MAC in 7-day-old mice decreases with increasing duration of anesthesia, as is the case for rats,[6] Istaphanous *et al.*[1] would have used a relatively greater dose of sevoflurane than isoflurane and an even greater dose than that of desflurane. It might be prudent, for the time being, to keep an open mind regarding the relative neurotoxicity of the three volatile agents tested.

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In Reply:

We would like to thank Drs. Stratmann and Alvi for their interest in our study.[1] In the study, we tried to determine the