The physiological effect of 1MAC sevoflurane with or without 50% Xenon in immature rats

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1 | BACKGROUND AND METHODS

Anesthetic-induced neurodegeneration in rats occurs across the first three postnatal weeks1 (human equivalent:fetus to preschooler), during which the central nervous system, respiratory control, and pharmacodynamics undergo huge changes. In immature rats, hypercarbia alone (mimicking isoflurane anesthesia-induced hypercarbia) induced neurodegeneration2 and Xenon reduces anesthetic-induced neurodegeneration.3

To facilitate comparison of equipotent anesthetic mixtures of sevoflurane and Xenon, we aimed to measure the mean concentration of sevoflurane ± 50% Xenon preventing purposeful movement in 50% of immature rats (MACsevo and MACsevoXe) on postnatal days (P)5, 10, and 15. 50% Xenon was used as it is clinically useful, offering potential neuroprotection and delivery with up to 50% oxygen.

These experiments were carried out and approved under Home Office License and with University ethical approval. For the measurement of MACsevo and MACsevoXe, three, mixed sex, rats of equal age were exposed to: 3.0% sevoflurane or 2.5% sevoflurane in 50% Xenon, respectively (estimated, a-priori, as MAC). Gasses were delivered using calibrated, low flow, rotameters, and monitoring ensured that CO2 rebreathing was limited to 2%. After 30 minutes, a 50 mm bulldog clamp was applied to the mid-portion of the tails until purposeful movement was seen (or 30 seconds maximum). According to the up-and-down method, this response rate dictated the concentration the subsequent three animals were exposed to (ie, where 2 or 3 animals moved, the concentration was increased by 0.2% or 0.4%, respectively, and vice versa). In this way, nine doses of sevoflurane ± Xenon were administered to each age group and doses 2-9 (dictated by rat responses) were used to calculate a mean: MAC (SD).

In further experiments, groups of six rats on P5, 10, and 15, were randomized to two-hour exposures to: MACsevo, MACsevoXe, sevoflurane alone in equal concentration to MACsevoXe (sevoControl), or 30% oxygen alone (Control). Respiratory rate was monitored throughout. Immediate decapitation allowed collection of mixed arterio-venous blood for analysis. Unless severe circulatory failure is present, the mean difference between venous and arterial pH and partial pressure of CO2 (PCO2) is negligible.4 We defined acidosis as pH < 7.35 and normal lactate as <3.0 mmol/L.

An independent samples t test was used to compare MACsevo with MACsevoXe at each age. ANOVA with Tamhane’s post hoc test (equal variance not assumed) was used to compare differences in MAC across the three ages and differences in physiology between treatment groups.
FIGURE 1  Median (IQR and range) of the average respiratory rates, and the partial pressure of CO\(_2\) (PCO\(_2\)), pH and lactate concentration in mixed arterio-venous blood taken from immature rats at three ages (postnatal days (P)5, 10, and 15), during and immediately after two-hour exposures to: 30% oxygen alone (Control), sevoControl (sevoflurane alone in equal concentration to that in MACsevoXe), MACsevo, or MACsevoXe. The differences between the exposure groups at each age were tested using one-way analysis of variance (\(P\) value shown in each panel and significant differences from Control (*), sevoControl (\(\ddagger\)), or MACsevo (\(\Omega\)) are shown (Tamhane's post hoc test). An open circle or star represents individual outliers and extreme outliers, respectively [Colour figure can be viewed at wileyonlinelibrary.com]
2 | RESULTS

MACsevo (SD) was higher on P10: 3.83% (0.42) than P5: 3.24% (0.27) ($P < .001$), and P15: 3.28% (0.30) ($P < .001$) and higher than MACsevoXe (SD) on P5, P10, and P15: 2.26% (0.22) ($P < .001$), 2.39% (0.26) ($P < .001$), and 2.37% (0.22) ($P < .001$) with no age difference. Of note, five pups on P5 died (all exposed to the highest concentrations used). They were allocated as no response to tail clamping for calculations (excluding them changed MAC slightly, but not the statistical comparisons).

The physiology results are presented in the Figure 1. Blood was successfully analyzed from 65/72 animals (lactate in 57). In the Control group, pH was normal at all ages. 53/54 animals exposed to sevoflurane ± Xenon survived but were acidic. A dose effect, where sevoflurane alone lowered RR, was seen at all ages. However, this effect was only seen in PCO$_2$ and pH on P5 and P10. Differences between the MAC groups were only seen on P10.

Only animals in the MACsevoXe groups had raised lactate (three on P5 with pH 6.72-6.82, lactate 8.22-10.03 mmol/L, one on P10 with pH 7.05, lactate 3.02 mmol/L). An additional group was therefore exposed on P5 and showed similar results.

3 | CONCLUSIONS

MACsevo was higher on P10 than P5 and P15, in keeping with another rat study and with humans (peaking during infancy). 50% Xenon had a significant sevoflurane-sparing effect. Respiratory depression and acidosis were severe, but comparable between MACsevo and MACsevoXe, potentially enabling robust comparison of any neuroprotective effect in future. In the younger animals, respiratory depression was marked, and co-administration of Xenon and sevoflurane appeared to increase lactate. On P15, there is evidence that the rats were better able to compensate for respiratory depression. The physiological derangements shown in our study highlight the need for large animal models for optimal translation to the clinic.

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