Bountra, K., & Gill, H. (2020). The Physiological Effect of 1MAC Sevoflurane with or without 50% Xenon in Immature Rats. *Paediatric Anaesthesia*. https://doi.org/10.1111/pan.13933

Pediatric Anesthesia

The Physiological Effect of 1MAC Sevoflurane with or without 50% Xenon in Immature Rats

Journal:	*Pediatric Anesthesia*
Manuscript ID	PAN-2020-0200.R1
Wiley - Manuscript type:	Short Report
Date Submitted by the Author:	n/a
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Key Words:	General anesthesia, pharmacodynamics < Drugs, Neurodevelopment, inhaled agents < Drugs, sevoflurane < inhaled agents < Drugs

i. Title: The Physiological Effect of 1MAC Sevoflurane with or without 50% Xenon in Immature Rats

ii. Running title: MAC Sevoflurane +/- Xenon in Immature Rats

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Keywords: Xenon, anesthesia, postnatal development, pharmacokinetics

Funding Statement: This work was funded by The Academy of Medical Sciences Starter Grant for Clinical Lecturers (AMS-SGCL13-Gill). HG was funded by NIHR during this work (CL2014-25-003).

Background and Methods

Anesthetic-induced neurodegeneration in rats occurs across the first three postnatal weeks[1] (human equivalent: fetus to pre-schooler), during which the central nervous system, respiratory control and pharmacodynamics undergo huge changes. In immature rats, hypercarbia alone (mimicking isoflurane anesthesia-induced hypercarbia) induced neurodegeneration[2] 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 50mm bulldog clamp was applied to the mid-portion of the tails until purposeful movement was seen (or 30secs maximum). According with the up-and-down method, this response rate dictated the concentration the subsequent three animals were exposed to (i.e. 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 randomised 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 <3.0mmol/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.

Results

MACsevo (SD) was higher on P10: 3.83% (0.42) than P5: 3.24% (0.27) ($p<0.001$), and P15: 3.28% (0.30) ($p<0.001$) and higher than MACsevoXe (SD) on P5, P10 and P15: 2.26% (0.22) ($p<0.001$), 2.39% (0.26) ($p<0.001$) and 2.37% (0.22) ($p<0.001$) 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. Blood was successfully analysed 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 acidotic. A dose effect, where sevoflurane alone lowered RR, was seen at all ages. However, this effect was only seen in PCO2 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 8.22-10.03mmol/L, one on P10 with pH 7.05, lactate 3.02mmol/L). An additional group was therefore exposed on P5 and showed similar results.

Conclusions

MACsevo was higher on P10 than P5 and P15, in keeping with another rat study[5] 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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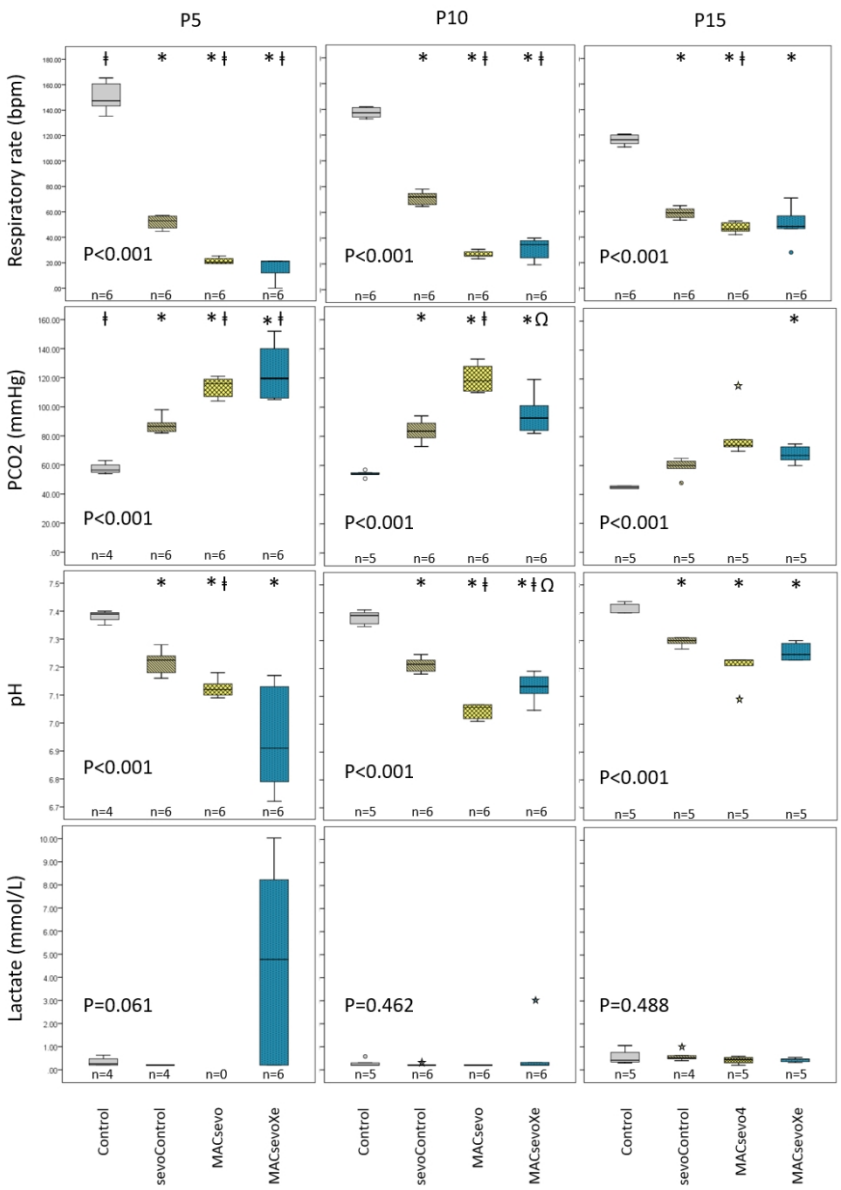
Figure legend:

Median (IQR and range) of the average respiratory rates, and the partial pressure of CO2 (PCO2), 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 (ǂ), or MACsevo (Ω) are shown (Tamhane's post hoc test). An open circle or star represents individual outliers and extreme outliers, respectively.



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