Serum fluoride levels following commencement of methoxyflurane for patient analgesia in an ambulance service

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Editor—Methoxyflurane, once a frequently used anaesthetic agent,[1] is re-emerging as an inhalation analgesic. In modern practice, it is given in doses of up to 6 mL via a proprietary patient-controlled self-delivery device[2] with an activated carbon filter designed to adsorb some methoxyflurane vapour from the patient's exhaled breath.[3] Methoxyflurane is an organic vapour, identified as causing local environmental contamination when administered in anaesthesia or analgesia, and can subsequently be detected on the breath and in the urine of occupationally exposed staff members.[4] Methoxyflurane is eliminated directly by exhalation and in the urine, and is also metabolised to fluoride and other products.[5] Fluoride is also eliminated renally, but can be bound to body tissue and bone.

Changes in New Zealand ambulance clinical practice guidelines resulted in an ambulance service introducing methoxyflurane as one of several pre-hospital analgesic options. This transition provided an opportunity to determine if serum fluoride accumulation occurred in newly exposed workers. This study received University of Canterbury Human Ethics Committee approval (reference HEC 2017/23/LR) and ambulance service Research Committee approval, and was entered into the Australian New Zealand Clinical Trials Registry (ID ACTRN12617001334392).

Twelve Emergency Medical Technician ambulance staff gave written informed consent. Those staff were requested to provide blood samples once during each of months 0, 1, 4, 8, 12, 18, and 24, where month 0 was the month in which methoxyflurane was introduced into clinical practice. One participant withdrew, whereas the remaining 11 participants provided a total of 63 serum fluoride samples. Serum fluoride concentration was determined for each blood sample by professional laboratory technicians at Canterbury Health Laboratories using a calibrated fluoride ion measurement electrode. Serum fluoride sample concentration determined by the laboratory ranged between 0.3 and 4.0 μmol L^{-1} over the study period. Fig. 1 shows the empirical cumulative distribution functions for serum fluoride results from month 0 (filled circles) and the combined data from months 1 through 24 (empty circles). Empirical cumulative distribution functions estimated a true cumulative distribution function in a stepwise manner from measured data.

The cumulative probabilities from months 1–24 exhibited increased levels of serum fluoride from month 0 (baseline) results (Fig. 1). For any given serum fluoride level, this finding indicates an increased likelihood of this level or less being identified in month 0 compared with subsequent months. Therefore, this finding implies serum fluoride results may have been elevated above baseline after introduction of methoxyflurane in month 0. However, this finding was not statistically significant: a two-sample two-sided Kolmogorov–Smirnov test comparing month 0 data with months 1–24 found a non-significant result (P=0.9995). A power analysis determined the sample size n=12 was needed to observe a difference of 1 μmol L^{-1} to be significant with 80% power. The rightward shift seen in Fig. 1 is generally less than 1 μmol L^{-1}.

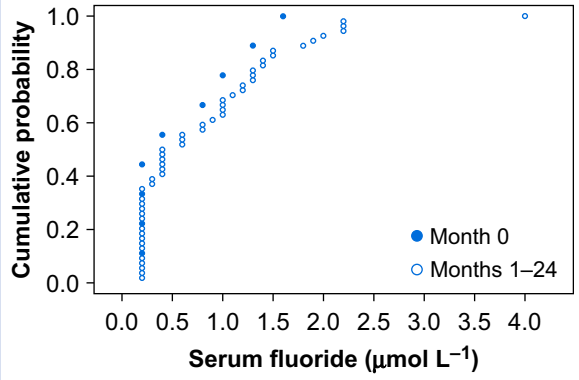

Fig 1. Empirical cumulative distribution functions for the serum fluoride results of: month 0 (filled circles); and the combined data from months 1 through 24 (empty circles).

This cumulative distribution analysis suggests serum fluoride levels of ambulance officers occupationally exposed to methoxyflurane do not increase significantly. Even if statistical significance was achieved in identifying an increase, the serum fluoride values determined in this study suggest it might be clinically unimportant.

Delays in obtaining ethical approval resulted in serum fluoride results taken within the initial month of methoxyflurane availability rather than before. This delay potentially raised baseline levels, and obscured observation of early initial increases in serum fluoride. Nonetheless, the serum fluoride

values determined by this study provide some reassurance of safety from renal toxicity in ambulance officers occupationally exposed while administering methoxyflurane analgesia. However, this result might depend on use of the activated carbon filter, as occurred in this ambulance service, and on exposure frequency and duration consistent with this ambulance service's clinical practice, as well as on the environment in which methoxyflurane is administered. Therefore, these results may not be applicable to other services utilising methoxyflurane more frequently, or in less-ventilated environments.

Authors' contributions

Study design: all authors.
Data collection: SJA, PDD.
Drafting of the manuscript: SJA
Critical interpretation and revision of the manuscript: SJA, PDD, DP, JGC
All authors give final approval for publication and agree to be accountable for all aspects of the work.

Declarations of interest

The authors declare they have no conflict of interest.

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References

1. Van Poznak A. Methoxyflurane and teflurane. In: Chenoweth MB, editor. *Modern inhalation anaesthetics*. Berlin, Germany: Springer; 1972. p. 77–92
2. Douglas Pharmaceuticals Ltd. *Penthrox New Zealand data sheet* 2020. Available from: https://medsafe.govt.nz/profs/datasheet/p/penthroxinh.pdf. [Accessed 29 April 2020]
3. Ruff R, Kerr S, Kerr D, Zalcberg D, Stevens J. Occupational exposure to methoxyflurane administered for procedural sedation: an observational study of 40 exposures. *Br J Anaesth* 2018; **120**: 1435–7
4. Corbett TH, Ball GL. Chronic exposure to methoxyflurane: a possible occupational hazard to anesthesiologists. *Anesthesiology* 1971; **34**: 532–7
5. Yoshimura N, Holaday DA, Fiserova-Bergerova V. Metabolism of methoxyflurane in man. *Anesthesiology* 1976; **44**: 372–9

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Making anaesthesiology more inclusive: the time for action is now

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Editor—The oft-mentioned 'American Dream' is the idea that, with enough gumption, anyone can advance in society. The recent killings of George Floyd, Breonna Taylor, and countless other Black Americans by authority figures, however, echo a centuries-long pattern of dangerous systemic bias in the USA. The fantasy that equal opportunity exists has been revealed as a false narrative, but protests in all 50 states show that society is ready, even aching, for change. It is imperative that institutions turn a mirror inwards to dismantle entrenched injustices, and academic medicine is by no means exempt from this prescription. This is an anaesthesia-targeted piece based on a more general article recently published.[1]

How can anaesthesiology move towards inclusion? The problem seems daunting at first. It is difficult to take an accounting of academic anaesthesiologists by race, as it is a self-reported measure; many abstain from answering the question.[2] It is estimated, however, that Black physicians comprise 3% of the academic anaesthesiology workforce (13% of the general population)[3,4] and under-represented in medicine (URiM) physicians 6% (34% of the population). In 2017, there were fewer URiM anaesthesiologists in leadership positions than women.[2] Increasing representation is crucial, but so are promotion and retention of URiM faculty; these improvements require fostering a workplace where everyone belongs. How though do we begin and who should be accountable? In short, we begin today, and everyone is a stakeholder.

Anaesthesiology departments are in a unique position to be at the forefront of change. We care for patients from every corner of the hospital in multidisciplinary teams, interacting with a range of specialists. Our far-reaching influence on hospital culture confers a moral responsibility to implement solutions to inequality, but evidence shows that increasing diversity can improve efficiency and profits as well. Further, a diverse physician workforce correlates with better outcomes for minority patients.[5] Thus, in the era of glaring racial disparities, in COVID–19, institutions ought to attract employees from URiM backgrounds. There are numerous ways to overcome obstacles that exist in developing an inclusive