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EDITORIAL

Methoxyflurane: inspiration of the old to breathe life into the new

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"The thing which hath been, it is that which shall be;
and that which is done is that which shall be done:
and there is no new thing under the sun."
Holy Bible, King James Version, Ecclesiastes 1:9

"There are more things in heaven and earth, Horatio,
Than are dreamt of in your philosophy."
Hamlet to Horatio, Hamlet 1.5.167-8

The history of modern anaesthesia – from "*...no humbug!*" to HFNO – has a remarkably short span for the degree of scientific advancement and technological complexity we currently enjoy. Indeed, the data-saturated clinical and research environments within the speciality may lead us to presume that development of new therapies is continuously accelerating. Remove the electronics, however, and examination of the therapeutics at our disposal reveals a different story. Using inhaled agents as an example: Scientific descriptions of the use of ether and diethyl ether in the 1500s are available. Priestley's 'airs' of oxygen and nitrous oxide date from the late 1700s, although it was a century later by the time anyone suggested that administering the nitrous oxide *with* oxygen was perhaps a safer plan. Morton's 1846 *Etherdome* demonstration of effective operative anaesthesia in humans precipitated a gust of inhalational invention that also saw chloroform becoming commonplace, but it was only in the 1920s that volatile anaesthesia using ethylene and cyclopropane began to resemble anything like modern delivery methods. The explosive potential of early agents holds an ironic twist for the discovery/development of the halogenated/fluorinated volatiles, which stemmed from the field of chemistry advanced to support the Manhattan Project. Steadily, the names of agents familiar to those practising anaesthesia today emerged: halothane (in clinical use from 1956), methoxyflurane (1960), enflurane (1966), isoflurane (1972), and then a two-decade hiatus before the introduction of desflurane (1992) and sevoflurane (1994). While the latter may feel recent, it is sobering to consider that we are now reaching the point at which our "newest" inhalational agents were introduced before our registrars were born. (Xenon has been excluded from this discussion, as it is still not, nor is it likely to be, in regular clinical use).

Examine your drug or anaesthesia cart in the operating theatre, and the same story will emerge. Morphine: 1805. Guedel airway: 1933. Macintosh laryngoscope: 1943. Lignocaine: 1944. Ketamine: 1964. Propofol is a youngster: 1986. Coca and opium fade into the mists of time.

Clearly, the pace of quality improvement in anaesthesia has not been determined by the rate of acquisition of new tools. The consistent (even if marginal) gains today are being made in fields such outcomes analysis using big data, human factors awareness, and addressing anaesthesia non-technical skills. Nonetheless, the drive to innovate and improve is relentless. In this edition of the journal, numerous authors report on novel strategies using "old" drugs and approaches repurposed for the African setting or modern world. While conventional wisdom dictates that we cannot teach an old dog new tricks, can we perhaps learn new tricks from an old dog?

Continuing with inhalational agents as an example, two research papers in the journal address the use of methoxyflurane analgesia for paediatric burns dressing changes in the South African context. Initially described as a volatile anaesthetic agent in the early 1960s,[1] methoxyflurane is matched only by nitrous oxide (N_2O) in providing analgesia at sub-anaesthetic partial pressures. Unlike N_2O, however, it does not require cylinders or other breathing apparatus to administer: the currently licensed method is a disposable, handheld inhaler that functions as a simple draw-over vaporiser. While use for anaesthesia was flagged by the mid-1960s and evaporated in the 1970s due to dose-related renal injury, analgesic use appears safe, has continued in some regions, and is experiencing a steady global resurgence.[2-4] The proposed advantages – potent analgesia without immediate need for intravenous access, rapid onset, self-administration and titration by patients, mild sedation and/or anxiolysis, and absence of cardiorespiratory side-effects – are particularly desirable in a resource-constrained Africa setting. Although previously described for procedural analgosedation,[5-9] including in paediatric burns,[10,11] this new research begins to provide new insights in the South African context.

Wall and colleagues describe two months of respective data describing the use of methoxyflurane for dressing changes in 95 children under 12 years in Pietermaritzburg.[12] Reflecting on the use of intramuscular ketamine as the current cornerstone, they introduced inhalational analgesia to try and reduce the requirements for monitoring and prolonged recovery in the light of this heavy caseload. Despite a modified technique using practitioner-administered inhalation with a reduced dose (1 ml rather than the normal 3 ml in the inhaler), they recorded effective analgesia in three-quarters of patients. Regrettably, the absence of monitoring within the clinical area and small sample size limit our ability to ascertain safety of the intervention, but the

lack of significant adverse events is reassuring. While concerns are raised regarding the cost of methoxyflurane compared to ketamine, other recent work has suggested that avoiding the additional staff and requirements for procedural sedation may result in an overall saving.[13]

Reporting from the Witwatersrand, Wellbeloved et al. describe a small prospective study using methoxyflurane for a further 12 paediatric patients undergoing burns dressing changes.[14] Although they noted rapid onset and recovery, and good analgesia during dressing removal/application, levels of analgesia during wound scrubbing were generally inadequate. In contrast to Wall et al., they documented vital signs and good sedation/anxiolysis, but were overall dissatisfied with the requirement for another practitioner, limited staff satisfaction, and inadequate potency for the procedure.[12] Again, however, the lack of serious adverse events was reassuring.

The location of the studies may be of relevance for more than just the context. In their paper, Wellbeloved et al. question whether the poor performance of methoxyflurane could be attributed to the approximately 1 750 m altitude of Johannesburg,[14] with an assumption that methoxyflurane performs similarly to nitrous oxide, losing efficacy with decreasing atmospheric pressure.[15,16] Perhaps this could be used in defence of the 25% of patients with inadequate analgesia in Pietermaritzburg, at 600 m above sea level? Alas not: the true situation is more complex, and relies on an astute understanding of the differing behaviour of gases, volatiles, and their delivery systems.[17] As noted by Windsor et al. in 2009, saturated vapour pressure does not change with decreasing ambient pressure, and thus with a draw-over vaporiser, a consistent partial pressure of methoxyflurane should be delivered.[18] While *in vivo* study is still underway, this has more recently been confirmed *in vitro* in hypobaric chamber experiments spanning moderate to extreme altitude.[19] This is borne out by a case report of procedural analgesia undertaken at 4 470 m in the Himalaya, in which methoxyflurane was highly effective.[20]

Methoxyflurane as a drug cannot be examined in isolation without consideration of the delivery method. Modern vaporisers are sophisticated and compensate for many variables, but Windsor et al. notes that the simplicity of the inhaler may make it susceptible to cold.[18] It is also of interest that clinical studies of methoxyflurane show a much greater frequency and intensity of sedation in paediatric patients, especially young children, which runs contrary to our understanding of the action of volatile anaesthetics. Although not yet formally studied, this may be related to the fixed internal volume of the inhaler: as tidal volume decreases, the proportion of inspired gas which has become saturated will increase, and thus the mean alveolar concentration (and partial pressure) may increase proportionally. In the work by Wall et al., a reduced volume of methoxyflurane was added to the device, but it is unknown if this is enough to sufficiently soak the wick to generate saturation in the chamber.[12] Until adequate *in vitro* testing can be undertaken, we must not neglect to make use of our understanding of basic principles to understand the *in vivo* findings.

Perhaps, although the Teacher narrating *Ecclesiastes* would have us believe that there is nothing new under the sun, we should not be seeking the novel, but reconsidering how we apply our existing tools to better effect. Shakespeare's Hamlet, admonishing his friend and fellow scholar Horatio, suggests not that there are infinite things to discover, but rather that we are more limited by our own philosophy: Our *way* of thinking confines us more than the available knowledge. Once we recognise that our current science does not hold all the answers, we can begin to learn anew. The strength in older agents such as methoxyflurane may not be their intrinsic properties alone, but in finding how to leverage those properties to advantage in our context.

Undoubtedly, we must not stop seeking new techniques, new drugs, and new insights from fresh data. We must also, however, practise frequent metacognition: reflecting on whether our quest to find solutions to old and new clinical problems is skewed to favour the novel. Do we miss the opportunities to use solutions in new ways? Deliberate shifts in mental perspective may offer insights not readily elucidated by larger datasets examined with the same dated methods. *That which hath been* exists already *in heaven and earth* for us to find, if only our philosophy can be as limitless as our dreams. Best said, perhaps, by the oft-misquoted Proust:

> *"The only true voyage of discovery ...*
> *would not be to visit strange lands,*
> *but to possess other eyes."*
> Marcel Proust, "Remembrance of Things Past",
> Volume 5, 1923 (Transl. CK Moncrief)

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