Desflurane in modern anaesthetic practice: walking on thin ice(caps)?

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The third-generation volatile anaesthetic agents desflurane and sevoflurane were introduced into clinical practice in 1990 in response to the perceived need for rapid return of consciousness after 'ambulatory' surgery.[1] Initially marketed by two competing pharmaceutical companies, their relative merits have been debated for three decades.[2] Of the two, desflurane has a lower solubility in blood and therefore the fastest offset, providing a rapid emergence, which is more notable in obese patients and following prolonged anaesthesia.[2] Furthermore, some authorities (including the United States' Food and Drug Administration (FDA)) have deemed desflurane to be more suitable than sevoflurane for low-flow anaesthesia, as it undergoes only negligible metabolism and minimal reaction with soda lime.[3] However, desflurane has several well-known disadvantages, including a pungent odour (making it a respiratory irritant), lower potency, and environmental impacts related to its manufacture, administration and discharge into the atmosphere, calling into question its continued use as a general anaesthetic agent [1-2,4]

The clinical impacts of desflurane

Total intravenous anaesthesia (TIVA) and regional anaesthesia are becoming increasingly popular for environmental and clinical reasons, with regional anaesthesia advocated preferentially during the current coronavirus crisis to preserve drug stocks and avoid aerosol-generating procedures.[5,6] However, national studies suggest that the most common method of delivering general anaesthesia involves intravenous induction and inhalational maintenance.[5,7] Mainly historical data indicates that desflurane's faster elimination from the body facilitates rapid-turnover operating lists and may benefit some higher-risk patients, but there is scant clinical evidence to confirm these benefits in current anaesthetic practice. A recent observational study of over 100,000 cases by Zucco and colleagues, for example, found no difference in postoperative pulmonary complications between patients anaesthetised with sevoflurane and desflurane when adjusted for confounding factors.[8]

One potential advantage of desflurane is the faster time to recovery of consciousness and tracheal extubation. However, whilst meta-analyses of randomised controlled trials (RCTs) have confirmed that this is consistently a statistically significant finding (table 1), the magnitude of this effect is minimal (only a few minutes in most circumstances), and it does not appear that this translates to shorter patient stays in the post-anaesthesia care unit (PACU).[8-12,14] Furthermore, as pointed out by Macario and colleagues, because RCT study protocols tend to require the use of a constant concentration of general anaesthetic agent up to the point of wound closure, the common clinical practice of tapering the anaesthetic dose as the surgical stimulus reduces is not represented, and this may further reduce any 'real world' difference between agents.[10] We contend that a trivially more rapid emergence from general anaesthesia with desflurane compared to sevoflurane may be of greater promotional benefit to the manufacturer than either clinical benefit to the patient or organisational benefit to surgical operating efficiency.

[table 1 here]

Whilst many previous studies of desflurane have been concerned with its pharmacokinetic qualities, in the current issue of the *British Journal of Anaesthesia*, Ryu and colleagues focus on an important *pharmacodynamic* difference between volatile agents.[15] In this meticulously-controlled study, participants who were scheduled for arthroscopic knee surgery were randomised to receive an additional 35 minutes of anaesthesia before their operation with one minimum alveolar concentration (MAC) of either sevoflurane or desflurane, following a target-controlled induction with propofol and muscle relaxation with rocuronium. Perfusion index (a measure of peripheral perfusion derived from the pulse oximeter signal), mean arterial pressure (MAP) and heart rate were recorded every minute throughout the study period, which included a standardised noxious stimulus (tetany from a peripheral nerve stimulator) after 30 minutes of vaporiser adjustment and equilibration time. The desflurane group demonstrated a significantly higher perfusion index (indicating inferior peripheral perfusion) and a significantly lower MAP than the sevoflurane group. These findings, the authors suggest, indicate that desflurane has more potent vasodilatory properties than sevoflurane at an equivalent dose, at a magnitude that may be associated with harm.[15]

Intraoperative hypotension is associated with adverse patient outcomes including mortality, acute kidney injury, myocardial infarction, and wound infection in settings including orthopaedic trauma, vascular, thoracic, and general surgery.[16-19] Concerningly, these are all surgical specialties in which high-risk and prolonged operations are relatively commonplace and therefore the use of desflurane may be most tempting for clinicians. Furthermore, a survey of UK practice indicates that desflurane appears to be more commonly used in older patients, who are at higher risk of the complications of hypotension.[7] The mean pre-stimulation MAP in Ryu and colleagues' desflurane group was 73mmHg, compared to 81mmHg in the sevoflurane group.[15] Though one MAC of volatile agent is arguably a higher dose of anaesthetic than was required given the lack of 'surgical' stimulation, these findings do have potential clinical significance. A recent systematic review by Wesselink and colleagues concluded that the risk of end-organ injury begins to increase at a MAP of <80mmHg for a duration >10 minutes.[20] Whilst it cannot be determined if the (comparatively young and fit) participants in Ryu's study came to any harm as patient outcomes were not assessed, this is a potentially important signal and requires further investigation in older and more comorbid populations.[15]

The environmental impacts of volatile anaesthetic agents

The environmental effects of inhaled anaesthetic agents were recognised before the introduction of sevoflurane and desflurane, though early focus was on the potential for chloride ions liberated by the ultraviolet photolysis of agents such as isoflurane (but not sevoflurane or desflurane) to contribute to the destruction of the ozone layer.[1] Latterly however, attention has been brought to bear more prominently on the action of inhaled agents as 'greenhouse gases',[4,21-24] contributing to anthropogenic global warming through radiative forcing i.e. the absorption of infrared radiation that would otherwise escape into space. The degree to which a substance released into the atmosphere contributes to global warming depends on two factors: firstly the radiative efficiency – the amount of infrared radiation absorbed, which is determined by the number and type of atomic bonds within the structure of the molecule, and secondly, whether there are any naturally-occurring molecules

(e.g. water vapour) that would otherwise absorb infrared radiation at the same wavelengths.[22,23]

The global warming potential (GWP) of greenhouse gases differs over time, depending on the lifespan of the molecule, with more atmospherically-persistent molecules having a greater cumulative impact. The GWP_{20} and GWP_{100} express the global warming potential of a substance over 20 and 100 years, respectively, in comparison to the effect of an equal mass of carbon dioxide. In anaesthetic practice, the differences in molecular mass and potency between volatile agents can make comparison on the basis of GWP challenging. Özelsel and colleagues' concept of carbon dioxide equivalencies (CDE) addresses this issue by multiplying the GWP by the mass of anaesthetic agent used per hour at a given MAC and fresh gas flow (table 2), thereby enabling a clinically relevant comparison.[22]

[table 2 here]

Though sevoflurane is generally considered to be the least damaging volatile anaesthetic from a climate change perspective, life cycle analysis has demonstrated that its GWP_{100} is approximately three orders of magnitude greater than an equivalent dose of propofol TIVA.[4] It is for this reason that the National Health Service Sustainable Development Unit has designated volatile anaesthetic agents, and desflurane in particular, to be a 'carbon hotspot'.[24] The difference between the GWP of anaesthetic agents is more pronounced at 100 years than at closer time horizons, owing to the greater environmental persistence of desflurane. This raises the question of what time horizon should be used when making policy and practice decisions. Recently, It has been suggested that the 20- and 100-year time horizons underplay the atmospheric effects of volatile agents in the face of a pressing climate crisis, because their global warming effects will remain at their atmospheric release levels if their use continues unabated.[22] Regardless of their comparative environmental impacts, *both* desflurane and sevoflurane have profound global warming impacts, such that anaesthetists seriously need to consider the default use of volatile agents for general anaesthesia.[21]

Desflurane: a 'triple bottom line' approach

Desflurane, then, has little evidence of important patient benefit, considerable environmental impacts at a time of climate crisis, and now appears to have evidence of potential for harm.[4,8-15] Given these widespread drawbacks, anaesthetists have to question the rationale for its continued use. As with any practice, the risks and benefits associated with desflurane use can be conceptualised using the so-called 'triple bottom line' approach by considering impacts on 'people' (e.g. the patient, staff members and broader society), 'planet' (i.e. environmental sustainability) and the 'public purse' (i.e. healthcare finances).[23,25]

People:
Arguably, the most important element of decision-making in anaesthetic practice relates to patient safety. Here, there is little evidence of any benefit to desflurane, and the degree of hypotension demonstrated in Ryu's study is a cause for concern, particularly in older or comorbid patients.[8-15] In terms of quality of care, desflurane is consistently associated with more rapid emergence from anaesthesia and tracheal extubation, however these benefits are small in magnitude and do not lead to any improvement in discharge times.[8-12,14] As a

consequence, these benefits are likely to be noticed only by the anaesthetic team, but not by the patient or operating theatre staff more generally. Although patient outcomes are of paramount importance for the anaesthetist, this does not mean that the effects of climate change on communities worldwide should be discounted.[25]

Planet:
Depending on the time horizon used, the GWP of desflurane is between five and twenty times more than that of sevoflurane[4] Though technologies to capture and re-process desflurane have been developed and are currently being trialled in some healthcare institutions, these would have to be exceptionally efficient to overcome this magnitude of difference.[21,23,25] Likewise, although sevoflurane is not licensed for low flow anaesthesia in some countries despite evidence of the safety of this technique, even at fresh gas flows of 1-2l.min^{-1} it remains markedly less environmentally harmful than low-flow desflurane in terms of climate change.[3,4] Furthermore, evidence supports the preferential use of total intravenous, or regional, compared to inhalational anaesthesia in limiting the climate impacts of anaesthetic practice.[4,6,21,23,24]

Public Purse:
Desflurane is approximately one-third the potency of sevoflurane and, though it was initially less expensive whilst 'on patent' it is now typically more costly due to the market forces created by the wider availability of generic sevoflurane (240ml desflurane ~£90, 250ml sevoflurane ~£60; personal communication).[1] Even accounting for the negligible metabolism and low solubility of desflurane, and its (minor) benefits in the speed of early recovery from anaesthesia, at an equal fresh gas flow and MAC desflurane has consistently been found to be more expensive than sevoflurane.[26] Therefore, it is only in countries where sevoflurane is unlicensed for low-flow anaesthesia that a cost effectiveness argument could be made in favour of desflurane.[3] It should be noted however, that the additional non-drug costs to healthcare institutions (e.g. heating the desflurane vaporiser) and public finances more broadly (e.g. as a consequence of global warming) are not accounted for in existing cost analyses.

In conclusion, anaesthetists have a responsibility not only to care for the patient in front of them, but also to safeguard the health and welfare of future generations.[21,25] Ryu et al.'s study in this issue of the *British Journal of Anaesthesia* adds to existing evidence aligning these two responsibilities through the discontinuation of desflurane use and manufacture.[8,15] Individual anaesthetists, as well as the wider profession, can choose how to deliver general anaesthesia. We accept that inhalational anaesthetic agents may be appropriate in certain circumstances, but assumptions about the specific clinical benefits of desflurane based on its physiochemical properties are breaking down. In our opinion, the arguments against its use are now overwhelming. We strongly encourage anaesthetists who are still using desflurane to reconsider the evidence for its use, and ask themselves how they might transition to using less environmentally harmful alternatives.

Authors' Contributions
All authors conceived, wrote, and edited the manuscript.

Declaration of Interests

CS is a former member of the editorial board of *BJA Education.* The authors declare no other interests.

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Tables

Study	Context	Desflurane vs Sevoflurane			Desflurane vs Propofol			Notes
		Emergence	Extubation	PACU Discharge	Emergence	Extubation	PACU Discharge	
Gupta 2004[9]	Adult patients. Ambulatory surgery	- <1 min	- <1 min	+ 6 mins	- 1.3 mins	NR	NR	Less PONV in propofol group
Macario 2005[10]	Adult and paediatric patients. Ambulatory and inpatient surgery	-1.7 mins	-1.3 mins	NS	NR	NR	NR	No difference in PONV between groups
Liu 2015[11]	Patients with BMI > 30 $kg.m^{-2}$. Ambulatory and inpatient surgery	-3.09 mins	-3.88 mins	+1.28 mins	- 10.7 min	- 13.2 min	NR	No difference in PONV or analgesic requirement between groups
Stevanovic 2015[12]	Adult patients. Laryngeal mask airway	-3.81 mins	-0.7 mins*	NR	NR	NR	NR	No difference in cough or laryngospasm between groups
Lim 2016[13]	Paediatric patients. Ambulatory surgery.	-2.74 mins	-2.21 mins	NR	NR	NR	NR	No difference in incidence or severity of emergence agitation between groups
Guo 2017[14]	Paediatric patients. Ambulatory and inpatient surgery	NS	-3.27 mins	NS	NS	-3.83 mins	NS	No difference in PONV or analgesic requirement between groups. Less emergence agitation with propofol vs desflurane or sevoflurane.

Table 1: Meta-analyses of RCTs comparing time to emergence, tracheal extubation and PACU discharge of patients anaesthetised with desflurane, sevoflurane and propofol TIVA. NS = not significant; NR = not reported; PONV = postoperative nausea and vomiting; *removal of supraglottic airway.

	GWP_1	CDE_1 ($kg.h^{-1}$)	GWP_{20}	CDE_{20} ($kg.h^{-1}$)	GWP_{100}	CDE_{100} ($kg.h^{-1}$)
Sevoflurane	4285	21.43	796	3.980	216	1.08
Desflurane	8526	107.45	5513	69.49	1778	22.42

Table 2: Global warming potentials (GWP) of sevoflurane and desflurane, at 1, 20 and 100 years, and corresponding carbon dioxide equivalents (CDE) per hour of anaesthesia at 1 MAC and $0.5l.min^{-1}$ fresh gas flow. One hour of desflurane use at 1MAC and $0.5l.min^{-1}$ fresh gas flow has a GWP_{100} equivalent to 22.42 kg CO_2. This is comparable to driving 90 miles in a typical UK family car, and over 20 times greater than if sevoflurane were used. Data adapted from Özelsel et al.[22]