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Published in:
British Journal of Anaesthesia

DOI:
10.1016/j.bja.2020.04.076

Publication date:
2020

BJA
British Journal of Anaesthesia

Volume 125, Number 2, August 2020

British Journal of Anaesthesia, 125 (2): 118–121 (2020)
doi: 10.1016/j.bja.2020.04.076
Advance Access Publication Date: 1 May 2020

COVID-19 and the anaesthetist: a Special Series

EDITORIAL

Sevoflurane, a sigh of relief in COVID-19?

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Keywords: ARDS; COVID-19; ICU; sedation; sepsis; sevoflurane; volatile anaesthetic

Currently coronavirus disease 2019 (COVID-19) is holding the world in its grip. Numbers of infected individuals continue to increase each day and worldwide mortality rate attributable to COVID-19 is estimated as 6.8%.[1] The primary cause of death is respiratory failure as a result of acute respiratory distress syndrome (ARDS). Treatment is mainly supportive with a high failure rate, and effective preventive and treatment strategies are needed.

ARDS is characterised by injury to epithelial and endothelial cells, which triggers the innate and subsequently the adaptive immune system, and leads to an inflammatory cascade of cytokines and altered permeability of the alveolar capillary membrane. This results in an increase in alveolar oedema, interstitial oedema, or both, and the development of a systemic inflammatory response.[2] Mehta and colleagues[3] highlight the similarity of patients with a fulminant COVID-19 associated with ARDS and death with the secondary haemophagocytic lymphohistiocytosis syndrome. This hyperinflammatory syndrome is characterised by hypercytokinaemia ('cytokine storm') and multiple organ failure. The cytokine profile is characterised by increased interleukin-2, interleukin-7, granulocyte colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-α, and tumour necrosis factor-α (TNF-α). Mehta and colleagues[3] suggest that this group of patients could benefit from immunosuppressive strategies, and several agents targeting innate and adaptive immune responses (chloroquine, methylprednisolone, tacrolimus, tocilizumab, sarilumab, bevacizumab) are being tested (NCT04324463, NCT04317092, NCT04315298, NCT04341038, NCT04275414).

Another adjunct treatment that might be of some benefit in COVID-19 is inhalation of volatile anaesthetics. Because of the rapid increase of infected individuals with severe ARDS requiring emergent medical treatment and mechanical ventilation, ICUs all over the world have been flooded with patients, exhausting critical care resources. These patients require sedation, most frequently using the i.v. sedative midazolam or anaesthetic propofol, together with an opioid and neuromuscular blocking agent. Shortages of these drugs are

occurring, and alternative drug options must be considered. A low-cost alternative sedation strategy could be the use of volatile anaesthetic agents such as sevoflurane. Volatile anaesthetics are associated with faster onset and offset, fewer hallucinations, and reduced opioid needs compared with i.v. sedatives. Use of volatile anaesthetics for sedation in ICU patients is increasingly being considered. In Germany, the DAS taskforce 2015 proposes the use of volatile anaesthetics for moderate-to-deep sedation as an option in their 'evidence- and consensus-based guidelines on the management of analgesia, sedation, and delirium in intensive care'.[4]

Safety considerations of long-term use of volatile anaesthetics

Several trials have evaluated the safety of long-term sedation with volatile anaesthetics in the ICU, with durations reported between 1 and 12 days and end-tidal concentrations of 0.5 vol % and 0.5–1.0 vol% for isoflurane and sevoflurane, respectively.[5–7] A retrospective analysis of 200 critically ill surgical patients admitted to the ICU reported reduced in-hospital mortality (odds ratio 0.35; 95% confidence interval 0.18–0.68) and 1-yr mortality (odds ratio 0.41; 95% confidence interval 0.21–0.81) in patients sedated with isoflurane compared with propofol-midazolam.[6] A limitation of this analysis was the potential of selection bias. In an RCT, sedation with sevoflurane (0.5 vol%) for a mean of 50 h resulted in improved haemodynamic stability, improved awakening quality score, and reduced opioid consumption compared with propofol or midazolam sedation.[7] Mean plasma fluoride concentration was 82 μM (12–220 μM). Although this is above the nephrotoxic threshold of 50 μM, no renal or hepatic injury was reported.[7,8] This threshold of 50 μM is based on clinical experiments with methoxyflurane that showed a dose-related correlation between inorganic fluoride (a metabolite of all halogenated volatile anaesthetics) concentration and renal dysfunction.[8] Subsequently, this threshold was applied to other volatile anaesthetics, although higher fluoride concentrations have been measured in the case of sevoflurane without clinical signs of renal injury.[9,10] Polyuria and nephrogenic diabetes insipidus (NDI) have been observed after long-term sedation with volatile anaesthetics. Cabibel and colleagues[11] reported three cases in which development of NDI was associated with prolonged (4, 6, and 13 days) sedation with sevoflurane (1.0 vol%). In a retrospective study, L'Heudé and colleagues[12] analysed ICU patients who developed NDI and were exposed to longer duration (178 [118–261] h *vs* 66 [20–119] h; $P<0.01$) and higher doses (1.3 [1.2–1.5] vol% *vs* 1 [0.8–1.2] vol% $P=0.02$) of sevoflurane. However robust data on the safety of long-term use of volatile anaesthetics are missing. None of sevoflurane, isoflurane, or desflurane are approved for ICU sedation and their use for this purpose would be off-label and experimental.

Methods of administration

Various publications report on the administration of volatile anaesthetics with conventional ICU ventilators using specific administration devices such as AnaConDa® (Sedana Medical, Danderyd, Sweden) and Mirus® (Pall Medical, Dreieich, Germany).[13] During this COVID-19 pandemic, many hospitals were forced to use anaesthesia ventilators in the ICU with the possibility to administer volatile anaesthetics without the need of these specific devices. Institutions using anaesthesia ventilators in the ICU should be aware that use of these ventilators in the ICU is off-label and a risk-benefit assessment should be carefully made by the responsible healthcare professionals. Clinical teams should be trained to understand the specific features of these devices and fundamental differences between anaesthesia and conventional ICU ventilators. More specifically, when using anaesthesia ventilators at the ICU to administer volatile anaesthetics for a longer period of time, consideration of the fresh gas flow is important. In contrast to the use of low or minimal fresh gas flows in the operating theatre when administering volatile anaesthetics in an attempt to minimise environmental effects and costs,[14] higher fresh gas flows might be required when using anaesthesia ventilators in the ICU to avoid rapid exhaustion of carbon dioxide absorbers, water traps, excessive standing water in the breathing circuit, and condensation in filters and valves compromising the ventilator functionality. Various solutions including active charcoal filters and alternative scavenging systems have been proposed to avoid air pollution by volatile anaesthetics in the ICU.[15]

Potential beneficial effects of volatile anaesthetics in COVID-19

Volatile anaesthetics have immune modulating properties either by direct effects on immune cells or indirect effects on cellular protective pathways in endothelial or epithelial cells that reduce death signals and the subsequent inflammatory response.[16] Protective effects of volatile anaesthetics have been shown in ischaemia and reperfusion injury in various organs, and increasing evidence indicates protective roles of volatile anaesthetics in sepsis and ARDS. In a sepsis model of caecal ligation and puncture, mice treated with a volatile anaesthetic showed improved overall survival and reduced 7-day mortality, with the greatest effect exerted by sevoflurane.[17] Alanine transaminase and aspartate transaminase concentrations were lower in the sevoflurane-treated group, as were concentrations of interleukin-6 and MCP-1.[17] In a lipopolysaccharide-induced sepsis model in rats, concentrations of MCP-1, interleukin-6, and cytokine-induced neutrophil chemoattractant protein-1 measured 3, 6, and 12 h after lipopolysaccharide infusion were lower in sevoflurane-treated rats compared with propofol-treated rats.[18] Koutsogiannaki and colleagues[19] showed that improved survival in sevoflurane-treated mice subjected to sepsis was associated with less apoptosis in the spleen. Sevoflurane reduced neutrophil apoptosis by a Fas death domain-Fas-associated death domain interaction.

Several trials have addressed the potential benefits of volatile anaesthetics in animals and patients with ARDS. In a porcine model of ARDS, sevoflurane improved Pa_{O_2}/Fi_{O_2} ratio 4 h after administration compared with propofol. Concentrations of interleukin-1β, interleukin-6, and TNF-α in bronchoalveolar lavage were lower in the sevoflurane group, as was the polymorphonuclear neutrophil count.[2] Reduced permeability of the alveolar capillary membrane and lower extravascular lung water index was seen in the sevoflurane-treated pigs. In a clinical trial, Jabaudon and colleagues[20] compared the effect of sevoflurane sedation with midazolam sedation in ARDS patients. Treatment with sevoflurane improved the Pa_{O_2}/Fi_{O_2} ratio and reduced concentrations of interleukin-6 and TNF-α in sevoflurane-treated patients.

MacDonald and colleagues[21] reported that the use of halogenated volatile anaesthetics in mice was accompanied by modulation of the type 1 interferon response to influenza, and that volatile anaesthetic exposure resulted in decreased bacterial burden, improved clinical score, and reduced lung injury. Against viral infections such as the measles, volatile anaesthetics have proved to be able to decrease viral load.[22–24] Volatile anaesthetics also exhibit antibacterial properties against *Streptococcus pneumoniae* and *Haemophilus influenzae*, providing some protection against bacterial superinfection in the setting of viral inflammation.[25]

Conclusions

The current situation makes it feasible to investigate the potential beneficial effects of volatile anaesthetics on systemic inflammation, sepsis, and ARDS in mechanically ventilated COVID-19 patients, while at the same time augmenting the range of sedative drugs in this still increasing ICU population. We advocate seizing this exceptional opportunity to study this hypothesis worldwide. It is imperative that well-designed dose finding trials or RCTs are conducted according to the guidelines of good clinical practice, both for the drug itself and for the medical devices applied to administer the drug in the ICU.

Funding

MMRFS: his research group/department received (over the last 3 years) research grants and consultancy fees from The Medicines Company (Parsippany, NJ, USA), Masimo (Irvine, CA, USA), Fresenius (Bad Homburg, Germany), Dräger (Lübeck, Germany), Paion (Aachen, Germany), Medtronic (Dublin, Ireland). He receives royalties on intellectual property from Demed Medical (Temse, Belgium) and the Ghent University (Gent, Belgium).

Declarations of interest

MMRFS is a director of the *British Journal of Anaesthesia*. The other authors declare that they have no conflicts of interest.

References

1. WHO. *Coronavirus disease 2019 (COVID-19) situation report-93*. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200401-sitrep-72-covid-19.pdf?sfvrsn=3dd8971b_2. [Accessed 23 April 2020]
2. Ferrando C, Aguilar G, Piqueras L, Soro M, Moreno J, Belda FJ. Sevoflurane, but not propofol, reduces the lung inflammatory response and improves oxygenation in an acute respiratory distress syndrome model: a randomised laboratory study. *Eur J Anaesthesiol* 2013; **30**: 455–63
3. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; **395**: 1033–4
4. DAS-Taskforce 2015, Baron R, Binder A, et al. Evidence and consensus based guideline for the management of delirium, analgesia, and sedation in intensive care medicine. Revision 2015 (DAS-Guideline 2015) - short version. *Ger Med Sci* 2015; **13**. Doc19
5. Laferriere-Langlois P, d'Aragon F, Manzanares W. Halogenated volatile anesthetics in the intensive care unit: current knowledge on an upcoming practice. *Minerva Anestesiol* 2017; **83**: 737–48
6. Bellgardt M, Bomberg H, Herzog-Niescery J, et al. Survival after long-term isoflurane sedation as opposed to intravenous sedation in critically ill surgical patients: retrospective analysis. *Eur J Anaesthesiol* 2016; **33**: 6–13
7. Mesnil M, Capdevila X, Bringuier S, et al. Long-term sedation in intensive care unit: a randomized comparison between inhaled sevoflurane and intravenous propofol or midazolam. *Intensive Care Med* 2011; **37**: 933–41
8. Cousins MJ, Mazze RI. Methoxyflurane nephrotoxicity. A study of dose response in man. *JAMA* 1973; **225**: 1611–6
9. Higuchi H, Sumikura H, Sumita S, et al. Renal function in patients with high serum fluoride concentrations after prolonged sevoflurane anesthesia. *Anesthesiology* 1995; **83**: 449–58
10. Röhm KD, Mengistu A, Boldt J, Mayer J, Beck G, Piper SN. Renal integrity in sevoflurane sedation in the intensive care unit with the anesthetic-conserving device: a comparison with intravenous propofol sedation. *Anesth Analg* 2009; **108**: 1848–54
11. Cabibel R, Gerard L, Maiter D, Collin V, Hantson P. Complete nephrogenic diabetes insipidus after prolonged sevoflurane sedation: a case report of 3 cases. *A A Pract* 2019; **12**: 155–9
12. L'Heudé M, Poignant S, Elaroussi D, Espitalier F, Ferrandière M, Laffon M. Nephrogenic diabetes insipidus associated with prolonged sedation with sevoflurane in the intensive care unit. *Br J Anaesth* 2019; **122**: e73–5
13. Bomberg H, Groesdonk HV, Bellgardt M, Volk T, Meiser A. AnaConDa™ and Mirus™ for intensive care sedation, 24 h desflurane versus isoflurane in one patient. *Springerplus* 2016; **5**: 420
14. Sulbaek Andersen MP, Sander SP, Nielsen OJ, Wagner DS, Sanford Jr TJ, Wallington TJ. Inhalation anaesthetics and climate change. *Br J Anaesth* 2010; **105**: 760–6
15. Soukup J, Schärff K, Kubosch K, Pohl C, Bomplitz M, Kompardt J. State of the art: sedation concepts with volatile anesthetics in critically Ill patients. *J Crit Care* 2009; **24**: 535–44
16. Stollings LM, Jia LJ, Tang P, Dou H, Lu B, Xu Y. Immune modulation by volatile anesthetics. *Anesthesiology* 2016; **125**: 399–411
17. Herrmann IK, Castellon M, Schwartz DE, et al. Volatile anesthetics improve survival after cecal ligation and puncture. *Anesthesiology* 2013; **119**: 901–6
18. Beck-Schimmer B, Baumann L, Restin T, et al. Sevoflurane attenuates systemic inflammation compared with propofol, but does not modulate neuroinflammation: a laboratory rat study. *Eur J Anaesthesiol* 2017; **34**: 764–75
19. Koutsogiannaki S, Hou L, Babazada H, et al. The volatile anesthetic sevoflurane reduces neutrophil apoptosis via Fas death domain-Fas-associated death domain interaction. *FASEB J* 2019; **33**: 12668–79
20. Jabaudon M, Boucher P, Imhoff E, et al. Sevoflurane for sedation in acute respiratory distress syndrome. A randomized controlled pilot study. *Am J Respir Crit Care Med* 2017; **195**: 792–800
21. MacDonald BA, Chakravarthy KV, Davidson BA, et al. Halothane modulates the type i interferon response to influenza and minimizes the risk of secondary bacterial

pneumonia through maintenance of neutrophil recruitment in an animal model. *Anesthesiology* 2015; **123**: 590–602
22. Knight PR, Nahrwold ML, Bedows E. Anesthetic action and virus replication: inhibition of measles virus replication in cells exposed to halothane. *Antimicrob Agents Chemother* 1980; **17**: 890–6
23. Knight PR, Nahrwold ML, Bedows E. Inhibiting effects of enflurane and isoflurane anesthesia on measles virus replication: comparison with halothane. *Antimicrob Agents Chemother* 1981; **20**: 298–306
24. Bedows E, Davidson BA, Knight PR. Effect of halothane on the replication of animal viruses. *Antimicrob Agents Chemother* 1984; **25**: 719–24
25. Mehta S, Behr G, Kenyon D. The effect of volatile anaesthetics on common respiratory pathogens. Halothane, trichloroethylene and methoxyflurane. *Anaesthesia* 1974; **29**: 280–9