Toxicity of inhaled agents after prolonged administration

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Abstract Inhaled anesthetics have been utilized mostly for general anesthesia in the operating room and oftentimes for sedation and for treatment of refractory status epilepticus and status asthmaticus in the intensive care unit. These contexts in the ICU setting are related to potential for prolonged administration wherein potential organ toxicity is a concern. Over the last decade, several clinical and animal studies of neurotoxicity attributable to inhaled anesthetics have been emerging, particularly in extremes of age. This review overviews potential for and potential mechanisms of neurotoxicity and systemic toxicity of prolonged inhaled anesthesia and clinical scenarios where inhaled anesthesia has been used in order to assess safety of possible prolonged use for sedation. High dose inhaled agents are associated with postoperative cognitive dysfunction (POCD) and other situations. However, thus far no strong indication of problematic neuro or organ toxicity has been demonstrated after prolonged use of low dose volatile anesthesia.

Keywords Neurotoxicity · Sedation · Critical care · ICU · Inhaled agents · Volatile anesthetics

1 Introduction

Inhaled anesthetics have been widely used since the nineteenth century for general anesthesia as they possess several relevant favorable effects for surgery, including amnesia,

skeletal muscle relaxation, control of the sympathetic nervous system, and analgesia. Additionally, they provide other beneficial physiological effects such as seizure suppression and bronchodilation, and therefore are occasionally implemented in the situations of status epilepticus and status asthmaticus unresponsive to other treatment modalities, and more recently, for sedation in the intensive care unit (ICU), all three contexts associated with potential for prolonged administration. Organ toxicity is rare in patients exposed to inhaled anesthetics for surgery. However, the use of inhaled agents for sedation and treatment of refractory status epilepticus and status asthmaticus is often protracted which raises a concern about the potential for organ toxicity. Much of the concern arises from organ toxicity reported with earlier anesthetics which are little used presently; e.g., hepatotoxicity with halothane [1]; and nephrotoxicity with methoxyflurane [2] and enflurane [3]. Numerous studies demonstrating hepatotoxicity and nephrotoxicity associated with inhaled anesthetics were not found to be attributable to the compounds per se, but their metabolites from CYP-P450-mediated biotransformation. Notably, in the last decade, evidence of neurotoxicity (probably not related to cytochromes) caused by volatile anesthetics has become evident in many clinical and animal studies, especially in extremes of ages. The goal of this review is to summarize data regarding systemic and neurologic toxicity which may be relevant to clinical situations associated with prolonged use of inhaled anesthetics.

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2 Neurotoxicity of inhaled anesthetics

2.1 Preclinical studies

Inhaled anesthetics possess highly lipid soluble properties allowing them to easily penetrate into the central nervous system (CNS). Although their effects on the CNS have been thought to be diminished after inhalation anesthetic discontinuation and emergence from anesthesia, in fact a decline of cognitive function has been observed well after cessation of anesthesia and surgery [4]. This implies that their CNS effects (or perhaps associated neuroinflammation) may be longer than previously thought. However, it is very difficult to determine what actually causes cognitive impairment, particularly in the postoperative period. It may be attributable to pre-existing medical/neurologic problems, anesthetic drugs, surgery, stress response, or some combination.

In an aged rodent model, isoflurane and isoflurane with nitrous oxide anesthesia were associated with impairment in spatial memory for 1–3 weeks [5, 6], whereas no lasting memory dysfunction was observed after propofol anesthesia of 2 h [7]. These data indicate that an individual anesthetic drug per se, rather than generic general anesthesia, may be a crucial contributor to postanesthesia cognitive impairment. Various inhaled anesthetics have been demonstrated to affect cognitive function in preclinical models. Impairment of memory and spatial learning were observed in aged and adult rodents receiving isoflurane [8], sevoflurane [9, 10], nitrous oxide [11], and sevoflurane with nitrous oxide [12]. Exposure to 70% nitrous oxide produced lasting memory impairment in aged rats [11] thought to be due to nitrous oxide causing injury manifest as a vacuolar reaction [13], whereas lower doses may be neuroprotective. The dose–response relationship of N₂O neuroprotection/neurotoxicity resembles that seen with ketamine, an NMDA antagonist as is N₂O [14]. Conversely, some neurobehavioral studies showed positive effects of volatile agents, isoflurane [15, 16] and halothane [17], on cognitive function possibly via an up-regulation in NMDA receptor 2B subunit expression in the hippocampus [15]. Thus the preclinical data regarding cognitive deficits are not uniform but do indicate potential for injury and thus are concerning regarding relevance to humans.

2.2 Neuroinflammation

Neuroinflammation has been shown to play a pivotal role in the pathogenesis of neurodegeneration and the development of postoperative cognitive dysfunction (POCD) [18–20], and is, moreover, associated with anesthesia, surgery, trauma, hospitalization, and various drugs [21]. The elevations of proinflammatory cytokines have been found in both the CNS and systemic circulation in surgical patients [22, 23],

the latter of which can further stimulate CNS inflammatory response by inducing the release of other cytokines from glia cells [24]. Wu et al. [25] demonstrated that isoflurane anesthesia increased the proinflammatory cytokines including IL-1 β , IL-6, and TNF- α in brain tissues of mice with unclear mechanisms. The neuroinflammation and POCD was improved in rodents receiving inflammatory inhibitors including an IL-1 antagonist [26] and an anti-TNF agent [27]. These data infer that neuroinflammation associates with POCD to some extent and it is tempting to speculate regarding the potential of anti-proinflammatory drugs to preclude POCD. See Fig. 1.

2.3 Post operative cognitive dysfunction in humans

The incidence of POCD has been reported to be 25.6 and 9.9% at 1 week and 3 months after surgery respectively with advanced age found to be a major risk factor [28]. Aging brain is thought to be vulnerable to an insult (such as anesthesia) due to a decline of several structures, chemicals, and neuronal functions in the brain, in sum creating a condition of decreased reserve such that a small perturbation cannot be compensated. Moreover, neuroinflammation triggered by any insult will be more exaggerated in the aged brain compared with young brain; thought to be due to massive activation of microglia [29]. A long duration of anesthesia also appears to predispose patients to POCD [28] with deeper level of anesthesia associated with postoperative delirium, a type of POCD [30]. This leads to the notion that anesthetics may aggravate neurodegenerative processes or directly damage the brain (i.e. neurotoxicity) especially when prolonged anesthesia is provided. A case control study demonstrated no association between general anesthesia and dementia; however, this association was found in a subgroup of patients older than 65 years [31]. Williams et al. conducted a randomized controlled trial (RCT) of 262 old adult patients undergoing elective total knee replacement and observed that the incidence of POCD in patients receiving general anesthesia was no different compared to those receiving epidural anesthesia [32]. Despite the several preclinical studies supporting cognitive impairment pertaining to volatile anesthetics [5, 8, 11], the clinical human data remains inconclusive.

Although the mechanisms of POCD remain unclear, many hypotheses have been proposed, including direct toxic effects by altering calcium homeostasis [33–35], neuroinflammation by surgical stress response [36], age-sensitive suppression of neuronal stem cell function [16], and augmentation of endogenous neurodegenerative processes [37]. In both in vitro and in vivo studies, inhaled anesthetics can cause neuronal cell damage via activation of inositol 1,4,5-trisphosphate (IP₃) receptors on the endoplasmic reticulum (ER) membrane resulting in excessive calcium release

Fig. 1 Factors and molecular events associated with pathogenesis of cognitive decline [22]. Reprinted from Terrando et al. [22], perioperative cognitive decline in the aging population, with permission from Elsevier

from the ER which triggers apoptosis [33–35]. Nonetheless, this effect differs among inhaled anesthetics. Isoflurane caused greater neurodegeneration than sevoflurane at equipotent exposures [34]. A more detailed summary of preclinical and human studies of neurotoxicity related to volatile anesthetics is tabulated in Tables 1 and 2.

3 Clinical indications for prolonged inhaled anesthetics

3.1 Sedation

Critically ill patients are routinely provided sedation to alleviate pain, to control anxiety and agitation, and to facilitate ventilator synchronization. Moreover, sedation plays an essential role in management in some specific situations such as targeted temperature management, intracranial hypertension, status asthmaticus, and refractory status epilepticus. Many studies have demonstrated sedation in the general ICU is associated with poor outcomes, including increased duration of mechanical ventilation and prolonged hospital stay [41], and therefore minimal sedation is recommended in the ICU setting.

Although the guidelines for sedation in critically ill patients by the American College of Critical Care Medicine do not mention inhaled agents [42], several review studies suggest volatile agents, such as isoflurane or sevoflurane, as an alternative for traditional intravenous ICU sedation. Inhaled anesthetics can cause cerebral vasodilation (uncoupled to associated hypometabolism) at high doses posing a

risk of exacerbation of intracranial hypertension, and therefore have been historically avoided in brain-injured patients at risk of elevated ICP [43]. However, volatile anesthetics can provide many advantages including rapid emergence times, ability to continuously monitor the end-tidal concentration of gas allowing more precise titration, sufficient conscious depression at low concentration without autonomic disturbances [44], and drug elimination independent of the liver and the kidneys. Many preclinical studies have revealed the potential neuroprotective effect of isoflurane [45–47] and sevoflurane [48–50] regardless of the time of administration, although the long-term neuroprotective effects are still unproven.

Compared to propofol, isoflurane was related to a decrease in cortical spreading depolarization (CSD), a depolarization wave thought to be an additional mechanism of secondary brain injury [51], and higher baseline blood flow and plasma glucose [52] while increasing brain:plasma glucose ratio [53], suggesting possibly beneficial effects of isoflurane in brain injury patients. This is supported by a retrospective study of anesthetics used for endovascular management of stroke by Sivasankar et al. Patients who received volatile anesthesia did better than those receiving total intravenous anesthesia [54]. This might be explained by Hoffman et al's observations of higher brain PO_2 with volatile versus intravenous anesthesia in humans undergoing temporary focal ischemia during aneurysm surgery [55].

Bösel et al. investigated the effects of isoflurane sedation on cerebral oxygenation, circulation, and pressure in cerebrovascular intensive care patients. An intravenous agent (propofol or midazolam) was initiated then replaced by 0.5

Table 1 Preclinical studies of neurotoxicity associated with inhaled anesthetics

Study	Animal model and number	Age	Groups and anesthetic gas and dose	Mean or ranges duration of anesthetic gas (h)	Potential neurotoxicity	Outcome	Conclusion
Dutton et al. [8]	Sprague–Dawley rats; n = 264	Unknown	Rats receiving isoflurane while trained to fear context, then divided into 3 groups: isoflurane (0.12–1%) was either discontinued, maintained unchanged, or rapidly increased to 1.0 MAC for 1 h immediately after training	N/a	Yes	Isoflurane administration during fear conditioning, but not posttraining administration, dose-dependently suppressed fear conditioning	Isoflurane provides intense dose-dependent anterograde but not retrograde amnesia for classic fear conditioning
Jevtovic et al. [13]	Female Sprague–Dawley rats	Adult	150% nitrous oxide/50% oxygen for various durations from 1 to 16 h versus control (room air)	1–16	Yes	A maximum vacuole reaction was observed in PC/RSC neurons in brains examined immediately after 3 h of N ₂ O exposure, which was markedly diminished at 1 h after discontinuation and disappeared at 3 h, whereas prolonged exposure for 8 h or more caused neuronal cell death	Short-term exposure of adult rats to N ₂ O causes injury to PC/RSC neurons that is rapidly reversible, but prolonged N ₂ O exposure causes neuronal cell death
Culley et al. [6]	Rats; n = 344	6 and 18 months	1.2% isoflurane/70% nitrous oxide/oxygen versus control (30% oxygen)	2	Yes	Anesthetized aged rats failed to improve with repeated testing, whereas young rats showed an improvement, and took longer to complete the maze than aged control rats	Isoflurane with nitrous oxide anesthesia produces a sustained learning impairment in aged rats, but not in young rats, at 1 and 3 weeks after exposure

Table 1 (continued)

Study	Animal model and number	Age	Groups and anesthetic gas and dose	Mean or ranges duration of anesthetic gas (h)	Potential neurotoxicity	Outcome	Conclusion
Culley et al. [5]	Rats; n = 344	18 months	1.2% isoflurane, 1.2% isoflurane with 70% nitrous oxide, and control (oxygen)	2	Yes	Rats anesthetized with 1.2% isoflurane with 70% nitrous oxide made fewer correct choices before first error on a 12-arm radial maze	Spatial memory is impaired for 2 weeks after general anesthesia in aged rats independent of whether nitrous oxide is used
Culley et al. [11]	Fischer rats; n = 344	18 months	70% nitrous oxide + 30% oxygen versus 70% nitrogen + 30% oxygen (control)	4	Yes	The rats exposed to nitrous oxide took more time to complete the maze and made fewer correct choices before first error	Sedation with 70% nitrous oxide produces lasting impairment in spatial working memory in aged rats
Bianchi et al. [38]	Tg2576 transgenic mice and nontransgenic littermates	12 months	0.9–1% isoflurane versus 0.8–1% halothane	2 h per day for 5 days (total of 10 h)	Yes	At 12 months of age, anesthetic exposure did not further enhance cognitive decline in the transgenic mice; halothane enhances plaque deposition in the Tg2576 mouse model, but that isoflurane does not; in wild-type animals, isoflurane causes a decrease in cognitive performance whereas halothane does not	Anesthetics influence cognition and amyloidogenesis, but that the mechanistic relationship remains unclear
Rammes et al. [15]	Male C57BL/6J mice	4–5 months	1% isoflurane in oxygen/air (FiO ₂ = 0.5) versus nonanesthetized mice (control)	2	No	Anesthetized mice showed better cognitive performance; NR2B subunits of the NMDA receptors were selectively up-regulated in hippocampal neurons after anesthesia	Isoflurane anesthesia induces a hippocampus-specific elevation of NR2B subunit composition, enhances LTP in CA1 neurons, and produces hippocampal-dependent cognitive improvement

Table 1 (continued)

Study	Animal model and number	Age	Groups and anesthetic gas and dose	Mean or ranges duration of anesthetic gas (h)	Potential neurotoxicity	Outcome	Conclusion
Stratmann et al. [16]	Male rats; n = 161	7 and 60 days	1–4% isoflurane versus sham control	4	Undetermined	Isoflurane improved spatial reference memory of P60 rats long-term, but it caused a delayed-onset, progressive, persistent hippocampal deficit in P7 rats in fear conditioning and spatial reference memory tasks	Isoflurane differentially affects both neurogenesis and long-term neurocognitive function in P60 and P7 rats
Wiklund et al. [9]	Wild-type mice and mice with altered nicotinic cholinergic neurotransmission (beta2KO); n = 100	Young (3–4 months) and aged (15–18 months)	Control, 2.6% sevoflurane, or sham groups	2	Yes	Anesthetized wild-type, both young and aged, and beta2KO mice showed impaired memory	Sevoflurane anesthesia causes memory impairment in mice regardless of beta2 receptor-mediated nicotinic cholinergic neurotransmission
Liu et al. [10]	Male Sprague–Dawley rats; n = 40	Adult	Sevoflurane (0.5, 1, or 2%) versus 70% nitrogen + 30% oxygen (control)	2	Yes	2% sevoflurane induced significant impairment of retention performance on a 24-h test and inhibited phosphorylation of GSK-3 β in the hippocampus 2 h after training	Sevoflurane exposure can impair consolidation of IA memory in rats, which may be due to suppression of GSK-3 β phosphorylation in the hippocampus

Table 1 (continued)

Study	Animal model and number	Age	Groups and anesthetic gas and dose	Mean or ranges duration of anesthetic gas (h)	Potential neurotoxicity	Outcome	Conclusion
Tang et al. [17]	Triple-transgenic AD (3xTgAD) mice; n = 256	2, 4, and 6 months	0.9–1.1% halothane, 0.9–1.1% isoflurane, or control (40% oxygen with nitrogen)	5 h once a week for 4 weeks (total of 20 h)	No	Learning and memory improved after halothane exposure in the 2-month-old group relative to controls, but no changes in the isoflurane group; level of phospho-tau in the hippocampus was increased 2 months after anesthesia, especially in the 6-month exposure group, but changes in amyloid, caspase, microglia, or synaptophysin levels were not detected	Exposure to two different inhalation-type anesthetics during the presymptomatic phase of AD does not accelerate cognitive decline
Xiong et al. [12]	Male Sprague Dawley rats; n = 40	18 months	1.3% sevoflurane with 50% nitrous oxide versus control (oxygen)	4	Yes	Sevoflurane with nitrous oxide exposure induced a significant deficit in spatial learning acquisition and memory retention at 48 h	General anesthesia with 1.3% sevoflurane and 50% N ₂ O impaired hippocampus-dependent learning and memory in aged rats
DeYoung et al. [39]	Female Sprague Dawley rats; n = 11	Adult	0.5% sevoflurane	7 days	No	No evidence of microgliosis, astrogliosis, neuronal apoptosis, necrosis, amyloidosis, and phosphorylated-tau accumulation	Long exposures to low concentration of isoflurane have no overt consequences on neuropathology

Table 2 Clinical studies of postoperative cognitive dysfunction in humans

Study	Design	Location	Participants and number of participants	Intervention	Results
Williams et al. [32]	Prospective, randomized controlled trial	New York, USA	262 patients undergoing elective primary total knee replacement with a median age of 69 years; 70% women	Epidural versus general anesthesia	No significant differences between the epidural and general anesthesia groups in cognitive test results at either 1 week or 6 months
Moller et al. [28]	Prospective cohort, multicenter study	13 hospitals in eight European countries and USA	1218 patients; aged at least 60 years old presenting for major abdominal, non-cardiac thoracic, or orthopedic surgery under general anesthesia; control group was recruited with the same criteria but not admitted to hospital	Neuropsychological tests was assessed before and 1 week and 3 months after major non-cardiac surgery	The incidence of POCD at 1 week and 3 months after surgery were 25.8% and 9.9% compared with 3.4% and 2.8%, respectively, of controls. Increasing age and duration of anesthesia, little education, a second operation, postoperative infections, and respiratory complications were risk factors for early postoperative cognitive dysfunction, but only age was a risk factor for late postoperative cognitive dysfunction
Steinmetz et al. [4]	Observational multicenter study	Europe and USA	2,536 patients; men and women aged 40 years or older presenting for major or minor noncardiac surgery during regional or general anesthesia	Cognitive function was assessed by a neuropsychological test battery at three time points: before, at 1 week after, and at 3 months after noncardiac surgery	POCD at 3 months, but not at 1 week, was associated with increased mortality (hazard ratio, 1.63 [95% confidence interval, 1.11–2.38]; $P=0.01$)
Tang et al. [40]	Prospective, non-randomized trial	Philadelphia, USA	11 patients undergoing idiopathic nasal CSF leak correction	Total intravenous propofol and remifentanyl or inhalational sevoflurane, depending on provider choice	Mean CSF amyloid- β (1–42) was unchanged, but total-tau and phosphorylated-tau increased until at least 48 h; total-tau, phosphorylated-tau, or amyloid- β (1–42) concentrations were not different between anesthetic groups; CSF interleukin-10, S100Beta, and tumor necrosis factor α were increased similarly in both groups at 24 h, but interleukin-6 was increased more in the inhalational group

Table 2 (continued)

Study	Design	Location	Participants and number of participants	Intervention	Results
Chan et al. [30]	Prospective, randomized controlled trial	Hong Kong	921 elderly (≥ 60 years) patients undergoing major noncardiac surgery	Patients were randomly assigned to receive either BIS-guided anesthesia or routine care	BIS-guided anesthesia reduced volatile anesthetics by 30%; fewer patients with delirium in the BIS group compared with routine care (15.6% vs. 24.1%, $P=0.01$); patients in the BIS group had a lower rate of POCD at 3 months compared with routine care (odds ratio 0.67; 95% CI, 0.32–0.98; $P=0.025$)
Sprung et al. [31]	Retrospective, population-based, nested, case-control study	Minnesota, USA	877 patients (≥ 45 years old) with dementia, each with a corresponding control		Anesthetic exposure was not significantly associated with dementia (95% CI, 0.73–1.10; $P=0.27$); no significant association was found when exposure was quantified as number of procedures

MAC of isoflurane for an average of 3.5 days. Regional cerebral tissue oxygen saturation was increased while oxygen saturation was unchanged resulting in a reduction in cerebral oxygen extraction. Surprisingly, no significant changes of intracranial pressure and middle cerebral artery mean flow velocity were observed after switching to isoflurane [56] which could be explained by vasodilating effect of isoflurane on the small arterioles rather than the large arteries [57], or perhaps a dose low enough to not produce a significant hyperemia to produce an ICP increase.

Notably, many recent studies in the ICU setting demonstrated positive clinical outcomes of volatile sedation when compared to intravenous sedation. An RCT study by Kong et al. [58] reported that ICU patients with isoflurane sedation had a longer duration of satisfactory sedation, sustained stable sedative levels, and demonstrated more rapid recovery from sedation than those with midazolam. Moreover, the degree of sedation with isoflurane was easily and rapidly controlled compared to midazolam. Sackey et al. [59] conducted a prospective RCT in 40 patients admitted to the general ICU who received sedation for up to 96 h by either isoflurane or midazolam, observing a trend toward lower incidence of long-term hallucination or abnormal ideation after isoflurane sedation, and reporting that 6-month mortality rates were 4 out of 20 patients with isoflurane sedation and 7 of 20 patients with midazolam sedation. More recently, Bellgardt et al. conducted a retrospective cohort study in 200 critically ill surgical patients, comparing the mortality after long-term sedation (> 96 h) with either isoflurane or propofol/midazolam. The patients sedated with isoflurane had the lower in-hospital and 365-day mortality than those sedated with propofol/midazolam [60]. Although mechanisms of these observations are yet to be elucidated, these findings, nonetheless, should draw more attention to the advantageous use of inhaled agents in the ICU setting.

For the purpose of sedation, the duration of inhaled agents' administration is generally longer (days to weeks) than with routine use of general anesthesia for surgery (hours), causing a concern about organ toxicity. To date, no clinical human studies have demonstrated hepatotoxicity or nephrotoxicity associated with inhalation sedation (in contrast to surgical anesthesia doses [61, 62]). Perbet et al. investigated nephrotoxic effects of 48-h sevoflurane for sedation in 12 non-obese patients without hepatic or renal failure admitted to ICU. The mean fluoride concentration was 51.7 $\mu\text{mol/L}$ on day 1 and 68.1 $\mu\text{mol/L}$ on day 2, which is higher than the accepted toxic concentration threshold of 50 $\mu\text{mol/L}$. However, no kidney injury was observed according to the AKIN criteria [63]. Tanigami et al. studied the toxicity of isoflurane (0.5–1 MAC) sedation for a mean of 94 MAC-hours (range, 13–248 MAC hours) in 40 patients undergoing mechanical ventilation after cardiac surgery. No patients experienced serum

inorganic fluoride above the nephrotoxic level or developed evidence of renal toxicity, or hepatic dysfunction [64]. In a case series of 3 children sedated with isoflurane (range of duration 144–196 h) in the ICU, 2 patients with abdominal complications and 1 patient with refractory status epilepticus, creatinine clearance and serum fluoride level if measured were within normal limits after sedation [65]. Notably, the use of MAC-hours as a measure of degree of exposure arguably can be misleading if organ toxicity is related to an absolute high concentration of anesthetic, e.g. 6 MAC hours at a 2-MAC given for 3 h may be very toxic whereas 6 MAC hours at 0.2 MAC given for 30 h may be perfectly safe.

Although inhaled anesthetics have many benefits suitable for ICU sedation with no report of clinically significant organ toxicity in this context, its feasibility is a concern and several technical prerequisites must be met as ICU ventilators are designed to function differently from anesthesia machines. In 2005, the anesthetic conserving device (AnaConDa) was introduced as a promising tool for ICU sedation with volatile anesthetics and is compatible with isoflurane and sevoflurane. Soda lime is not necessary in this device. Fluoride level may increase with prolonged administration [44]. However, it still has some limitations including, but not limited to, incompatibility with desflurane, special care regarding its preparation and its administration needed, and containing a dead space of 100 mL which may preclude its use in children. Moreover, most standard gas monitors cannot display inspiratory and end-tidal concentration correctly [44, 66]. Despite these limitations, many studies have shown better performance of inhalation sedation via the AnaConDa device compared to conventional sedation. Sackey et al. [67] compared isoflurane versus midazolam for ICU sedation for up to 96 h in 40 ventilator-dependent patients and showed that patients undergoing isoflurane sedation via the AnaConDa device had shorter wake-up time and time to follow verbal command. L'Her et al. [68] demonstrated the feasibility and efficacy of prolonged isoflurane sedation (up to 348 h) via the AnaConDa device in ICU patients, who need midazolam more than 0.05 mg/kg/h to reach the desired sedation levels, and no significant hemodynamic changes, hepatic dysfunction, and renal injury were observed. Similarly, Röhm et al. [69] showed that post CABG surgery patients receiving sevoflurane via the AnaConDa device had shorter recovery time and length of hospital stay than those receiving propofol for sedation. Notably, to date, both volatile anesthetics for ICU sedation and the AnaConDa device have not been approved by the US FDA, even though several favorable outcomes of inhalation sedation are obviously identified.

4 Refractory status epilepticus (RSE)

Refractory status epilepticus (RSE) is a life-threatening neurological emergency requiring ICU admission. There is no consensus of the precise definition of RSE. The proposed definitions differ in the number of antiepileptic medications implemented (e.g. 2 or 3) and the duration of seizure (e.g. < 1, 1, or 2 h). The most accepted criteria are defined as persistent seizure that continues despite treatment with benzodiazepines and one antiepileptic drug.

The annual incidence of status epilepticus (SE) is 10–40/100,000. Approximately one-third of those will develop RSE. The mortality rate of RSE is about 16–39% which is three times higher than of responsive status epilepticus [70]. Only 20.7% of patients with RSE will return to baseline clinical conditions compared to 62.6% of those with nonrefractory SE [71]. These clinical epidemiologic data are supported by preclinical [72–76] and clinical [77] studies. The management of SE is thus aimed to rapidly control seizure, provide an element of neuroprotection, and avoid complications. In early SE intravenous benzodiazepine is the drug of choice. Second line antiepileptic medication (e.g. phenytoin, phenobarbital, or valproate) is used if patients are unresponsive to benzodiazepines after 30 min. Unless these treatments are effective, at this point RSE is diagnosed wherein general anesthesia is recommended to achieve a level of burst suppression [78]. The commonly used anesthetic agents include thiopental (or pentobarbital), propofol, and midazolam. Prolonged administration of intravenous anesthetics however can pose the risks of drug accumulation, cardiorespiratory depression, hepatic and renal dysfunction, pneumonia (benzodiazepines and barbiturates primarily), and propofol infusion syndrome. In one systematic review of 193 patients with RSE comparing the effectiveness of pentobarbital, propofol, and midazolam, patients treated with pentobarbital achieved the highest success in controlling RSE; however, patients who received pentobarbital experienced acute failure in 8%, breakthrough seizures in 12%, withdrawal seizures within 48 h in 43%, and hypotension requiring vasopressors in 77% [79]. Unfortunately, most studies comparing intravenous agents may not account for pharmacokinetic or dose-related pharmacodynamics differences such that equipotent doses may not have been compared. Moreover, given that withdrawal of barbiturates and benzodiazepines in conditions of addiction is associated with seizure [80, 81], there is always concern with these drugs that their use, although stopping seizures, exacerbates the proconvulsant condition upon their withdrawal, making it difficult to determine if they helped or not.

The use of inhaled anesthetics has emerged as an alternative treatment of RSE with several advantageous properties including apparent reliable efficacy, rapid onset of action, easy titration to attain the burst suppression, and potential

neuroprotection [45, 47–49]. Moreover, continuous monitoring of end-tidal concentrations in the context of continuous EEG monitoring can yield valuable information regarding pharmacodynamic response of the seizure condition. Observation of changing end tidal concentration needed to yield a given degree of EEG suppression of seizure can be helpful information [82, 83].

Thus far, there has been overall a paucity of published literature on the use of inhaled anesthetics for RSE treatment. Not all inhaled anesthetics are thought to be suitable for RSE management. Sevoflurane probably should be avoided since it can activate epileptiform discharges in non-epileptic patients [84]. Zeiler et al. performed a systemic review of 46 RSE patients (28 adults and 18 children) treated with modern inhalation anesthetics. Isoflurane was the most commonly used agent, followed by desflurane. The successful termination of RSE with inhaled anesthetics was found in 92.9% of adults and 94.4% of children. Of those, an immediate response to volatile administration was demonstrated. Desflurane seemed to be less effective than isoflurane as all patients receiving desflurane ($n = 2$) displayed seizure reduction, but could not reach burst suppression as opposed to isoflurane which was utilized as a salvage treatment in these patients [85]. Kofke et al. reported a case series of 9 RSE patients with 11 occasions in 7 North American hospitals. Isoflurane successfully terminated seizure in all patients with burst suppression achieved, but in 8 of 11 patients seizures resumed after discontinuation of isoflurane [82]. Xenon, a monoatomic gas possessing the very high tissue solubility (relative to other noble gases) is an NMDA antagonist [86] with potential antiapoptotic and neuroprotective effects; at subanesthetic levels, was also reported to successfully treat RSE caused by asphyxial encephalopathy in neonates [87]. Maze et al. [88] moreover reported findings indicating a specific advantage of xenon in attenuating neonatal anesthetic neurotoxicity.

Despite several beneficial properties of inhaled anesthetics for RSE management, their disadvantages deserve mention, particularly in prolonged high-dose administration wherein toxicity may be more likely to become apparent. Fugate et al. reported 2 RSE cases treated with prolonged high-dose isoflurane, 34 days with end tidal concentration ranging from 0.7 to 2.2% in a 25 year-old man and 85 days with an end tidal concentration ranging from 0.5 to 2.5% in a 4 year-old girl, both of whom developed MRI changes in the thalamus and cerebellum which, however, ameliorated after isoflurane discontinuation. This suggests that isoflurane might contribute to the seizure-associated MRI signal changes in a dose and duration-dependent manner. If MRI signal abnormalities can reflect neurodegeneration, isoflurane may be neurotoxic, contradicting reports of neuroprotective effects in animals. The authors suggested a possible critical point, beyond which neuroprotection

shifts to neurotoxicity [89]. However, the reversibility of the lesions with isoflurane might indicate that the effects are not permanent.

More recently, Ikeda et al. [90] compared isoflurane versus intravenous anesthetics for RSE treatment. Significant hippocampal change evidenced by MRI was found more often in patients treated with isoflurane and was related to duration of isoflurane treatment, but not average end-tidal concentration. Notwithstanding the absence of proper controls it is tempting to speculate that these MRI changes may be caused by isoflurane-induced neurotoxicity but does not discount the possibility of neural injury by status epilepticus itself, despite achieving cortical electrographic burst suppression. Notably, MRI changes associated with status epilepticus frequently arise in the hippocampus [91]. Moreover, in a preclinical rodent study of status epilepticus, Kofke et al. [92] showed histologic neuroprotection with midazolam but not with isoflurane. It is thus a concern that isoflurane causes MRI changes but it is totally unclear if this corresponds to permanent damage, and needs to be placed in the context of neurotoxic RSE which likely would lead to worse damage if untreated.

With respect to non-neurologic organ toxicity, increased urine fluoride level was observed in RSE patients receiving isoflurane without apparent evidence of nephrotoxicity [82, 83, 93, 94]. It is notable that antiepileptic drugs, such as phenobarbital, phenytoin, and carbamazepine, induce cytochrome P450 in the liver which theoretically would increase metabolism of isoflurane to fluoride. Similarly, although occasionally reported perioperatively with inhaled anesthetics [61, 62], none of these patients experienced hepatotoxicity [83, 94]. Inhaled anesthetics can contribute to cardiovascular complications due to myocardial depression, decreased systemic vascular resistance, suppression of baroreceptor responses, or arrhythmogenic properties. Hypotension has been reported in RSE patients receiving either isoflurane only or isoflurane with desflurane, all of whom required vasopressors to maintain adequate mean arterial pressure [82, 85, 93, 94]. Conceivably the hemodynamic effects contribute to the MRI changes in the context of hypermetabolism. Blenow's [95] observations with hypotension attenuating seizures in rodents would suggest the possibility of hemodynamic side effects contributing to attenuation of seizures with volatile anesthetics.

5 Refractory status asthmaticus

Asthma is a chronic respiratory disease characterized by airway hyper-reactivity, bronchoconstriction, airway inflammation, and mucous plugging, resulting in increased airway resistance, lower airway obstruction, and air trapping. Status asthmaticus (SA) is a life-threatening exacerbation of asthma

which is unresponsive to standard therapies (i.e. systemic and inhaled short acting β_2 -agonists and corticosteroids) which may lead to progressive respiratory failure and death. The World Health Organization estimates approximately 300 million people throughout the world suffer from asthma, particularly in children [96]. Epidemiologic data of pediatric patients with status asthmaticus admitted to hospitals in New Jersey demonstrated that the rate of children needing ICU admission is increasing, although an unchanged rate of mechanical ventilation (0.2/1000) was observed [97]. Management should be initiated promptly to prevent impaired oxygenation and ventilation. First-line therapies include oxygen supplementation, inhaled rapid acting β_2 -agonists, inhaled anticholinergics, systemic glucocorticosteroids and intravenous magnesium sulphate. Second-line therapies consist of intravenous β_2 -agonists, methylxanthines, and noninvasive positive pressure ventilation (NIPPV). Other additional therapies may include recombinant human deoxyribonuclease (DNase), ketamine, heliox, epinephrine, inhalational anesthetics, and extracorporeal membrane oxygenation (ECMO) [98].

Inhaled anesthetics have beneficial physiologic effects including airway smooth muscle relaxation which contributes to reversal of bronchospasm. Therefore, they are occasionally implemented in patients with status asthmaticus refractory to standard therapies. The efficacy of volatile anesthetics for SA treatment has been confirmed in many studies showing rapid and significant improvement of gas exchange and peak inspiratory pressure after volatile anesthetic administration [98–101]. In addition, inhaled agents can produce sedation and relaxation of skeletal muscle in a dose-dependent fashion both of which may further facilitate ventilation. Although all inhaled anesthetics share bronchodilatory properties, there is some extent of difference among these agents. Halothane is thought to be the most potent bronchodilator [102]; however, its use is limited because of its adverse effects including myocardial depression, arrhythmogenic potential (especially with concomitant catecholamine administration), and hepatotoxicity [103] thought made worse in the context of hypoxemia seen with nocturnal desaturation [104]. Whether hypoxemia with asthma relates to this is not known. Desflurane demonstrated a bronchodilator effect at 1 MAC, but increased airway resistance was identified at 2 MAC, whereas a bronchodilator effect was observed at both 1 and 2 MAC of isoflurane and sevoflurane [105]. Desflurane is generally avoided since elevated airway resistance was demonstrated in children with airway reactivity [106]. By the reason of low cost, high bronchodilator potency, and ability to use low gas flow, isoflurane is thus frequently employed for SA treatment [98].

Asthma commonly occurs in children whose many organ systems are immature, potentially increasing susceptibility to organ toxicity. A retrospective review of 31 children

treated with isoflurane (0.3–2.5% with duration ranging from 1 to 181 h) reported hypotension requiring vasopressors in 24 (77%), transient arrhythmia without cardiovascular instability in 3 (10%), neurologic side effects in 3 (10%), and pneumothorax in 1 (3%) patient. Of those with neurologic side effects, 2 patients experienced abnormal movement (maximum isoflurane dose of 0.8 and 1.8%, with duration of 31 and 111 h, respectively), 1 patient developed a syndrome including restlessness, jitteriness, and agitation; all neurological side effects that were resolved after discontinuation of isoflurane [99]. Perhaps these observations are related to a report of seizure with anesthetic induction by isoflurane [107]. These data nonetheless suggest no correlation between dose and/or duration of isoflurane and organ toxicity complications. Carrie et al. presented a case series of 3 SA children, in which 2 patients received isoflurane for up to 16–17 days. No organ toxicity complication was reported in these two cases, but the other patient in whom isoflurane was employed for 3 days experienced mild hypotension. Weaning intravenous β_2 -agonists after starting inhaled anesthetics is typically done in order to diminish cardiovascular side effects [98].

There has been a paucity of case reports regarding the use of sevoflurane in the setting of SA. Mori et al. demonstrated 2 patients with SA successfully treated by 30 and 104 h of sevoflurane. Increased serum inorganic fluoride level above the accepted toxic threshold (> 50 mmol/L) was detected with the peak of 61.1 mmol/L at 4 h after discontinuation of sevoflurane. However, serum creatinine and BUN were unchanged [108]. Watanabe et al. reported a case report of 3-month old with mild laryngomalacia who experienced severe bronchospasm resistant to conventional therapies and required intubation. Successful treatment was achieved by administration of sevoflurane for 94 h. Transient mild increase in liver transaminase was observed. A serum fluoride concentration was 24.2 mmol/L [109]. Given the theoretical concern for compound A and fluoride nephrotoxicity it is notable that no renal dysfunction was reported in association with prolonged sevoflurane.

6 Conclusion

Several reports indicate potential efficacious use of prolonged inhaled anesthesia for status epilepticus, for status asthmaticus, and as sedation in critically ill patients. Given historic evidence of organ toxicity with short term use of some twentieth century inhaled anesthetics (carbon tetrachloride, chloroform, halothane, methoxyflurane, and so on) it is appropriate to have a measure of concern for safety of prolonged inhaled anesthesia with modern anesthetics. This concern is enhanced by the several preclinical animal studies suggesting some evidence of neurotoxicity of volatile

anesthetics. Moreover, no clinical studies conclusively demonstrate safety of prolonged inhaled anesthesia, although several clinical studies reporting on prolonged inhaled anesthesia have not shown significantly problematic, reproducible neuro or systemic organ toxicity.

These concerns are balanced by a risk–benefit type of analysis. Although the organ toxicity of prolonged anesthesia is not conclusively demonstrated, there are reports of prolonged inhalational anesthesia attenuating life threatening status epilepticus and status asthmaticus, such that the clear short term benefits in many instances outweigh the unknown (and probably unlikely) potential for long term problems secondary to treating these otherwise life threatening conditions. Moreover, used as sedation, prolonged inhaled anesthesia in early reports appears to have encouraging effects which improve recovery after critical illness. However, based on perioperative preclinical and clinical reports there should reasonably be some concerns about the long-term post anesthetic effects of prolonged inhalation sedation in ICU patients who may be highly susceptible to neurotoxicity (i.e., extreme aged or brain injured patients). Such issues have barely been investigated. Further studies both animal models and human studies (prospective, retrospective, and epidemiologic data) will be needed to elucidate these questions. Until such studies are done, and based on the life-saving potential of prolonged inhaled anesthesia, we cautiously nonetheless conclude that prolonged inhaled anesthesia used for status epilepticus, status asthmaticus, and critical care agitation or delirium is a reasonable alternative therapy when done in a judicious manner with due consideration of the unlikely potential for serious organ toxicity while attenuating the consequences of otherwise life threatening conditions.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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