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Inhaled Sevoflurane sedation in the intensive care unit. A case report and narrative literature review

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Summary : This article aims at reviewing, in recent literature, the interest and good practice of using volatile sedation with sevoflurane in an intensive care setting. Although rarely used in the intensive care unit (ICU) compared to intravenous sedation, inhaled sedation may be a good alternative to insure comfort to ICU patients. Current literature demonstrates that sevoflurane, administrated through a specifically designed device, the AnaConDa, provides safe and good quality sedation to those patients. Long-term inhaled sevoflurane sedation (ISS) (>96 hours) would be associated to lower agitation, improved pain control, and lower mortality than intravenous sedation. The properties of sevoflurane may be of further advantage in specific intensive care situations such as bronchospasm, postoperative sedation after cardiothoracic surgery, or in agitated patients due to alcohol or other drugs withdrawal. Other studies suggest superiority of ISS in case of pulmonary arterial hypertension, chronic obstructive pulmonary disease, and acute respiratory distress syndrome. We here illustrate our literature review with a case of severe bronchospasm successfully managed using ISS.

Key words : AnaConDa, sevoflurane, inhaled sedation, critical care.

Introduction

The use of volatile agents to anesthetize patients in surgical theatres has been approved for decades. Volatile agents such as sevoflurane have well-known useful pharmacological properties, but are actually underused in the intensive care unit (ICU). This is mainly due to technical issues. In this article, we provide a case report involving inhaled sevoflurane sedation (ISS) and review the use of ISS according to recent literature. We propose, in appendix, two tables summarizing the indications/contraindications, as well as the advantages/disadvantages of ISS, in order to help to an appropriate of it in the ICU (Tables 1 and 2).

Case Report

A 67-year-old woman with a complicated oncological and surgical history was initially admitted in the ICU after an abdominal laparotomy for a suspected peritonitis. At the end of the surgical procedure, she experienced a severe bronchospasm following a sugammadex administration. The bronchospasm resisted to classical medical

Table 1
Indications/Contradications

INDICATIONS	CONTRADICATIONS	DEBATED
Bronchospasm	**Hemodynamic instability**	**ARDS**
Severe acute asthma	**Malignant hyperthermia (MH)**	**Status epilepticus?**
Difficult sedation: (addiction, alcoholism, withdrawal)	**Neuromuscular disease with predisposition to MH**	
Post cardiothoracic surgery	**Acute intracranial hypertension**	

Table 2
Advantages/Disadvantages

ADVANTAGES	DISADVANTAGES
Rapid onset	**Cost**
Extubation delay and wake up time	**Increased dead space**
Quality of awakening / Agitation score (RASS)	**Reflection of CO_2**
Analgesic effect and Pain score	**Need of a scavenging system**
Effective bronchodilator	**Vasodilator effect**
Hepatic and renal safety	

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therapies, including deepening of anesthesia, use of intravenous (IV) ketamine, magnesium sulfate, neuromuscular blocking agents, corticoids, lidocain, adrenaline, and inhaled administration of beta-2 agonist (salbutamol). The bronchospasm origin was unclear, but most probably related to a septic phenomenon during the laparotomy, or to a toxic etiology involving sugammadex. Anaphylaxis was disproved by the serum tryptase dosage, which was negative. The bronchospasm was ultimately successfully treated using prolonged ISS during 3 days in the ICU. We acknowledge the possibility that the relief of bronchospasm can simply be a combination of circumstances, and might not only be due to sevoflurane administration. We decided to perform this literature review a few days after patient discharge from the ICU. Unfortunately, respiratory data such as pressure, and tidal volume were not recorded. Those data could have supported an eventual causal link between the relief of bronchospasm and sevoflurane inhalation. Sevoflurane administration was performed using the AnaConDa® system (ACD-Anaesthetic Conserving Device; Sedana Medical AB, Uppsala, Sweden) (Fig. 1).

Discussion

In the intensive care setting, the ideal sedative agent should offer a rapid onset, effectiveness and sedation of good quality, analgesic effects, a short delay for recovery and ventilation weaning. In addition, it should be easy to use, have few side effects, as well as low cost. The most commonly used sedation in the ICU is currently based on the intravenous administration of analgesic molecules such as fentanyl, sufentanil, or remifentanil, associated, whenever required, with sedative molecules such as propofol, midazolam, or dexmedetomedine. Inhaled sedation using volatile agents such as sevoflurane could challenge intravenous sedation. In our ICU, the first line sedation is intravenous, using an analgesic molecule such as sufentanil or remifentanil, and a hypnotic molecule when necessary (mainly propofol). Midazolam is only used in patients with severe hemodynamic instability conditions or in cases of withdrawal. The AnaConDa device for inhaled sevoflurane sedation is currently still a second line sedation tool, especially because we only have one monitoring of respiratory gas concentration available. This monitoring is necessary to guide end-tidal sevoflurane concentration, and to achieve the target Richmond Agitation Sedation Score (RASS). Our experience mainly concerns bronchospastic patients and, in a few cases, alcohol withdrawal patients.

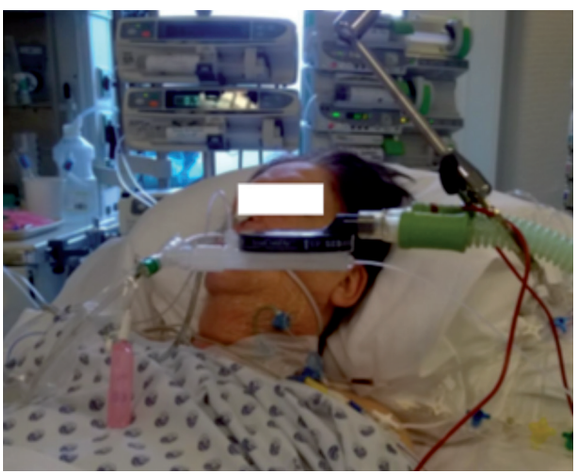

Fig. 1. — Example of AnaConDa device used in the intensive care unit

The pharmacokinetic properties of volatile agents and their use in the operative room is safe and well known, but their safety and efficacy for a long-term sedation (>72 hours) in the ICU was relatively unknown until the study by Mesnil et al (1). They compared long term sedation with ISS to intravenous sedation (propofol or midazolam). All patients were receiving additional remifentanil to achieve analog-sedation, whose depth was evaluated using the Ramsay scale and a pain score. Delay for recovery and extubation upon cessation of administration were much shorter in their ISS group as compared to their propofol and midazolam group (18.6 ± 11.8 and 33.6 ± 13.1 min in the sevoflurane group, 91.3 ± 35.2 and 326.11 ± 360.2 min in the propofol group, and 260.2 ± 150.2 and 599.6 ± 586.6 min in the midazolam group, respectively). The quality of recovery with regard to agitation and pain scores 24 hours after sedation were better with ISS. The quality of sedation as assessed by the Ramsay scale was similar between groups, but the incidence of low blood pressure episodes as defined by a mean arterial pressure (MAP) between 65 and 90 mmHg and the incidence of delirium were higher in the two intravenous groups (1).

The literature reports a lot of severe life-threatening asthma cases that were controlled by the use of an ISS. Volatile agents such as sevoflurane are effective bronchodilators, and can reduce the air-trapping and dynamic hyperinflation of the lungs. These properties are often used in the operating room. Nowadays, these hypnotic agents can also easily be used out of the operating theatres, thanks to

the development of the AnaConDa system (ACD). ACD enables the delivery of volatile agents by any standard ICU ventilator (2). It includes a bacterial and heat-and-moisture-exchanger (HME) filter, with a miniature vaporizer that is continuously supplied in volatile agents by a polypropylene syringe pump. Ninety percent of the delivered agent is recycled thanks to the activated charcoal membrane that absorbs the vapor during expiration, then desorbs it back to the patient during inspiration (this property is called the reflection of sevoflurane). The ratio of sevoflurane concentrations on both sides of the reflector is constant, and the concentration is ten times higher on the patient side than on the ventilator side (3). Although 90% of sevoflurane is recycled, a scavenging system is needed to limit environment pollution and staff exposure in the ICU (4). To optimize the properties of the AnaConDa device, the developers suggest a single one-day use. However, in our experience, three or four days with the same device don't affect the quality of sedation, provided that the device stays horizontal. If it doesn't, the condensation water of the exhaled gas accumulates in the heat-and-moisture-exchanger, and can alter the reflection of sevoflurane and therefore sedation. The level of sedation is reached by adapting the infusion rate to the end tidal expiration fraction of sevoflurane. R. Chabanne et al. demonstrated that, using the ACD alone as a simple heated humidifier breathing filter (i.e. without sevoflurane) increases the work of breathing (from 1.7 ± 1.1 to 2.3 ± 1.2 J/l), the minute ventilation, the intrinsic positive end-expiratory pressure (from 1.3 ± 2.6 to 4.7 ± 4.2cmH_20), the inspiratory pressure swings, and decreases patients comfort. However, adding sevoflurane normalizes all these parameters and suggest that ISS is possible even during a weaning process (5). Another disadvantage of the ACD is the increase of the dead space as compared to standard HME. Actually, the dead space is larger than the internal volume of the device (100ml), due to the reflection of CO_2. Sturesson et al. showed a CO_2 reservoir effect of 180 ml in excess of the ACD internal volume (6). Another study shows that normocapnia cannot be achieved when using tidal volumes below 6 $ml.kg^{-1}$, regardless of the ventilation frequency (7). Therefore, ISS with ACD could be problematic for low tidal volume ventilation patterns such as needed for pediatric patients and for "protective ventilation" settings in acute respiratory distress syndrome (ARDS) patients. Additionally, the use of a heating humidifier is contraindicated while using the ACD. This could potentially lead to insufficient endobronchial warming and humidification. However, ISS with ACD should not be totally prohibited in ARDS patients, insofar as it has been recently suggested that sevoflurane could modulate the lung inflammation, leading to a beneficial effect. Indeed, in an animal study on pigs, Ferrando et al. compared ISS to propofol sedation while monitoring the PaO_2/FiO ratio, and the cytokine concentrations in bronchoalveolar lavages. Their results suggested that sevoflurane decreases lung inflammation, and could improve oxygenation in a better way than propofol sedation (8). Furthermore, Sevoflurane could have some beneficial impact on pulmonary arterial hypertension (PAH), as suggested in some studies. For example, Fyntanidou et al. demonstrated that ISS can reduce pulmonary pressure in a porcine model of endotoxin-induced acute PAH.

Volatile agents also have some well-established effects on the brain. Through their vasodilatation effect on cerebral vessels and inhibiting effect on cerebral autoregulation, they may increase intracranial pressure (ICP). This effect, combined with a vasodilatation effect on the systemic vessels and a subsequent decrease in mean arterial pressure (MAP), can potentially lead to a decrease in cerebral perfusion pressure (CPP). These properties limit the use of volatile sedation in intensive care patients with brain lesions, including trauma, stroke, or subarachnoid hemorrhage. However, it is also established that they have some beneficial effects on the brain, such as non-ischemic preconditioning when being used at concentrations lower than 1 minimal alveolar concentration (MAC). Bösel and Purrucker studied the change from a propofol intravenous sedation to an ISS in a brain lesion ICU population. Sevoflurane was used at 0.5 MAC, and led to an adequate sedation in the majority of cases. In 2/3 patients, ICP moderately increased (2.4 SD mmHg) in the short term, and remained stable in the long term. This increase had poor clinical relevance. They didn't observe any significant change in the middle cerebral artery mean flow velocity (MVF) and found no reduction in the fractional tissue oxygen extraction. However, a decrease of MAP (-7.8 SD mmHg) and CPP (-10.2 SD mmHg) occurred. By contrast, in 1/3 patients, a significant increase in ICP associated with a consistent decrease of MAP led to the termination of the ISS. The patients at the highest risk when using ISS are those with a low baseline cerebral compliance at the time of the switch from intravenous sedation to ISS, that is those with large intra-cerebral hemorrhage, higher requirements for

osmotherapy, or higher ICP values, for example (9). The authors concluded that ISS can be used in brain lesion intensive care patients, provided that a full multimodal neuromonitoring is used, including the measure of ICP, and particularly if the cerebral compliance is strongly affected (10).

Literature reports also the interest of ISS in patients whose sedation is difficult. Prolonged intravenous sedation can induce drug tolerance or dependence. ISS could be a good alternative in this population, including in alcoholic, addicted or withdrawal patients. The study of Redaelli et al. reinforces this potential interest. These authors shifted from difficult intravenous sedation defined by high sedative drug dosage (propofol ≥300 $mg.h^{-1}$ or midazolam ≥8 $mg.h^{-1}$ to reach a RASS of -4), inadequate immobility (no neuromuscular blocking agents were used), more than 2 hypnotic medications to reach the RASS target, or hypertriglyceridemia under propofol sedation, to ISS. They did it in an ARDS population. ISS allowed to reach the target RASS without alteration of renal function or hemodynamic conditions (11).

The potential nephrotoxicity of older halogenated agents such as enflurane is well documented. In contrast, the newest halogenated molecules such as sevoflurane are not considered nephrotoxic, because their metabolic rate is low. Only 5% of sevoflurane is metabolized into inorganic fluorides and hexafluoroisopropanol. A single-blinded study led by Kerstin and Röhm, compared inhaled sevoflurane sedation (ISS) (9.2 ± 4.3 hours) through the ACD to intravenous propofol (9.3 ± 4.7 hours) during postoperative sedation up to 24h after a major abdominal, vascular or thoracic surgery. Inorganic fluoride levels increased after 24 hours of sevoflurane exposure (39 ± 25 μmol/l), and remained elevated during 48 hours after cessation of sedation end. However, no effect on renal function was evidenced. The authors concluded that this short-term sedation in both study groups doesn't affect renal function postoperatively (12). Similar results were obtained after long-term sedation. Gallego et al. studied the renal and hepatic integrity of female pigs during a long-term (72 hours) ISS. No differences were found regarding renal function as assessed by plasma creatinine and urea levels, as well as creatinine clearance, and regarding hepatic function, whereas inorganic fluoride concentration increased. The authors concluded that long-term sedation doesn't affect the renal or hepatic function (13).

The interest of sevoflurane ISS was also studied after cardiothoracic surgery. Kerstin et al. showed that, following coronary artery bypass graft (CABG) surgery, the mean recovery and extubation/ventilator times (22 *vs* 151 min) were shorter in the sevoflurane group than in the propofol group. The length of ICU stay was comparable between groups, but the hospital length of stay was significantly shorter in the sevoflurane group. The side effects related to sedation were similar (14). Another study demonstrated a cardioprotective effect of sevoflurane. It showed that inhaled sevoflurane sedation compared to propofol sedation during off-pump coronary artery bypass decreases myocardial injury markers such as troponin I and N-terminal pro-brain natriuretic peptide. The results were better if the ISS was used both in the operating room and in the ICU than if it was used in the operating room only (15).

Several authors have studied global survival rate after long-term inhaled sedation in opposition to intravenous sedation. Long-term inhaled sedation was well tolerated in ICU patients. For example, Bellgardt et al. compared isoflurane sedation to IV sedation (propofol/midazolam) in the same ICU population. Confounders such as coronary heart disease, chronic obstructive pulmonary disease, acute renal failure, creatinine plasma level, age, and SAPS II (Simplified acute Physiology Score II) where controlled. Patients were continuously sedated and ventilated for more than 96 hours. They demonstrated a lower risk of death of sevoflurane patients during their hospital stay (40% *vs* 63%, P = 0.005), and within the first years after discharge (50% *vs* 70%, P = 0.013) (16).

Finally, most of the above-mentioned studies report similar costs for inhaled and intravenous sedation, but global costs are higher for ISS, due to the cost of the ACD device itself, especially if it is replaced every 24 hours.

Conclusion

ISS have several advantages for sedation outside the operating room. Several studies show its superiority over intravenous sedation in specific circumstances. ICU physicians should be aware of these advantages, and take account of them to update their practice of sedation.

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