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Why aren't the halogenated agents used in the intensive care unit ? Contributions of the AnaConDa device

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Summary : The pharmacokinetic properties of volatile anesthetics agents (rapid therapeutic efficacy, high therapeutic index) and their pharmacodynamics properties suggest that they may be ideally suited to provide adequate sedation in intensive care unit (ICU) patient. They can provide sedation without a risk of accumulation, allowing recovery shortly after stopping their administration. However, their use in the ICU is not yet widespread. Possible causes of this underutilization include a lack of suitable device appended to resuscitation ventilators, ignorance of their method of use, risk of contamination of the ICU environment by volatile anesthetic agents in the absence of any evacuation system, and high cost consecutive to the use of high fresh gas flow rates.
AnaConDa, which appeared in the years 2000, is a modified heat exchanger, allowing the administration, through direct infusion, of volatile anesthetics agents. Placed between the endotracheal tube and the Y-piece of the respirator circuit, it has all the necessary elements for the administration of volatile anesthetic agents by intensive care ventilators. The AnaConDa comprises a vaporizer, a semi-open circuit, a carbon dioxide filter, and an antibacterial filter. Moreover, its handling is easy, even by untrained staffs.
The purpose of this narrative review article is to analyze the feasibility of AnaConDa use in the ICU, at the light of published studies comparing sedation by halogenated agents with sedation by intravenous agents in the ICU, in terms of efficacy for a standard ICU population, as well as for specific populations, and to analyze the cost and safety of such a practice.

Key words : halogenated agents ; intensive care ; Anaconda ; cost ; security.

Introduction

The pharmacokinetic properties of halogenated agents (rapid therapeutic onset and high therapeutic index) and their pharmacodynamics properties suggest that they may be ideally suited to provide adequate sedation for intensive care unit (ICU) patients. Indeed, they offer the possibility to provide sedation without a risk of accumulation, hence enabling faster recovery after stopping their administration. However, their use in the ICU is not yet widespread. Possible causes of this underutilization are a lack of suitable device appended to resuscitation ventilators, lack of knowledge of their method of use, risk of contamination of the ICU environment by halogenated gases in the absence of any gas scavenging system on ICU ventilators, and high cost consecutive to the use of high fresh gas flow rates.
The AnaConDa system (Fig. 1), which appeared in the 2000s, is a modified heat exchanger enabling the administration of halogenated agents by direct inhalation. Placed between the endotracheal tube and the Y-piece of the ventilator circuit, it has all the necessary elements for the administration of halogenated agents through an ICU ventilator. Those elements include a vaporizer, a carbon filter for conservation and re-inhalation of volatile anesthetic agents, and an antibacterial filter. Moreover, its handling is easy, even for untrained staffs.
The purpose of this article is to review studies comparing sedation by halogenated agents with sedation by intravenous agents in the ICU, with respect to cost, safety and efficacy in standard ICU populations, as well as in specific subgroups of patients.

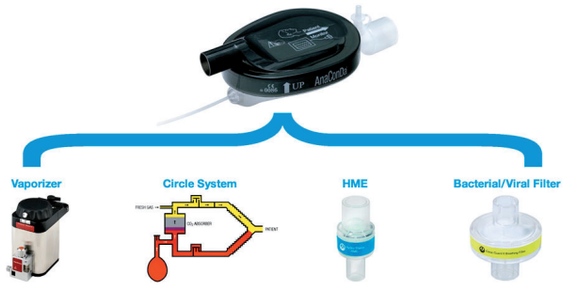

Fig. 1 — The AnaConDa system: This system incorporates a vaporizer, a heat exchanger, a bacterial filter, and is appended to the circle circuit of the ventilator

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The benefits of halogenated agents in the Intensive Care Unit:

As Jerath notes in her article published in 2016 (1), halogenated agents possess several properties of interest, both sedative and non-sedative such as bronchodilation, anticonvulsant activity, and protection against ischemia-reperfusion injury.
Unfortunately, halogenated agents are underused in the ICU for the aforementioned reasons. The respiratory tract is not first choice for the administration of drugs in the ICU. This could be explained by concerns about the risk of lung complications, or simply about unfamiliarity with this mode of administration.
In 2013, L' Her published a technical note specifying the potential indications for the AnaConDa and describing the main principles of its use as well as its possible drawbacks (2). This note reminds us that absorption and elimination of halogenated agents occur mainly through the respiratory tract, which limits accumulation in frail patients, and in those affected by metabolic disorders such as acute renal failure, or disturbances of hepatic functions.
Table 1 lists the indications and contraindications of halogenated agents:

Table 1 — Indications and contraindications of halogenated agents

Indications	Contraindications
Difficult sedation Repeated neurological examination Risk factors for difficult sedation Status epilepticus Severe acute asthma Therapeutic hypothermia after cardiac arrest Acute respiratory distress syndrom	Genetic predisposition to malignant hyperthermia (patient and family history) Hepatitis with halothane Neuromuscular diseases

A. General population: Efficacy of sedation and delay for recovery

In 1989, Kong and Associates published (3) a randomized controlled trial concerning 60 ventilated intubated patients receiving sedation for a maximum of 24 hours, either by isoflurane or midazolam. They compared an administration of 0.02 to 0.2 mg/Kg/h of midazolam to isoflurane sedation with an end-of-expiratory target between 0.1 and 0.6%. They showed more effective sedation in the isoflurane group and shorter recovery times when compared to intravenous midazolam.
A few years later, Spencer et al. published a randomized controlled trial (4) concerning 60 patients requiring more than 24 hours of sedation. Patients received either midazolam or isoflurane. The sedation protocol was the same as the one of Kong in terms of midazolam administration and isoflurane concentration. Follow-up was performed up to one week after sedation. The study endpoints were hemodynamic events, respiratory effects, catecholamine levels, and biochemical changes in renal and hepatic functions. In agreement with the Kong team, the authors reported faster recovery with isoflurane. Moreover, they did not report any increased incidence of adverse events in the isoflurane group.
In 2004, Sackey et al. published a randomized, single-blind controlled trial (5) comparing the use of midazolam or isoflurane in 40 patients requiring prolonged sedation (maximum 96 hours), in the ICU department of Karolinska Hospital in Stocholm. As a conclusion, they noted that the effectiveness of sedation was comparable in both groups. Nevertheless, the delay to tracheal extubation was significantly longer after discontinuation of midazolam sedation (10 minutes as compared to 250 minutes). Additionally, isoflurane did not cause more hypotensive events than midazolam. When it came to the length of stay in the ICU, the authors did not find any significant difference between groups.
In 2003, Meiser et al. (6) compared sedation with desflurane to propofol in 60 ICU patients who had undergone major surgery. This study was randomized into two groups. The sedation objective was a bispectral index (BIS) value of 60. The average sedation time was 10.6 hours. The authors highlighted a faster recovery time but also faster cognitive recovery in the desflurane group as compared to the propofol group. Noteworthy, the authors reported significantly higher systolic arterial pressure after cessation of sedation in the desflurane group than in the propofol group.
In 2008, L'her et al. published a prospective study (7) on 15 intubated patients, ventilated during more than 24 hours. They compared midazolam/sufentanil with isoflurane/sufentanil sedation in terms of cost, efficacy, and adverse events defined as hypotension, acute renal failure, and hepatic impairment. They objectified that sedation with isoflurane is more effective in patients who are not sufficiently sedated by midazolam/sufentanyl, and that there is no significant difference in the occurrence of adverse events for an average sedation of 4 days in the isoflurane/sufentanil group. On the other hand, regardless of the duration of sedation

by isoflurane, a complete recovery was observed within 4 hours after stopping sedation.

In 2011, Mesnil et al. published a study in 60 patients randomized in 3 groups (sevoflurane/propofol/midazolam) (8) to assess the effects of sedations that last more than 24 hours, in terms of efficacy, morphine consumption, cognitive impairment, as well as renal and hepatic functions. Data analysis was performed only on 47 patients. As expected, they reported a shorter recovery delay with sevoflurane (18.6 ± 11.8 minutes) than with propofol (91.3 ± 35.2 minutes) or midazolam (260.2 ± 150.2 minutes). Sedation efficacy was not of better quality with one technique than with the other. Interestingly, morphine consumption 24 hours after tracheal extubation was lower in the sevoflurane group than in the two intravenous groups. The quality of the revival seemed better in the sevoflurane group. This is supported by the fact that authors noticed episodes of hallucinations in the intravenous sedation groups, whereas those hallucinations did not occur for patients treated with sevoflurane. No sedation technique was superior in terms of liver or kidney impairment. The authors provided some information regarding workplace exposure during the use of inhaled sedation with the AnaConDa device, and found a very low concentration of sevoflurane (only 0.3 ± 0.1 ppm) in the environment.

In 2008, Sackey et al. resumed the analysis of the data of the patients recruited for their study published in 2004, and published the observed psychological effects in 40 patients requiring sedation for duration between 12 and 96 hours, under mechanical ventilation (9). Patients were randomized into two homogeneous groups, and received either midazolam or isoflurane. The psychological assessment was done by the nursing team first during the stay in the ICU, and second after 6 months, using standardized tests (HADS hospital anxiety and depression scale). The authors found a tendency to a lower incidence of hallucinations and confusion syndrome in patients sedated with isoflurane. Unfortunately, the sample was not large enough to have relevant statistical significance. Moreover, the authors had no information on the possible existence of psychiatric pathology, and the early assessment was subjective.

A more global retrospective study conducted by Bellgardt (10) in 2016 compared mortality in 200 surgical patients hospitalized in the ICU. The comparison dealt with mortality rate depending on whether their 96 hours (at least) sedation was performed using isoflurane, propofol or midazolam. Follow up lasted one year and data analysis was adjusted according to patient renal, respiratory, or cardiac history, as well as age. Seventy-two patients received isoflurane, while 128 received intravenous sedation. Bellgardt noted a lower in-hospital and first year mortality rate in patients sedated with isoflurane as compared to those sedated with proporol or midazolam (40 and 63 %, and 50 and 70%, respectively).

B. Effect on specific population subgroups:

- Cardiovascular diseases

In 2005, Hanafy et al. conducted a study in 24 patients requiring sedation for less than 24 hours after elective coronary bypass surgery. In this randomized study (11), patients received either 0.5% end-tidal isoflurane or midazolam (between 0.02 and 0.05 mg/Kg/h). The outcome criteria were the same as those of Spencer with the exception that they included the measurement of cardiac enzymes. In this study, as in the previous one, recovery was faster in the isoflurane group than in the midazolam group, including delay to mobilization and getting patients to sit in a chair. There were no significant differences between the two groups in terms of biochemical modifications.

In 2014, Hellstrom et al. conducted a retrospective study (12) including 12 patients to evaluate the post-conditioning effect of isoflurane associated with 24 hours of hypothermia on the ischemic-reperfusion injury after cardiac arrest. This small sample study shows that the use of isoflurane enables an increase in left ventricular ejection fraction after 6 months through an effect on mitochondria. It also shows that isoflurane improves patient cognitive recovery as compared to propofol. These results are limited by the small sample size, the lack of information about the origin of cardiac arrest, and the lack of available information on pre-existing cardiac function.

These results, however, are in accordance with the findings of Lucchinetti's team (13). In 2007, the authors published their analysis of the response of 5 healthy volunteers to 15 minutes of ischemia of one arm with or without inhalation of sevoflurane (with an end-tidal target of 0.5 to 1%) during the pre-ischemic period. The authors were able to report a decrease in ischemia-reperfusion injury along with evidence of a lower activation of leukocytes after inhalation of sevoflurane.

- Heart diseases and strokes

In 2012, Villa et al. published a prospective cross-over study (14) evaluating the use of isoflurane on cerebral circulation and ICP in 13 sedated patients

after severe subarachnoid hemorrhage with clinical indication for intracranial pressure monitoring and having an ICP lower than 18 mmHg. It has already been reported in the literature that halogenated vapors increase cerebral blood flow and decrease CMRO2 in a dose-dependent manner, but little information was available about their impact on ICP. Their sedation protocol included the 3 following steps: propofol 3-4 mg/Kg/h for one hour, isoflurane 0.8% for one hour, and propofol at the same dose as during the first phase until the end of sedation. The cerebral blood flow was assessed by transcranial doppler. This study confirms that the use of halogenated vapors increases cerebral blood flow, decreases cerebral oxygen consumption, does not significantly increase intracranial pressure, and does not increase the need for vasopressors. In addition, it demonstrates that, at the moment of volatile anesthetic agent sedation cessation, the cerebral blood flow returns back to its phase 1 level. Consequently, halogenated agents could be of interest in the prevention of vasospasm in patients with severe subarachnoid hemorrhage.

In 1995, Bosel (15) et al. published a prospective study on the effect of isoflurane on 19 patients hospitalized in the ICU for cerebral pathology. Patients were initially sedated with intravenous agents, followed by isoflurane administered through the AnaConDa system for an average duration of 3.5 days and with an isoflurane concentration ranging between 0.5 and 0.68 %. The authors reported a 2.1 mmHg increase in ICP (intracranial pressure), a 6.5 mmHg decrease in MAP (men arterial pressure) on average after one hour of sedation and persisting until 12 hours, as well as a decrease of cerebral oxygen extraction of 0.24. The authors concluded that the use of isoflurane was acceptable in patients whose intracranial pressure is in the normal low range with adequate neurological monitoring because of its effects on mean arterial pressure, and therefore cerebral perfusion pressure. Similarly, Purrucker et al.(16) published an observational study on the effect of sevoflurane in 25 patients with acute cerebral or sub-arachnoid hemorrhage. Sedation was initiated with intravenous agents and then replaced by inhaled agents. Patients with a ICP higher than 25 mmHg, and refractory to medical treatment, and those with history of malignant hyperthermia were excluded (8 patients). Sedation was adjusted according to the RASS (Richmond Agitation sedation scale) score with an average sevoflurane concentration of 0.6 minimal alveolar concentration. The authors found a decrease in mean arterial pressure and cerebral perfusion pressure, even 6 hours after the initiation of sedation, an increase in intracranial pressure, but did not report a decrease in cerebral oxygen extraction, nor effects on cerebral circulation.

- Acute severe asthma and acute respiratory distress syndrom

In 1994, Maltais et al. (17) studied the effects of halogenated agents on ventilatory mechanics in patients with severe acute asthma and requiring mechanical ventilation. The authors administered isoflurane in 3 intubated, ventilated, sedated patients. The outcome parameters were airway pressure, flow and tidal volumes. Prior to the administration of the volatile anesthetic agent, dynamic hyperinflation, a high positive end-expiratory pressure need, and a decreased expiratory flow at low positive end-expiratory pressure levels were reported. It was in relation with a decreased airway pressure and better tidal volumes. Administration of isoflurane allowed a higher level of intrinsic positive end-expiratory pressure in patients with asthma that was refractory to conventional bronchodilator treatments. These results are in accordance with the findings of Bierman and al. (18), who published a case report on the use of isoflurane in a hospitalized patient suffering from severe acute asthma. The authors demonstrated a decrease in ventilation pressure in this patient who failed to respond to conventional bronchodilator treatments. No adverse effect was reported.

A more recent study (19) evaluated the effect of using sevoflurane on gaseous exchanges in patients with acute respiratory distress syndrome. In this controlled trial (with intention-to-treat analysis), the 50 patients were randomized into two equal groups; for 48 hours. One group received midazolam and the other sevoflurane. The included patients suffered from moderate to severe acute respiratory distress syndrome. The endpoints were the PaO2/FiO2 ratio, alveolar and plasma levels of cyokines, and the soluble form of advanced glycation end products (sRAGE). The authors found an increase in the PaO2 /FiO2 ratio in patients of the sevoflurane group (205 ± 56 as compared to 166 ± 59), and decreased markers of epithelial lesions and markers of inflammation with no adverse effects.

- Epilepsy

Two studies published in 1989 and 2004 investigated the effect of volatile anesthetic agents on patients with a status epilepticus. In 1989, Kofke (20) and al. reported on 9 intubated, ventilated patients, sedated with isoflurane for 1 to 55 hours. The authors noted

a disappearance of the seizure crisis in all cases, but a vasopressor support was needed. Particularly, no renal insufficiency was associated with the use of isoflurane. They concluded that isoflurane was effective at treating status epilepticus, and that it should only be used if intravenous agents (benzodiazepines, phenytoin, phenobarbital) are contraindicated.

In 2004, Mirsattari and al. (21) performed a retrospective analysis of data acquired during four-years on seven patients suffering from epilepsy that was refractory to intravenous treatments. Six out of seven patients received isoflurane, while only one received desflurane in addition to intravenous antiepileptic agents. Among the seven patients, three died because of underlying pathology. All presented burst suppression a few minutes after the initiation of inhaled sedation. Complications such as arterial hypotension or atelectasis were noticed in all patients. Out of seven patients, five had infections, three of them had paralytic ileus, and two of them had deep venous thrombosis. There was no effect on liver function.

At the light of the above-mentioned studies, it appears that halogenated agents have several advantages both in the general population of intensive care patients, and in specific population subgroups. Jerath (1) does, however, report two limitations to the use of AnaConDa. First, too abundant bronchial secretions can compromise proper administration of inhaled agents. Second, the compensation for the dead space in the circuit (ventilator and AnaConDa) imposes ventilation at tidal volumes that are greater than 350 ml, which limits the use of the device in the pediatric population.

Feasability/workplace exposure

The AnaConDa device makes the use of volatile anesthetic agents in the ICU much easier. Historically, their administration required the presence of a vaporizer on the ventilator, and a gas scavenging system. The ventilators used in the intensive care unit were not equipped with these kinds of devices, so volatile anesthetics could not be used. Thanks to the AnaConDa, it is now possible with any type of intensive care unit ventilator.

This was well demonstrated by Sackey et al. (22), who evaluated workplace contamination and isoflurane consumption in 15 intubated, ventilated, and sedated patients during periods ranging from 12 to 96 hours, and using isoflurane through the AnaConDa device. To do this, they established a standardized protocol for changing isoflurane syringes and opening the ventilation circuit (endotracheal aspiration, nebulization, and change of AnaConDa device). In addition, 10 out of the 15 patients benefited from an active gas scavenging system. Air pollution was assessed by spectrophotometry and the exposure of the nursing staff was assessed by a dosimeter. As a result, beyond a learning curve period concerning six of their patients, workplace exposure is rare, brief and not very intense. The ambient air pollution is well below the recommended American exposure threshold of 0.5 to 2. These limits must be re-evaluated upwards and are country-specific. They did not find any significant difference in the studied parameters between patients with and without an active gas scavenging system. Finally, the consumption of isoflurane was reduced by 75% as compared to consumption when using a conventional vaporizer.

Fig. 2 — Detailed representation of the AnaConDa device.

Cost

As populations age, health spending becomes a major issue that needs to be monitored.

In 2001, Enlund et al. published (23) the first randomized trial comparing the administration of isoflurane through a conventional vaporizer and administration through the AnaConDa device. A coaxial Mapleson D system (Bain) was used in both groups. This study evaluated the consumption of volatile anesthetic agents in 16 patients randomized into two groups. Enlund reported a 40% decrease in isoflurane consumption when the AnaConDa device was used as compared to the conventional vaporizer.

L'her et al. (7) compared the cost of midazolam sedation initiated at a dose of 0.05 mg/Kg/h combined with sufentanil at a dose of 0.2 µg/Kg/h adjusted to obtain a predefined Ramsay's score and isoflurane sedation associated with sufentanil. The protocol was prescribing an initial sedation with midazolam/sufentanil during the first 24 hours,

followed by the replacement of midazolam by isoflurane. Cost calculation included basic costs of medications, syringes and other devices, as well as cost of other necessary drugs (vasopressors, fluids, etc.). For isoflurane sedation, it included cost of fresh gases, volatile anesthetic agent, syringes, AnaConDa device, filters, and possible vasopressors, as well as sufentanil. In this study, the AnaConDa device was changed on a daily basis. Seven patients required an increase in midazolam dosage to 0.4 mg/Kg/h to achieve the desired degree of sedation. Only half of the amount of sufentanil was needed in patients sedated with isoflurane. The cost of sedation with isoflurane or midazolam was identical. However, when patients were not easy to sedate, requiring infusion of Midazolam at 0.4 mg/Kg/h, the cost of sedation with isoflurane was half cheaper than sedation with midazolam (110 € and 218 €, on average).

Conclusion

The use of volatile anesthetics in the ICU has long been limited because of technical difficulties. However, they may present ideal sedative agent properties. Their adverse effect profile, metabolism and almost on/off effect, with a short recovery delay are well known. They are particularly interesting for patients requiring frequent neurological evaluations, as well as for the prevention of pneumopathies acquired under mechanical ventilation.

Moreover, for difficult sedation and specific indications, volatile anesthetic agents represent an attractive alternative, at a lower cost. This appears to be the case for status epilepticus, in patients who present an ischemic pathology, or pulmonary disease such as ARDS or severe asthma. Even if volatile anesthetic agents do not have marketing authorization for intensive care use, they do not cause more hypotension (except in patients with cerebral pathology), bradycardia, acute renal failure, or liver dysfunction than any other type of sedation.

Volatile anesthetic agents have an immunomodulatory capacity, which has been shown in several studies, and must be taken into account when using them, while considering the specificities of each patient, and in particular immunosuppressed or immunocompromised patients.

The launch of AnaConDa offers new prospects to overcome the technical difficulties. It is no longer necessary to consider a gas scavenging system since it has a carbon filter that recycles 90% of the inhaled gases, therefore making it possible to limit the quantity of product to administer to the patients, the atmospheric pollution, and the exposure of the hospital staff to the halogenated gases. This is true provided that the respective ICU has an up-to date air conditioning system, with sufficient air turnover, which should be up to 10 liters per hour).

The growing interest in the routine use of volatile anesthetic agents in the ICU for patients and nursing staff safely raises new questions about the undesirable effects of long-term administration of these compounds. A multicenter study is in progress between the CHWAPI Tournai and the Saint-Luc University Clinics of Brussels in order to evaluate the occurrence of delirium after prolonged sedation by AnaConDa.

Table 2 summarizes the advantages and disadvantages of the use of volatile anesthetics in the ICU as discussed above:

In this review, all articles compare the use of volatile anesthetic agents to propofol or midazolam sedation. To our knowledge, there are no studies comparing volatile sedation and dexmedetomidine

Table 2
Halogenated agents in the intensive care unit: advantages and disadvantages

Halogenated agents in Intensive Care: Advantages and Disadvantages	
Avantages	Disadvantages
on / off effect : rapid wake up, easy neurological assessments, early extubation	Technical efforts
Sedation more effective in difficult to sedate patients (alcohol/drug dependant)	Investment in technical equipment
Prevention of ischemia reperfusion injury	Need for staff training
Increased cerebral blood flow, decreased cerebral oxygen consumption with no increase in intracranial pressure	
Prevention of vasospasm?	
Decreased consumption ofmorphine	
Use facilitated by the appearance of the AnaConDA: ease of knowledge assimilation, low atmospheric pollution, simple use, no need for a specific gas scavenging system	
Better cognitive recovery (apart from patients with pre-existing cognitive disorders)?	

sedaton. This can be explained by the fact that the indication of dexmedetomidine is mild to moderate sedation permitting patient cooperation, volatile anesthetic agents are used at present for deep sedation.

A new device, the Mirus, allows the administration of not only sevoflurane and isoflurane but also desflurane. In 2014, the Bomberg team (24, 25) evaluated the effectiveness of this device at the laboratory. In 2016, they reported the case of a patient suffering from an acute respiratory distress syndrome, and sedated with desflurane using this new device, and compared it with isoflurane sedation. Unsurprisingly, the patient recovered faster, but the consumption of desflurane was elevated, which led the authors to suggest improvements in the device. They did not report any adverse effects elsewhere.

Discussion

Taking account of the different results reported by the studies cited in this review, both for the beneficial effects of halogenated agents in the general population, but also for specific indications in some pathologies, the ease of knowledge assimilation, and the low workplace exposure, it seems legitimate to ask ourselves why volatile anesthetic agents are so rarely used in the ICU.

It can be assumed that, traditionally speaking, volatile anesthetics are used only by anesthesiologists, and not by resuscitators. A notable lack of information must also be taken into account. On the top of that, several practitioners are somewhat reluctant to use volatile anesthetic agents, similarly to their attitude in face of any device that is untested or new to them. They would become familiar with them only once their use has become more widespread.

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