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REVIEW

Current state of critically ill patients sedation with volatile anesthetics. Its role in renal and hepatic toxicity

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SUMMARY

The anesthetic-conserving device (AnaConDa™) facilitated, from a technical viewpoint, the routine use of volatile anesthetics in intensive care patients using ICU ventilators. To date, its use is currently time-limited by clinicians due to the potential renal and hepatic toxicity associated with the production of plasma fluoride after its metabolism, despite its advantages. We reviewed the available human and animal studies literature examining the use of volatile anesthetics as sedative agents and its role in renal and/or hepatic toxicity. We have very few studies concerning the prolonged administration of sevoflurane through the AnaConDa™ and its effect on renal and hepatic function. All of them agree that high levels of inorganic fluoride do not lead to renal or hepatic damage. Currently, the available information regarding prolonged sevoflurane sedation through AnaConDa™ is low. High concentrations of inorganic fluoride derived from the metabolism of halogenated agents are not harmful. According to recently published studies, volatile anesthetics on the ICU could adopt a permanent position in various intensive care analog-sedation concepts (even in long-term sedation) in future optimizing the treatment process.
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1. Introduction

Most patients admitted to Intensive Care Units (ICU) receive sedation at some point during their stay.[1,2]

Currently, we have several clinical guidelines for the sedation of patients admitted to the ICU.[3–5] The most recent are those published in Germany[6] and Spain.[7] According to these, the sedation of patients in the ICU is currently performed with intravenous agents (primarily propofol, midazolam and remifentanil).

Therefore sedation with volatile anesthetics in critical care patients ("inhalational sedation") could be a useful supplement to present intravenous analog-sedation protocols in the future.

The following review describes the technical and clinical aspects of inhalational sedation in critical care patients and discusses the current standards of knowledge in the use of volatile anesthetics in intensive care.

2. Methods

We reviewed the available human and animal studies literature examining the use of volatile anesthetics as sedative agents and their role in renal and/or hepatic toxicity. The search strategy involved crossing the keywords volatile anesthetics with the following general and specific terms: isoflurane, sevoflurane, halothane, enflurane, desflurane, AnaConDa™, propofol, midazolam, methoxyflurane, nephrotoxicity, hepatotoxicity, sedation and long-term. We have summarized several studies regarding the potential toxicity of volatile anesthetics.

3. Disadvantages of intravenous agents

These include accumulation, tolerance, hemodynamic effects, inability to measure clinical plasma concentrations, poorer sleep quality and the possibility of producing Propofol Infusion Syndrome (PRIS), amongst others.

The actual incidence of PRIS is unknown because its detection requires close monitoring of clinical and laboratory information from patients.[8] Recently there have been new cases worldwide (collected in various revisions).[9,10] Cumulative evidence to date has shown that PRIS may appear in any patient, its incidence is much

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higher than previously reported (reaching over 1% of patients sedated with propofol), mortality is close to 30% and usually appears with recommended doses, even after short periods of administration (hours).[11–13]

The FDA warns that the PRIS is more likely in the ICU when high dosage of various drugs such as inotropes and vasopressors (commonly used in critically ill patients) are used and when propofol is infused in high doses (>5 mg/kg/h, for more than 48 h).[14]

Most EU countries warn that the propofol for sedation in critical care should be restricted to patients over 16 years old, for up to seven days, and up to a maximum dose of 4–5 mg/kg/h or less if possible.

Remifentanil is a drug increasingly used as an analgesic and sedative, in all kinds of adult patients admitted to the ICU. However, its use as a sedative agent has not become widespread due to a number of unwanted effects, but particularly hyperalgesia during withdrawal.[15]

4. Volatile anesthetics as an alternative to intravenous sedation

Inhalation agents have recently been used in the ICU for critically ill patients undergoing sedation. Isoflurane, desflurane and sevoflurane have demonstrated clear benefits over intravenous sedation like shorter awakening, weaning and recovery times, improvement in sedation quality and lower medication costs.[16–25]

In addition, volatile anesthetics have some protective effects like bronchodilation,[26] providing greater hemodynamic stability,[27] myocardial preconditioning[28] and post-conditioning[29] and neuroprotective properties.[28]

The physical, chemical and pharmacokinetic effects of sevoflurane led it to become the first choice halogenated agent in the operating room.[23] Desflurane, due to its physical properties (vapor pressure of 673 mmHg at 20 °C), cannot be administered by another method different from this especial vaporizer. The advantages compared to isoflurane have been highlighted in several studies, including one meta-analysis.[30,31] Sevoflurane is preferred because it is less irritating provides faster induction and awakening, and it also has a low toxicity.[32]

Sedation with volatile anesthetics was not originally widely accepted due to technical reasons relating to its administration.[33] Anesthetic gases were initially administered via the standard vaporizer in combination with a ventilator (eg, Servo 900) and later as part of a "closed anesthesia system".[25] With the development of the Anesthetic Conserving Device (ACD, AnaConDa™, Sedana Medical, Uppsala, Sweden) (Figs. 1 and 2) in 1999 and the official presentation in 2004, it is now possible to administer volatile anesthetics (isoflurane and sevoflurane) through the ICU's common mechanical ventilators[34–37] and continuous measurement of its end tidal concentration.[38] The AnaConDa™-system is an anesthetic gas saver system: 90% of the gas remains within the respiratory machine. Only the residual 10% reaches the expiratory limb and the respiratory outlet. Hence there is a need to scavenge the anesthetic gas. Sackey et al.[39] were able to demonstrate that the occupational

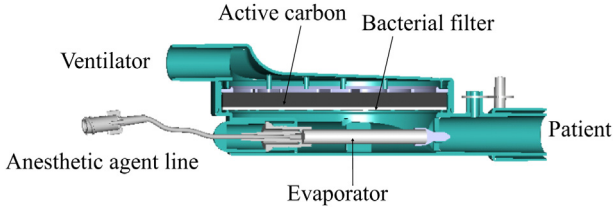

Fig. 1. AnaConDa™ device components. Sagittal view.

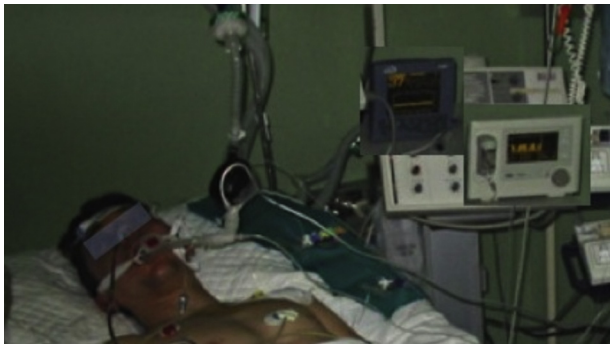

Fig. 2. The AnaConDa™ in place of the heat-moisture exchanging filter in the ventilation circuit. Level of consciousness measuring by BIS™. Vamos™ gas analyzer.

load from the volatile anesthetic, in the presence of a central anesthetic gas scavenging system at the bedside, is minimal and within the international standard (mean of 0.1 ppm), using isoflurane.

5. Renal and hepatic toxicity due to sevoflurane sedation?

Despite the advantages of inhalational sedation as compared with the intravenous method, its use is currently time-limited by clinicians due to the potential toxicity associated with the production of plasma fluoride after its metabolism, as recently discussed by Sackey et al.[33]

Sevoflurane has been used successfully for nearly two decades because of its rapid adjustment of the depth of anesthesia, rare adverse events and lack of cumulative effects.[46] Its elimination is mainly performed through the lungs; only approximately 5% of sevoflurane is metabolized, resulting in the formation of inorganic fluorides and hexafluoroisopropanol. According to findings from the early 1970s after methoxyflurane administration, plasma fluoride concentrations exceeding 50 μmol/L were postulated as a threshold for the development of polyuric acute renal failure.[28,51–53] This threshold was subsequently applied to other fluorinated anesthetics such as isoflurane and sevoflurane, although fluoride-related toxicity has never been observed in animals or in humans.[54,55] This is likely due to the 10-fold higher biotransformation rate of methoxyflurane compared with sevoflurane, which eventually led to the withdrawal of methoxyflurane for human use.

On the other hand, there is still controversy regarding the possible hepatotoxicity of halogenated agents. Halothane was most frequently associated with immunologically mediated liver damage[40] as a result of trifluoroacetic acid formation.[41] Unlike halothane, enflurane, isoflurane and desflurane, sevoflurane does not produce trifluoroacetic acid, but hexafluoroisopropanol. This compound is less likely to produce trifluoroacetic acid haptens. Moreover, the hexafluoroisopropanol does not accumulate quickly due to glucuronidation and elimination.[42]

The individual cases recently described in the literature by Turillazzi[43] and Singhal[44] occurred after sevoflurane anesthesia in patients with several risk factors, such as pre-existing renal failure and/or concomitant infection by Epstein–Barr virus and cytomegalovirus.

Relevant clinical studies of inhalational sedation evaluating renal and/or hepatic function using a conventional respiratory or anesthetic device with the vaporizer or AnaConDa™-system are summarized in Tables 1 and 2.

In a study by Spencer and Willats,[19,20] inhalational sedation with isoflurane could be successfully applied for longer than 24 h in 60 patients using the anesthesia ventilator Servo 900 (Maquet, Rastatt, Germany). In the isoflurane group, plasma fluoride increased from a

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