

A review of the practice of sedation with inhalational anaesthetics in the intensive care unit with the AnaConDa® device

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ABSTRACT

The intensive care unit (ICU) environment is often perceived to be hostile and frightening by patients due to unfamiliar surroundings coupled with presence of numerous personnel, monitors and other equipments as well as a loss of perception of time. Mechanical ventilation and multiple painful procedures that often need to be carried out in these critically ill patients add to their overall anxiety. Sedation is therefore required not only to allay the stress and anxiety, but also to allow for mechanical ventilation and other invasive therapeutic and diagnostic procedures to be performed. The conventional intravenous sedative agents used in ICUs suffer from problems of over sedation, tachyphylaxis, drug accumulation, organ specific elimination and often lead to patient agitation on withdrawal. All this tend to prolong the ventilatory as well as ICU and hospital discharge time, which increase the risk for infection and add to the overall increase in morbidity, mortality and hospital costs. In 2005, the anaesthetic conserving device (AnaConDa®) was marketed for ICU sedation with volatile anaesthetic agents. A number of trials have shown the effectiveness of using volatile anaesthetic agents for ICU sedation with the AnaConDa device. Compared with intravenous sedatives, use of volatile anaesthetic agents have resulted in shorter wake up and extubation time, lesser duration of mechanical ventilation and faster discharge from hospitals. This review shall focus on the benefits, technical pre-requisites and status of sedation with volatile anaesthetic agents in ICUs with the AnaConDa® device.

Key words: Anaesthetic conserving device, ICU sedation, isoflurane, midazolam, propofol, sevoflurane

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INTRODUCTION

Sedation and analgesia are often required in patients admitted to the intensive care unit (ICU) to allay anxiety and pain, allow for mechanical ventilation and to enable invasive diagnostic or therapeutic procedures to be carried out. Guidelines have been published for the use of sedative and analgesic drugs in the ICU; midazolam or propofol is recommended for short-term sedation (≤ 24 h), lorazepam for sedation of longer duration (≥ 24 h), haloperidol for delirium and morphine or fentanyl for analgesia.^[1,2] Despite these guidelines, large differences exist in the usage of

sedative and analgesic drugs in ICUs, primarily related to the patient profile as well as to the availability and familiarity of drugs. The ideal sedative agent should have a rapid onset and offset of action, allow for precise titration of sedation without causing haemodynamic perturbations, decrease the requirement for analgesia, should not accumulate with long-term use and be eliminated fairly rapidly on discontinuation apart from being cost-effective.

Unfortunately, most of the conventional drugs used for ICU sedation do not achieve these goals. Propofol, though theoretically attractive, is often

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used with caution in critically ill patients because of a syndrome of metabolic acidosis, rhabdomyolysis and renal and cardiac failure (especially if administered >5 mg/kg/day for >5–7 days),^[3] while tachyphylaxis and drug accumulation complicate the use of midazolam.^[4] Enthusiasm for the use of etomidate, the shortest acting intravenous hypnotic agent, is tempered by the fact that the drug causes adrenal suppression, and thus is not used as a continuous infusion for sedation.^[5] Dexmedetomidine, a highly selective α_2 receptor blocker, is increasingly being used for ICU sedation, but presently, experience with long-term use is limited due to problems of tachyphylaxis and respiratory depression in children.^[6] Additionally, use of dexmedetomidine is significantly limited by dose-related bradycardia, hypotension and the agitation that results from abrupt discontinuation of the drug.^[7] Primary use of opioids for sedation does not allow for rapid offset and awakening and results in depression of intestinal motility which may in turn interfere with early enteral feeding.^[8]

RATIONALE FOR THE USE OF VOLATILE ANAESTHETIC AGENTS FOR ICU SEDATION

Although volatile anaesthetic agents constitute a major part of general anaesthesia in the operating rooms, they are scarcely used for ICU sedation. This has been mainly due to the use of non-rebreathing high-flow ventilators in the ICU, lack of dedicated vapourisers for the high-flow systems, problems of ambient contamination with the anaesthetic vapour and unfamiliarity of the ICU staff with the use of these agents.^[8] However, theoretically, volatile anaesthetic agents have a lot of advantages as compared to intravenous agents. Both isoflurane and sevoflurane have rapid onset and offset of action which allows for quick onset of sedation and awakening. Volatile anaesthetics primarily act on the cerebral cortex, depressing the sensorium even at low concentrations, and leave autonomic functions like temperature control, blood pressure regulation and respiration relatively undisturbed.^[8]

In addition, sevoflurane in low-dose concentrations prevents encoding of emotionally disturbing information which can be a major reason for post-traumatic stress disorder (PTSD); PTSD significantly limits the quality of life post hospital discharge.^[8] Volatile anaesthetics accumulate very little and are largely excreted by the lungs, independent of liver and kidney elimination, which

may be an important consideration in patients with end-organ dysfunction. The miscellaneous properties of bronchodilatation and anti-epileptic activity of these agents are other attractive advantages when considering sedation in patients with refractory bronchospasm^[9,10] or epilepsy.^[11] Finally, volatile anaesthetics have been shown to possess cardio and cerebroprotective properties,^[12,13] which may result in improved cardiac and cerebral outcomes when sedation is continued with these agents in the ICU.

TECHNICAL PREREQUISITES FOR THE USE OF VOLATILE ANAESTHETICS FOR ICU SEDATION

For volatile anaesthetics to be used for ICU sedation, several technical prerequisites must be met. Most vapourisers used in anaesthesia machines will work inaccurately with the open high-flow ICU ventilators. Second, ICU ventilators are high-fidelity performers with a number of ventilatory modes which include both spontaneous as well as controlled ventilation, and therefore the delivered anaesthetic concentration will depend not only on the flow, but also on the minute ventilation.^[14] Third, the bulky anaesthesia machine is not only ill designed for ICU ventilation, but also lack of familiarity with the machine and limited alarms prevent it from being a standalone machine in the ICU. Finally, the main challenges with the use of volatile anaesthetic agents for ICU sedation are to conserve the anaesthetic gases using an open system and simultaneously avoid workplace contamination. Initial attempts at conserving anaesthetic vapours using an open system involved the development of a reflector which incorporated zeolite crystals.^[15,16] However, this was subsequently abandoned due to the possibility of zeolite inhalation causing pulmonary toxicity.

ANAESTHETIC CONSERVING DEVICE: THE ANACONDA®

In 2005, the anaesthetic conserving device AnaConDa® (AnaConDa®, Sedana Medical, Uppsala, Sweden) was marketed for ICU sedation with volatile anaesthetic agents.^[17,18] Basically, the AnaConDa® is a modified heat moisture exchanger (HME), which is incorporated into the respiratory circuit between the Y-piece and the patient instead of the usual HME [Figure 1]. It has an internal volume (dead space) of 100 mL and can be used with any standard ICU ventilator. The device contains a miniature porous evaporator rod that converts the volatile anaesthetic agent from liquid to vapour state. The liquid anaesthetic agent is continuously infused

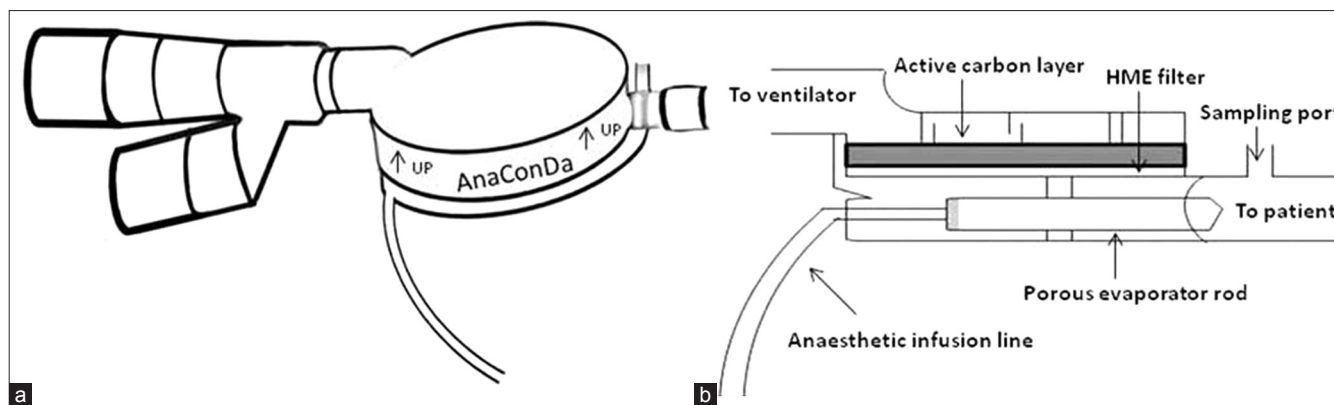


Figure 1: Schematic diagram of the AnaConDa® device. (a) The device is inserted between the Y-piece and the patient instead of the usual heat moisture exchange filter. (b) Cross section of the device illustrating the mechanism of action. Refer text for details

into the evaporator by an infusion pump incorporating a syringe system. Activated carbon fibres interwoven with the HME serve to adsorb, store and release the anaesthetic vapours.

During inspiration, the anaesthetic vapour cloud that forms on the evaporator is picked up by the air–oxygen gas mixture from the ventilator and delivered to the patient. During expiration, 90% of the anaesthetic vapour in the expired gas gets adsorbed on the carbon layer and is recycled to the patient in the next inspiratory cycle. The performance of the AnaConDa® reflector is accurate as long as its capacity is not exceeded. The reflecting capacity of the device is 10 mL of anaesthetic vapour contained in one expired breath (e.g. 1 vol.% in 1000 mL or 2 vol. % in 500 mL, etc.).^[14] Therefore, the infusion rates of the volatile anaesthetic agents need to be increased with increases in minute ventilation in order to keep the end-tidal anaesthetic concentrations constant. Resistance to gas flows at 60 L/min is 2.5 cm H₂O/L/s, which is comparable to the standard HME filters.

Each disposable AnaConDa® device comes with a device-specific 50-mL keyed colour-coded syringe and a 22-cm anaesthetic supply line. The syringe barrel and plunger are made of polypropylene while the piston is made of rubber. Other plastic syringes and extensions must not be used as volatile anaesthetic agents may dissolve these substances leading to the generation of potentially toxic products. Isoflurane and sevoflurane are drawn from their container bottles into the 50-mL syringes using special adaptors and perfused continuously using standard infusion pumps into the evaporator rod, independent of the respiratory cycle. The manufacturer recommends changing the device every 24 h. An important caveat is that bubbles should not be present in the syringe, since the liquid

anaesthetic agents will evaporate into these bubbles making them grow.^[8] Another point is that because of their high density (1.5 g/mL), volatile anaesthetics may exert a negative pressure if the infusion pumps are fixed high above the patients' head. This may lower the boiling point inside the syringe which can cause the growing bubbles to pump in liquid anaesthetic boluses into the device, a feature known as “autopumping,” which in turn may lead to severe overdose.^[8]

A total volume of 1.2 mL is required for prefilling the system. The infusion rates are usually started at approximately 5–10 mL/h. A sampling port from the AnaConDa® device allows the expired gas concentration to be continuously displayed on the gas monitor. Once the monitor detects the anaesthetic agent in the expired gas, the infusion rates can be titrated to achieve the desired level of sedation. For sedation, the end-tidal anaesthetic gas concentration should be slightly more than one-third of minimum alveolar concentration (MAC), i.e., slightly above MAC-awake.^[8] For isoflurane, rates of 2–5 mL/h (0.3–0.5 expired vol.%) and for sevoflurane 2–6 mL/h (0.5–1 expired vol. %) provide acceptable sedation.

Desflurane, because of its high vapour pressure, cannot be used in the system. The other limitation with the device is its dead space (100 mL), which limits its use in paediatric patients. Ambient pollution of volatile anaesthetics in the ICU is also an additional concern. Although 90% of the anaesthetic vapour is adsorbed onto the activated carbon fibres during expiration and recycled back to the patient, 10% of the vapour gas still needs to be scavenged. This can be done by using an active or passive scavenging system connected to the expiratory outlet of the ventilator in order to minimise the ambient pollution.

CLINICAL TRIALS OF ICU SEDATION WITH VOLATILE ANAESTHETIC AGENTS USING THE AnaConDa® DEVICE

Several trials have shown the benefit of using either isoflurane or sevoflurane for ICU sedation using the AnaConDa® device. Sackey *et al.*^[18] showed that prolonged sedation (<96 h) with either isoflurane or midazolam in patients admitted to a multidisciplinary ICU resulted in significantly shorter wake-up time in the isoflurane group as compared to the midazolam group (time to extubation 10 ± 5 min vs. 252 ± 271 min; time to follow verbal commands 10 ± 8 min vs. 110 ± 132 min), with comparable proportion of time within the desired sedation levels in both the groups. No increase in adverse haemodynamic events, or derangement of renal or hepatic parameters was noted with either sedation protocol.

Another study found that when isoflurane sedation was initiated in patients who required increasing doses of midazolam (>0.05 mg/kg/h of midazolam) to meet the desired sedation levels, compliance was achieved quickly with isoflurane, which resulted in stoppage of midazolam along with a concomitant reduction in the dose of sufentanyl; more importantly, wake-up time was significantly shortened and no adverse effects were demonstrated even after a mean duration of four sedation days.^[19] In addition, in patients who initially required a high dose of midazolam for achieving target sedation, sedation costs were lower with isoflurane.^[19]

Sevoflurane, the other volatile agent that can be used with the AnaConDa® device, has potential advantages over isoflurane with regard to a shorter duration of action and brief elimination time.^[20] In a study of postoperative short-term sedation (<12 h) with either sevoflurane or propofol in post cardiac surgery patients, Röhm *et al.*^[21] showed faster recovery with sevoflurane as compared to propofol (extubation time 22 min vs. 151 min). Although the length of ICU stay was similar in both groups, patients receiving sevoflurane sedation were extubated faster (9 ± 4 h vs. 12.5 ± 5.8 h) and were discharged earlier from hospital (10.6 ± 3.3 days vs. 14 ± 7.7 days). Pure sedation drug costs were comparable in the two groups, though the cost significantly increased in the sevoflurane group when the device costs were included.

Another elegant study by Mesnil *et al.*^[22] looked at the quality of awakening and post extubation morphine consumption apart from the wake-up and extubation

time in patients scheduled to receive long-term sedation (>24 h) with sevoflurane, propofol or midazolam. In addition to shorter extubation and wake-up time in the sevoflurane group as compared to the other two groups, the authors found that awakening quality was better in the sevoflurane group with lower episodes of hallucinations and agitation. The pain scores measured 24 h after termination of sedation were also lower in the sevoflurane group with reduced consumption of morphine, which the authors postulated could be due to the *N*-methyl-D-aspartate receptor antagonism by sevoflurane. A similar opioid sparing action of isoflurane has also been demonstrated.^[18]

Since organ protection has been demonstrated with volatile anaesthetic agents, the rationale of continuing this group of drugs for postoperative sedation has been postulated. Hellström *et al.*^[23] designed a trial to determine whether continuing sevoflurane sedation in the ICU in patients undergoing coronary bypass graft surgery conferred any advantages over propofol sedation. No significant difference could be demonstrated between the groups in the levels of cardiac Troponin T (cTnT), the primary outcome marker at 12 h postoperatively. However, a *post hoc* analysis revealed less pronounced increase in cTnT level 12 h postoperatively as compared to baseline values in the sevoflurane group but not in the propofol group. One of the main limitations in the study was that some patients with increased preoperative cTnT levels due to myocardial ischaemia were also included, and thus it could be argued that the distribution of data was skewed which may have accounted for an overall non-significant difference in the cTnT levels between the groups.

The risk of compound A formation with sevoflurane sedation is not a concern in the ICU since soda lime is not used. However, volatile anaesthetic agents generate inorganic fluoride metabolites which have been implicated in renal dysfunction. Based on data available from methoxyflurane, a level of 50 $\mu\text{mol/L}$ has been postulated as a threshold for development of polyuric renal failure.^[24]

Röhm *et al.*^[25] looked into the levels of α -glutathione-S-transferase (α -GST), a marker of proximal renal tubular injury in post surgical patients receiving either sevoflurane or propofol sedation in the ICU. Although α -GST increased significantly in both groups at 24 and 48 h postoperatively with respect to baseline in both groups, no significant difference

was seen between the groups at the same time points. Inorganic fluoride levels increased significantly after sevoflurane sedation at 24 h postoperatively and remained elevated at 48 h as compared to the propofol group. However, no correlation could be demonstrated between the increase in α -GST and the fluoride levels. Other markers of renal function remained unchanged between the two groups. The authors concluded that despite the increase in inorganic fluorides, renal function was comparable in the two groups and the elevation in fluorides in the sevoflurane group did not confer an increased risk of renal failure when used up to 48 h. Similar data regarding renal function have also been obtained with isoflurane sedation.^[18]

Optimal sedation in paediatric patients is often a difficult goal to achieve due to the altered pharmacokinetics and dynamics in children. A higher requirement and tolerance may lead to sedation polytherapy which can result in dangerous over sedation in this subset of patients. Therefore, volatile anaesthetic agents may be well suited for postoperative sedation in paediatric patients given their favourable pharmacokinetic profile. However, studies in paediatric population are largely limited with the AnaConDa[®] device due to its dead space (100 mL). Only a few isolated case reports exist.^[26,27]

In general, end-tidal concentration of 0.3–0.4% isoflurane results in adequate sedation with an overall lower requirement for other sedative and analgesic agents. When used for controlling epileptic activity, an end-tidal concentration of 0.9% has been found to be adequate. In children weighing <30 kg, suggestion has been made to incorporate the device in the inspiratory limb so as to reduce the dead space.^[26] However, in this position, the rebreathing effect of the device is lost, and instead, it merely serves as a vapouriser.

TECHNICAL LIMITATIONS OF THE AnaConDa[®] DEVICE

With the use of scavenging systems, ambient concentrations of either isoflurane or sevoflurane with the AnaConDa[®] device are within the acceptable limits of <1 ppm.^[19,22,28,29] The problems related to the use of device include slight increase in overall dead space, which may result in mild hypercapnia especially during weaning from mechanical ventilation. A closed loop tracheal suction system is advisable in such patients to prevent loss of the volatile agent into the environment. Although the syringes are colour coded and marked “Not for IV use,” inadvertent intravenous injection is

possible as the Luer-lock anaesthetic infusion line has a similar appearance to intravenous infusion lines.^[30] Additionally, workplace contamination may occur during refilling of the syringes.

Most current standard gas monitors are not calibrated for the AnaConDa[®] device as they do not factor the device dead space into consideration.^[8,31] During expiration, a vapour cloud builds up inside the device, which contains both agent as well as expired carbon dioxide (CO₂). During the next inspiration, this saturated vapour cloud is pushed to the patient. Therefore, the peak inspiratory vapour concentration of the anaesthetic agent is detected by the gas monitor as end-tidal concentration, as the vapour picked up by the sampling line also contains the expired CO₂. During the later part of inspiration, the monitors show a dip in the concentration as most of the vapour has passed to the patient. This dip is again displayed wrongly as inspired concentration as the gas is now relatively free of CO₂. Hence, the mean of the numbers is generally used to compute the end-tidal anaesthetic agent concentration.

CONCLUSION

At the current time, no inhalational agent is approved for ICU sedation and studies describing the use of isoflurane and sevoflurane with the AnaConDa[®] device are all “off label” studies.^[8,31] Additionally, due to new technology being introduced, unfamiliarity of ICU personnel with the device and other inherent limitations in methodology, none of the studies were blinded, which could have introduced certain biases in the interpretation of results. Though ambient anaesthetic agent concentrations were shown to be within the acceptable limits in all the studies, the effects of long-term exposure of ICU staff to ambient anaesthetic agent concentrations are unknown.

Despite these limitations, most of the studies have shown superiority of volatile anaesthetic agents over intravenous drugs for ICU sedation. Furthermore, anaesthetic consumption using the AnaConDa[®] device has been shown to be equivalent to that of the conventional circle system.^[32] Pure drug costs have also been shown to be either less than or comparable to conventional intravenous agents.^[19,21] More importantly, patients receiving volatile anaesthetics for sedation spent a shorter time on ventilator and could be discharged home faster than patients receiving conventional intravenous sedatives. Given the fact that ICU sedation continues

to be an elusive goal, and that longer duration of sedation increases the risk of infection,^[33] the need of the hour is to adapt to newer modes of sedation that allow for rapid titration, faster wake up, extubation and discharge. The excellent pharmacokinetic and favourable side-effect properties of volatile anaesthetic agents probably make them a good choice for ICU sedation, which may ultimately result in improved patient care and outcome.

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