

Technical aspects of isoflurane sedation in the ICU

Intensive care unit (ICU) patients receiving ventilator treatment commonly receive intravenous sedatives. Inhalational sedation is a promising alternative with short wake-up times and few side-effects in sedative doses. Difficulties in administration, high costs and environmental concerns are possible reasons for inhalational sedation not being used more routinely. The Anesthetic Conserving Device/AnaConDa® (ACD), a modified heat and moisture exchanger has been developed for simplified delivery of isoflurane or sevoflurane in the ICU setting. Features of the ACD include direct infusion of anaesthetic agent from a standard syringe pump to the ACD and rebreathing of anaesthetic agent, resulting in low agent expenditure while using standard high-flow ICU ventilators. Technical aspects of administration, monitoring, scavenging and paediatric use and future perspectives of the method are discussed.

Sedative agents are often used to reduce pain, anxiety and the autonomic stress response to critical illness and treatment in the intensive care unit (ICU) and to improve tolerance to mechanical ventilation. The most commonly used sedatives in the US and Europe are the benzodiazepines midazolam and lorazepam and propofol, in combination with opiate analgesics.^{1,2}

Wake-up times may be prolonged in the critically ill after prolonged administration of the short-acting benzodiazepine midazolam.³⁻⁵ Critically ill patients may have delayed elimination of midazolam,³ especially if renal or hepatic dysfunction is present.⁴ Lorazepam infusions may also lead to prolonged wake-up times and there is a risk of propylene glycol toxicity when administered at higher therapeutic doses.⁶ Tolerance and withdrawal are well known problems associated with prolonged ICU sedation with these agents.

Propofol, an intravenous anaesthetic agent introduced in 1989, has many useful features in the anaesthesia setting: rapid onset, good titratability and relatively rapid emergence. It was quickly adopted as a sedative in the ICU and is considered more titratable than midazolam.⁶ In recent years, reports of potentially life-threatening side effects in critically ill adults and children have had an impact on its use in ICU patients.^{8,9} Prolonged administration in higher therapeutic doses may cause metabolic acidosis, rhabdomyolysis and cardiac failure, the mechanisms for which are beginning to be understood.⁹ The Society of Critical Care Medicine currently recommends that propofol be used with caution for long-term sedation,¹⁰ and the US Food and Drug Administration recommends that propofol not be used for paediatric sedation in the ICU due to the risk of propofol infusion syndrome.¹¹ Thus, the quest continues for the perfect sedative agent or combination of agents.

ICU SEDATION WITH ISOFLURANE

Isoflurane is an inhaled halogenated anaesthetic agent that

has been used extensively in operating rooms since the 1970s. In low therapeutic doses (end-tidal concentration 0.2–0.6%) isoflurane has sedative properties. Elimination of isoflurane is via exhalation of the drug and is thus independent of hepatic or renal function. There is a low degree of metabolism, generally considered to be less than 1%, in which inorganic fluorides are generated.

Several promising studies comparing isoflurane to intravenous sedatives for long-term sedation have been published,¹²⁻¹⁴ as well as case reports of successful isoflurane treatment for *status asthmaticus* and *status epilepticus*.^{15,16} Good titratability and short wake-up times without adverse effects have been reported by several investigators.¹²⁻¹⁴ Inorganic fluoride concentrations do not appear to reach toxic levels with prolonged administration and it remains debatable whether moderately elevated fluoride levels (50–100 $\mu\text{mol/l}$) are of concern.¹⁷

Despite these previously obtained promising data, the practice of isoflurane sedation in the ICU has not become widespread. One suggested explanation is that administration of isoflurane in the ICU setting has been difficult.^{12,18} In the early days of intensive care, ventilators in the operating room and ICU were similar. Over the past decades, specific ventilators for ICU use have been developed and become more advanced than anaesthesia ventilators with regard to respiratory modes. Modern ICU ventilation therapy augments spontaneous breathing, enables lung recruitment and limits work of breathing and iatrogenic barotrauma. Furthermore, anaesthesia machines are often more cumbersome and expensive than ICU ventilators and are not developed or approved for stand-alone use.

Until recently, the only alternative to bringing an anaesthesia machine from the operating room to the ICU for isoflurane treatment was to connect a vaporiser to the ICU ventilator. Adaptation of the ICU ventilator or breathing circuit is necessary, making isoflurane administration somewhat cumbersome. Adaptations described by different investigators include connecting a vaporiser in parallel between the oxygen blender and the inspiratory limb of a Servo-B ventilator,¹² connecting a vaporiser to the low-pressure port of a Servo 900 ventilator¹³ or incorporating an Oxford Miniature Vaporizer inside the circuit when using a Servo 300 ventilator.¹⁹ Modern ICU ventilators have high fresh gas flows, resulting in high agent consumption and cost when inhalational sedation is used. Less stringent room ventilation and scavenging requirements in the ICU compared to the operating room may also increase concern about staff exposure. These factors taken together may contribute to limiting inhalational sedation from use in wider clinical practice despite possible advantages for ICU patients.¹³

THE ANESTHETIC CONSERVING DEVICE/ANACONDA®

In the late 1990s, a new device for administering isoflurane

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Figure 1. The Anesthetic Conserving Device with isoflurane syringe.



or sevoflurane was developed (Figures 1–3). The Anesthetic Conserving Device /AnaConDa™ (ACD) is a modified heat and moisture exchanger (HME). As is the practice with HMEs, the ACD is placed between the Y-piece and the endotracheal tube (Figure 3). The dead-space is approximately 100 ml and airway resistance is 2.5 cmH₂O at 60 l/min air flow. The moisture-exchanging efficacy is 30 mgH₂O/l air at tidal volumes of 750 ml, which is similar to the efficacy of other currently available HMEs. The ACD also contains a viral and bacterial filter.

Besides incorporation of standard HME features, the ACD has an infusion line for injection of isoflurane/sevoflurane via a syringe pump to the ACD. In the ACD, the anaesthetic agent is delivered to a porous 'evaporator rod' (Figure 2). During inspiration, the fresh gas flow passing the ACD vaporises the anaesthetic agent that has reached the surface of the evaporator rod. During expiration, approximately 90% of exhaled anaesthetic agent from the patient is adsorbed to a lipophilic filter of active carbon in the ACD. At the next breath delivered to the patient, the anaesthetic agent is desorbed and inhaled. This reflection of anaesthetic agent results in: first, less agent consumption and, secondly, reduced concentration of

Figure 2. The Anesthetic Conserving Device, cross sectional view. 1 = Y-piece connector; 2 = Viral and bacterial filter; 3 = Active carbon filter; 4 = Keyed syringe connector and infusion line; 5 = "Evaporator rod"; 6 = Patient connector; 7 = Anaesthetic agent monitor port.

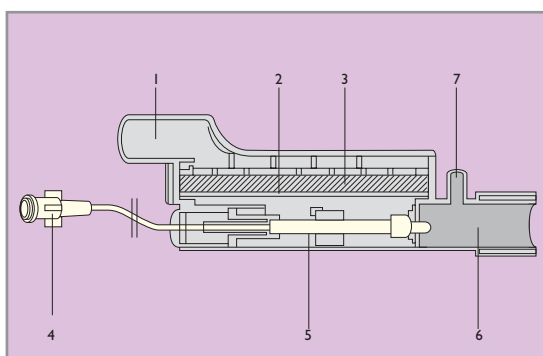
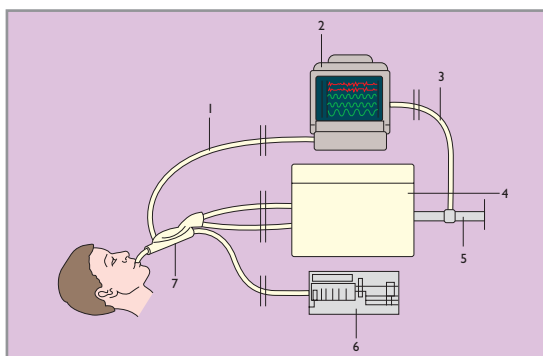


Figure 3. The Anesthetic Conserving Device in the circuit. 1 = Anaesthetic agent monitor line; 2 = Anaesthetic agent monitor; 3 = Waste gas from monitor connected to scavenging system; 4 = ICU ventilator; 5 = Anaesthetic agent scavenging from expiratory outlet; 6 = syringe pump; 7 = Anesthetic Conserving Device.



anaesthetic agent in the exhaled air-oxygen mix leaving the ventilator compared to the patient's end-tidal concentration.

While the experience of isoflurane and sevoflurane administration via the ACD is growing, the low boiling temperature of desflurane (23.5°C) makes it unsuitable for administration via the ACD.

Experiences with the ACD/AnaConDa®

During sevoflurane anaesthesia using the ACD sevoflurane consumption has been shown to be equivalent to that of a low-flow (approximately 1.5 L/min) circle system.^{20,21}

Isoflurane sedation of critically ill patients via the ACD in the ICU has been performed.^{22–25} In one study, patients receiving ventilator treatment were randomised to receive either isoflurane via the ACD or intravenous midazolam for up to four days, with short wake-up times (mean extubation time 10 minutes) following isoflurane sedation compared with midazolam-sedated patients (mean extubation time 250 minutes).²² Isoflurane consumption during ICU sedation averaged 2.1 ml/hour corresponding approximately to 25% of agent consumption using high flow ventilation and vaporiser.²³

The ACD has also been used for postoperative isoflurane sedation after coronary artery grafting, with faster emergence after termination of sedation than with intravenous sedation.²⁴ Initial experience with paediatric use has been reported²⁵ and is now being evaluated in postoperative sedation following paediatric cardiac surgery.

Technical considerations with the ACD

Administration of inhaled sedative agents with the ACD differs from traditional drawover vaporiser use. Familiarisation with the manufacturer's instruction manual is therefore required prior to use. In our unit, special in-training sessions were carried out with all staff, physicians and nurses prior to clinical use of the ACD. For ICU sedation with isoflurane via the ACD the following is needed:

- The ACD
- A conventional syringe pump
- An anaesthetic agent monitor
- An anaesthetic agent scavenging system

Administration

PRIMING OF THE ACD

Before use of a new ACD the infusion line needs to be filled. In our experience, priming of the ACD (infusion line) is best performed before connecting the ACD to the patient (Figure 2). The ACD is connected to a gas monitor, with the patient connector closed with a red cap and the Y-piece connector open. The infusion line (approximately 1 ml) is filled until isoflurane is detected by the monitor. For example, with an initial infusion rate of 20–30 ml/hour the infusion line is filled in 2–3 minutes. At this point the infusion rate is reduced to the suggested rate according to anticipated minute volume, which is most easily achieved using a nomogram provided by the manufacturer as a package insert. After an initial peak of isoflurane registered by the monitor, the isoflurane level falls to below 1% within a few minutes (due to the 100–200 ml/min flow of air through the ACD created by the monitor). At this stage the ACD can be connected to the patient.

Isoflurane should be stored at room temperature, in order



to avoid heat-induced volume expansion and bubble formation in the isoflurane syringe. It is moreover important to avoid elevating the syringe to a level high above the ACD. This may promote a passive flow of isoflurane in the infusion line when disconnecting the infusion line from the isoflurane syringe. A ventile will soon be incorporated in order to eliminate this potential problem (personal communication with the manufacturer). Another improvement in the new version of the ACD is a keyed syringe and infusion line connection (previously luer-lock), reducing the risk of accidental intravenous administration of isoflurane.

SYRINGE PUMP

Most modern syringe pumps can be programmed according to user specifications. We suggest that the maximum infusion rate for isoflurane in the syringe pump is set to 20 ml/hour and that bolus doses of isoflurane are limited to 0.5 ml, in order to reduce the risk of overdosage.

OTHER INHALED MEDICATIONS

In order to avoid loss of inhaled medication in the ACD filter, the nebuliser must be connected between the ACD and the endotracheal tube. In our experience the function of the ACD is not significantly affected by routine nebulisation of β_2 -agonists or ipratropium bromide four times daily. Ultrasound-driven nebulisers are recommended, as the isoflurane concentration may be reduced by air-driven nebulisers, necessitating a temporary increase of the isoflurane infusion rate.

Monitoring

While clinical sedation level is the primary tool for evaluation of adequate sedation, monitoring of isoflurane concentrations is necessary to ensure patient safety, to relate end-tidal concentrations to sedation depth and haemodynamic changes and to adequately sedate patients receiving neuromuscular blocking agents.

Different anaesthetic agent monitors are available, as well as gas monitoring modules and software for integration with many ICU monitoring systems. It is important that CO_2 is monitored simultaneously in order for the monitor to display inspiratory and end-tidal isoflurane concentrations correctly.²⁶ When using isoflurane for sedation, alarm limits may need setting at a lower level than the default, eg end-tidal isoflurane 1.5 %.

As the sampled air-oxygen-isoflurane mix is humidified there will be an accumulation of water in the monitor line. To avoid the need for frequent emptying of the water trap or accumulation of water in the monitor, a special water-permeable Nafion® line can be connected in series with the standard monitor line.

Environmental aspects

There are presently few data demonstrating any carcinogenic or teratogenic effects of exposure to trace concentrations of isoflurane.²⁷⁻²⁹ A study from 2004 of isoflurane sedation via the ACD in the ICU revealed low ambient isoflurane pollution, well below internationally accepted exposure limits.²³ Results will obviously vary somewhat depending on physical layout, room ventilation, extent of use and scavenging system.

PREPARATION

Filling of the isoflurane syringes should preferably be per-

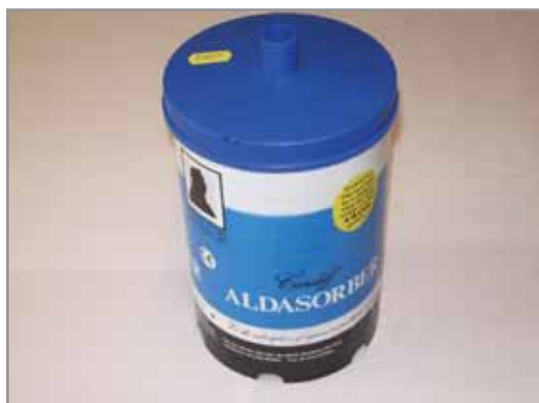


Figure 4. The Cardiff Aldasorber Medical filter.

formed in an ICU drug preparation room, thereby avoiding the risk of inadvertent spillage at the bedside. In our unit a special bottle adapter allows the filling of isoflurane syringes with a closed bottle technique.

SCAVENGING

Despite the relatively low concentration of isoflurane leaving the ventilator when the ACD is used (theoretically 0.03–0.05 %), scavenging of this isoflurane-containing air is recommended. Generally ICUs have passive or active waste gas outlets. If such outlets are present, an open reservoir with low pressure suctioning connected to the expiratory outlet of the ventilator can easily be connected to the waste gas outlet. If there are no outlets in the ICU, the expiratory outlet needs to be connected to an isoflurane adsorbing device. The Cardiff Aldasorber Medical Filter³⁰ (Figure 4) is a 1.2 kg active carbon cylinder with low gas flow resistance that can be directly connected with the ventilator's expiratory outlet. The Aldasorber has a capacity of maximally 200 g of isoflurane, sufficient for approximately 3–4 days of isoflurane sedation in adults.

VENTILATION

Room size and ventilation standards in ICUs may vary and thereby influence the rate at which potential isoflurane spillage is removed from the room. When active scavenging is performed there is no substantial pollution as the isoflurane delivery system and breathing circuit is closed. This is not true in the case of paediatric patients with uncuffed endotracheal tubes and study of contamination in this setting has yet to be performed.

OPEN VS. CLOSED SUCTION

In a study of ambient isoflurane pollution with the ACD, low levels of isoflurane were detected during interventions such as suctioning, despite the use of an open suctioning method.²³ Closed suction may imply an even lower degree of isoflurane contamination. In our experience, holding the expiratory pause function on the ventilator when interrupting the system reduces the risk of leakage.

Paediatric considerations

In our limited experience, the ACD in standard placement is of little value in children <30 kg, due to increased deadspace and airway resistance, resulting in CO_2 retention and increased work of breathing.²⁵ In smaller children the ACD can be placed in the inspiratory limb of the breathing circuit where it does not contribute to deadspace but still can be used for simple administration of isoflurane. This



adaptation implies that there is no rebreathing of isoflurane nor any heat- or moisture-exchanging function of the ACD, resulting in somewhat increased consumption of isoflurane and higher concentration of isoflurane passing into the scavenging system. In these small children, active humidifiers are commonly used and can be connected after the ACD in the inspiratory limb. Anaesthetic agent sampling is best performed from a separate port placed at the endotracheal tube, in order to obtain inspiratory as well as expiratory isoflurane concentrations.

Until modified ACDs are produced specifically for the pediatric population, this adaptation has proven valuable as an alternative for prolonged sedation of children, but requires additional training for physicians and nursing staff.

PRESENT AND FUTURE ROLE OF ISOFLURANE SEDATION VIA THE ACD

Currently, ICU sedation with isoflurane via the ACD may be a valuable alternative to intravenous sedation in the ICU, particularly in certain scenarios, e.g. delayed extubation where rapid waking is desired or during prolonged sedation where a 'drug holiday' may be desirable - alternating régimes and thus reducing tolerance and tachyphylaxis. Inhaled agents may promote spontaneous breathing modes of mechanical ventilation.²⁶ Postoperative inhalational sedation may possibly provide cardioprotective effects following cardiopulmonary bypass.³¹

The ACD as a novel method of isoflurane administration in the ICU may provide impetus for further development of other administration methods such as vaporiser technology for ICU ventilators, possibly with lower fresh gas flows to conserve agent expenditure over prolonged periods or newer anaesthesia machines with sophisticated ventilatory functions,

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