
Inhalational anaesthetics in the ICU: theory and practice of inhalational sedation in the ICU, economics, risk-benefit

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ICU sedation poses many problems. The action and side-effects of intravenous drugs in the severely ill patient population of an ICU are difficult to control. The incidence of post-traumatic stress disorder after long-term sedation is high. The recent focus on propofol infusion syndrome entails restrictions in the use of this drug. On the other hand, volatile anaesthetics very selectively suppress consciousness but leave many autonomic functions intact. In the absence of perception and disturbed information processing the number of adverse experiences should be lower, leading to a better psychological outcome. Respiration and intestinal motility are not depressed, facilitating modern therapeutic concepts such as early enteral feeding and augmentation of spontaneous breathing. Awakening after inhalational ICU sedation is quick and predictable, extubation can be planned and organized, and the time during which the patient needs very close observation will be short. Technological advances have greatly simplified the application of inhalational anaesthetics. New anaesthesia ventilators offer ventilatory modes and high flow generation comparable to ICU ventilators. However, they are not yet licensed for stand-alone use. The introduction of a volatile anaesthetic reflection filter for the first time enables the concept of inhalational sedation to be performed with very little effort by many ICUs. This 'anaesthetic conserving device' (AnaConDa[®]) is connected between the patient and a normal ICU ventilator, and it retains 90% of the volatile anaesthetic inside the patient just like a heat and moisture exchanger. In this chapter possible advantages of the new concept and the choice of the inhalational agent are discussed. The technical prerequisites are explained, and the practice and pitfalls of inhalational ICU sedation in general and when using the AnaConDa are described in detail.

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RATIONALE FOR THE USE OF VOLATILE ANAESTHETICS IN THE ICU

After removal of her meningioma, Mrs K, a 60-year-old lady, was sedated and ventilated overnight in a neurosurgical ICU. She awoke to find that she could not breathe freely and could not talk. She felt something inside her mouth and throat. She was hoping for relief when a nurse entered the room. But this nurse only checked the settings of the ventilator and then went off again. Mrs K describes her experience of complete helplessness: 'I thought I was lying in a coffin. This was the most horrifying experience I have ever had in my life'.

Sedation of ventilated patients in the ICU poses many problems. In a group of 150 ICU patients ventilated for longer than 48 hours, 50% remembered the endotracheal tube in place. Other common experiences were pain, fear, anxiety, lack of sleep, feeling tense, inability to speak/communicate, lack of control, nightmares, and loneliness'.¹ In survivors of acute respiratory distress syndrome the incidence of post-traumatic stress disorder (PTSD) was reported to be 27%. These patients had physically survived their life-threatening illness, but were psychologically so disturbed that this interfered substantially with their daily life.²

Other investigators showed that daily interruptions of sedative infusions reduced the duration of mechanical ventilation from 7 to 5 days and the mean ICU stay from 10 to 6.5 days.³ Their patients were closely watched by a study observer, who addressed them regularly, reassured them in a calm voice and restarted the sedative drugs as soon as the patients showed signs of wakefulness. The daily interruption of sedation did not result in adverse psychological outcomes.⁴ The message is not that we generally over-sedate patients, but that intravenous sedation is difficult to control. Additionally, understaffing may lead to a lack of attention to the patient, and patients left alone may have very stressful psychological experiences.

The use of etomidate, the shortest-acting intravenous hypnotic drug, for ICU sedation is precluded by profound suppression of the adrenal cortex. Propofol seems to be second-best choice, and has become popular in many countries. After the report on the deaths of five children in 1992⁵ and five adults in 2001⁶, 'propofol infusion syndrome' (PIS) was described as a severe—sometimes fatal—metabolic acidosis with rhabdomyolysis and renal and cardiac failure.⁷ The mechanism involves impaired fatty acid oxidation in mitochondria resulting in a deficient energy supply.⁸ PIS may be promoted by catecholamines and corticosteroids. Recently rhabdomyolysis after intravenous anaesthesia for cardiac surgery in a patient taking statins against hypercholesterolaemia was reported to the German authorities.⁹ The 'Arzneimittelkommission der deutschen Ärzteschaft' issued a warning, a reminder that propofol for ICU sedation should be used only in patients over 16 years of age, for up to 7 days, and to a maximum dose of 4 mg/kg/h or less if possible. They recommended frequent laboratory investigations to rule out metabolic acidosis as well as rhabdomyolysis and consideration of alternative treatment options such as benzodiazepines in severely ill patients.⁹

Prolonged use of other drugs for ICU sedation is associated with accumulation and poor control of action. For benzodiazepines, a quick onset of tolerance and a ceiling effect are characteristic. Opioids depress respiration and intestinal motility and thereby interfere with state-of-the-art therapeutic concepts such as augmentation of spontaneous breathing and early enteral nutrition. If patients become tolerant, very high doses have to be administered. For these reasons we believe it is worth looking for alternative options in long-term sedation.

POSSIBLE ADVANTAGES OF INHALATIONAL ICU SEDATION

Protection from the consequences of ischaemia in the heart, brain, kidneys and other organs (see Chapters 8–10) may obviously constitute a major advantage for our patients and particularly for severely ill ICU patients with haemodynamic instability or circulatory failure.

Regarding psychological aspects, a partly suppressed perception, possibly combined with hallucinations, may provoke emotionally disturbing experiences. Things perceived to refer to oneself cannot be understood rationally because of lack of communication and disturbed information processing, and may result in frightening experiences. Recently there was an impressive description of such perceptions by an anonymous intensive care physician who had become an intensive care patient himself. Even he did not understand what was going on around him.¹⁰ The number of such frightening experiences correlates with a poor psychological outcome.² Volatile anaesthetics act primarily on the more rostral brain structures like the cerebral cortex, and even at low concentrations may completely depress consciousness (MAC_{awake}) while leaving many autonomic functions (such as temperature control, blood pressure regulation or respiration) undisturbed. Return of consciousness is usually brisk, and there may be a short-lived excitation, but volatile anaesthetics can be said to act like on/off switches for consciousness. The hypothesis is that PTSD will occur very rarely after inhalational sedation.

Sevoflurane in very low concentrations seems to interfere with engraving of emotionally disturbing information in the amygdaloid bodies. When volunteers are shown a mixture of emotionally disturbing and emotionally neutral pictures, they will predominantly memorize the first ones. Low-dose sevoflurane inhalation abolishes this predominance (personal communication, G. Schelling, San Diego, USA).

Volatile anaesthetics give excellent control over their action. Onset of action is usually quick, especially when injection techniques are used as in the AnaConDa[®] or Zeus[®] (see below). The end-tidal fraction (F_{et}) of the volatile anaesthetics can be monitored, representing a precise indicator of the drug's concentration in the target organ much more reliable than any target-controlled infusion algorithm. Emergence times are shorter and more predictable than after intravenous sedation. This has been shown in many clinical trials.^{11–15} Volatile anaesthetics accumulate very little, and elimination is independent of liver and kidney function. More and more people now live to old age, and the mean age of ICU patients is continuously rising, making this advantage ever more important.

Many intravenous agents—e.g. propofol, opioids, or α_2 -agonists—interfere with haemodynamic regulation by causing vasodilation, myocardial depression or bradycardia. Ketamine increases blood pressure and heart rate, and thereby the workload of the heart. In contrast, xenon is renowned for its circulatory stability,

and this has been shown to be of benefit for ICU patients.¹⁴ With the exception of halothane, the newer volatile anaesthetics interfere very little with haemodynamics, especially in low concentrations. By lowering or increasing blood pressure with nitroprusside or phenylephrine in volunteers, Ebert et al showed that regulation of heart rate (baroreceptor reflex) and of peripheral sympathetic nerve activity was hardly disturbed at 0.5 MAC desflurane compared to the awake state.¹⁶ The sympathoadrenergic stimulation seen after a first sudden increase in desflurane concentration from 1 to 1.5 MAC¹⁷ is not relevant for ICU sedation as such high concentrations are not indicated. In fact we found heart rate to be more often in the normal range in patients sedated with desflurane compared to propofol.¹⁵

Volatile anaesthetics are potent bronchodilators. Unlike ketamine and most other agents, they do not act via acetylcholine or β_2 -receptors¹⁸ and thus may be tried when other agents have failed. The mechanism seems to involve nitric oxide as well as prostaglandins released by the epithelium.¹⁹ The bronchoconstriction seen in inhalational induction with desflurane is due to its pungent odour and is short-lived. Volatile anaesthetics have been used successfully for the treatment of status asthmaticus when other therapies have failed.^{20–25}

TECHNICAL PREREQUISITES

If volatile anaesthetics are to be used in the ICU, several preconditions must be met.

In order to minimize occupational exposure, a high turnover of room air of about 10 times per hour is recommended.²⁶ Workplace concentrations of volatile anaesthetics are usually highest not in the OR, where turnover of room air is high (≥ 15 times per hour), but in ICUs with poor air conditioning systems where after inhalational anaesthetics patients may continue to exhale considerable amounts of volatile anaesthetics. Therefore the use of anaesthesia gas scavenging (AGS) has been suggested even for intensive care respirators, when such patients are sedated with intravenous drugs.²⁶

AGS should be used with active or passive mechanical systems or with charcoal adsorption (Figure 1). Commercially available canisters containing 1 kg activated charcoal will effectively remove isoflurane from the expired air up to a weight increase of 300 g²⁷, which occurs after 12 hours or considerably later, if rebreathing techniques or a volatile anaesthetic reflection filter are used. Passive AGS means that a simple hose connected to the gas outlet of the ventilator conducts the expired air to the external atmosphere. In active AGS suction is applied to the gas outlet. Care must be taken that the suctioning does not interfere with the function of the ventilator. Suctioning should be performed with small negative pressures but should allow high flows. Traditionally, AGS uses large-bore pipes and hoses. Today containers that accommodate the expiratory tidal volume, which is suctioned away during the next inspiration, are standard practice (Figure 1). If such containers are used they can be connected to the small-bore vacuum system that is standard equipment in ICUs provided an appropriate flow is chosen and the outlet of the vacuum pump is not itself within a working environment. Johnston et al recommended active AGS with an inserted bag instead of the container. The flow could then be adjusted such that the bag is never completely full or completely empty.²² In Germany the Deutsche Forschungsgemeinschaft recommended maximum ambient concentrations (Maximale Arbeitsplatzkonzentrationen, MAK) of 100 ppm for nitrous oxide and 5 ppm for halothane. These MAK values were adopted by the German authorities. The European health authorities recommend MAK

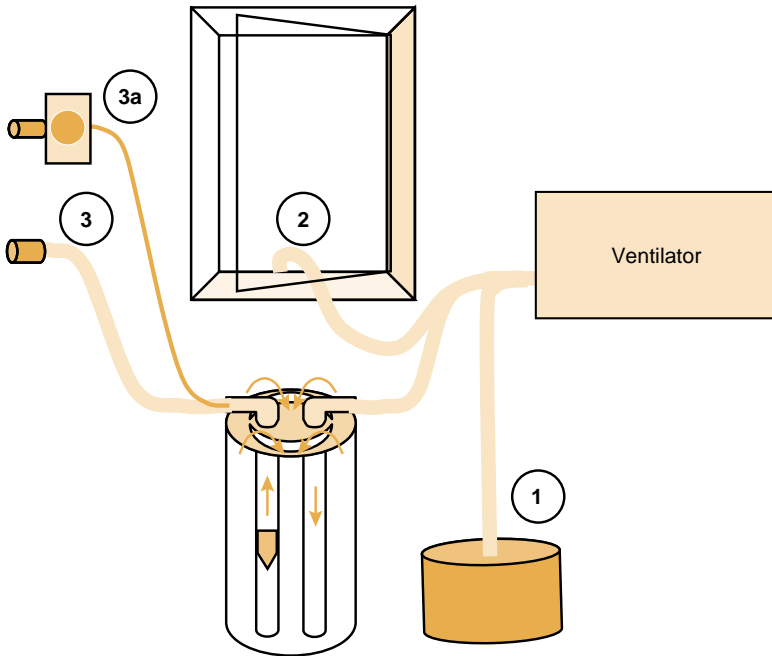


Figure 1. Anaesthesia gas scavenging with activated charcoal adsorption (1) or with passive (2) or active (3) mechanical systems. If a container or bag is used to accommodate the expired tidal volume before this is suctioned away during the next inspiration, these can be connected to the small-bore vacuum system intended for suctioning patients' secretions that is standard equipment in many ICUs (3a), provided an appropriate flow is chosen and the outlet of the vacuum pump is not itself situated within a working environment.

values of 10 ppm for isoflurane and 20 ppm for enflurane. For the newer volatile anaesthetics desflurane and sevoflurane no MAK values have been defined so far. If the agents are metabolized, fluoride can be determined in the urine of staff after a shift and should not exceed a biological threshold value of 7 mg/g creatinine in the urine.²⁸

Coleman et al evaluated active, passive and charcoal AGS during isoflurane sedation in three ICUs and found isoflurane levels in the ambient air of < 1 ppm on average.²⁷

Vaporizers deliver a set concentration of the volatile anaesthetics. They may work inaccurately with very low or very high flows. Vaporizers in the inspiratory limb of a circle or a half-open system have therefore been abandoned. Vaporizers are agent-specific, and severe overdosing may occur if the wrong agent is used.²⁹ Another possibility for delivering volatile anaesthetics is a direct injection technique, as in the AnaConDa (see below) with a normal syringe pump or in the new anaesthesia workstation Zeus (Dräger Medical, Lübeck Germany). These new modes of application are described in detail in Chapter 7.

Gas monitors are required as a safety check for the correct functioning of volatile anaesthetic delivery. Additionally, the F_{et} can be used to monitor the effective concentration in the target organ. Most monitors also display end-tidal CO_2 , which is a valuable aid when augmented spontaneous breathing is first installed as well as during the weaning process. The technical principles of monitoring volatile anaesthetics are described in detail by Schwartz.³⁰

The major reason why inhalational ICU sedation has not become more widely used, despite many favourable publications, is that up to now no commercially available ventilator fulfilled all the desired properties.

Augmentation of spontaneous breathing is now considered standard care and may be difficult to realize with an anaesthesia ventilator. Up-to-date ICU ventilators offer a wide variety of different ventilatory modes as well as a better ventilatory performance, higher flow generation, quicker-responding valves, etc. They are cheaper, smaller, and easier to handle. There is also a legal aspect: anaesthesia ventilators can only be operated in the presence of trained and specifically instructed staff, whereas ICU ventilators with their refined alarm set-up may be used as stand-alone machines. Therefore in the past ICU ventilators have been adapted for inhalational sedation. Breheny et al inserted a vaporizer between the oxygen blender and the low pressure port of a Servo-900 ventilator.³¹ Hoerauf et al used a Siemens-900C ventilator with a circle system.³² Millane et al connected a vaporizer in parallel between the oxygen blender and the inspiratory limb of a Servo-B ventilator.¹² Bedi et al used a Puritan Bennett ventilator connected to a totally closed bag-in-bottle system to ventilate their patients and apply xenon in the intensive care setting.¹⁴

In our randomized study comparing desflurane with propofol sedation we used a Cicero anaesthesia ventilator in pressure-controlled ventilation for up to 24 hours postoperatively.¹⁵ In our latest study we evaluated a prototype of the Zeus workstation for inhalational sedation with desflurane in 10 postoperative patients.³³ We conclude that the ventilator capabilities of the Zeus are comparable to modern ICU ventilators. In a pilot study 11 colleagues blinded to the ventilator judged breathing comfort with the Zeus to be as good as with six classical ICU ventilators.³⁴ Unfortunately, the Zeus is much more expensive than an ICU ventilator and is not licensed for stand-alone use. Therefore its use on the ICU cannot be recommended for routine clinical practice.

The introduction of a volatile anaesthetic reflection filter in 2004 constitutes a major technical breakthrough in the delivery of volatile anaesthetics for inhalational sedation in the ICU. After the first attempts with the potentially toxic material zeolite³⁵ (fibres, if inhaled, may cause pulmonary injury similarly to asbestos fibres), a new device called an 'anaesthetic conserving device' or AnaConDa (Sedana Medical, Sundbyberg, Sweden) incorporates activated charcoal fibres.³⁶ During expiration 90% of the volatile anaesthetic molecules condense on the surface and are released again during the next inspiration. The volatile anaesthetic is injected via a standard syringe pump into a porous rod called an evaporator situated on the patient side of the device. The new device eliminates the need for CO₂ absorption and rebreathing techniques while its efficiency corresponds to a circle system with a fresh gas flow of 1.5 L/min.^{37,38}

The AnaConDa can be used with any ICU ventilator. It includes a heat and moisture exchanger. It is for single patient use and should be changed after 24 hours for hygienic reasons. It comprises a dead space of 100 mL. A smaller version for use in children is under development. The AnaConDa can be used with isoflurane or sevoflurane. Desflurane is not reflected as not enough molecules will condense on the surface because of the higher vapour pressure. According to the inventor, technical modifications of the AnaConDa should allow the use of desflurane in the near future (personal communication, Hans Lambert, Sweden).

In a recent report isoflurane sedation via the AnaConDa was compared with midazolam sedation for up to 96 hours in 40 patients. The authors report shorter wake-up times after isoflurane and no serious side-effects in both groups. They conclude that the new device can be easily managed by nursing staff.³⁹

WHICH INHALATIONAL AGENT TO USE?

Up to now no inhalational agent has been licensed for ICU sedation. On the other hand there is no time limit for the duration of anaesthesia, and there is a vast experience with prolonged use of isoflurane in the literature.

Although 20 years ago halothane and nitrous oxide had been used for inhalational sedation, their use must be discouraged because of toxicological concerns. Halothane is heavily metabolized, leading to accumulation of bromide (which has CNS side-effects)²¹ as well as trifluoroacetate that binds to liver proteins and provides an epitope for antibodies that ultimately may destroy liver cells ('halothane hepatitis'). Nitrous oxide—by oxidizing the cobalt atom of cobalamine—interferes with the function of that vitamin.⁴⁰ Prolonged use has been associated with megaloblastic anaemia⁴¹ as well as myeloneuropathy (subacute combined degeneration of long tracts in the spinal chord).⁴²

Most studies on inhalational sedation were performed with isoflurane. Isoflurane has been used for almost two decades in some centres in Great Britain, Canada and the US. Common indications are status asthmaticus^{20–24} and status epilepticus.^{43–46} To abolish epileptic activity higher doses (up to 1 or 1.5 MAC) may be necessary. Plasma fluoride may increase up to 50 μmol ^{47–49}, but today this is no longer a matter of concern.^{50,51} Because the isoflurane molecule comprises one chloride atom that when released into the stratosphere may contribute to the destruction of the ozone layer, the newer volatile anaesthetics desflurane and sevoflurane (purely fluorinated agents) will replace isoflurane in the future.

Recently there has been a report on desflurane sedation over 15 days in a patient with an encephalopathy of unknown aetiology presenting in status epilepticus. No serious side-effects of desflurane were noted; the patient was later treated with isoflurane and many other antiepileptic drugs but finally died 156 days after admission.⁵² Apart from this report there is only one publication on the use of desflurane in the ICU.¹⁵ This is surprising as desflurane seems to fulfil all the desired properties: its pharmacokinetics promise extremely little accumulation and rapid emergence even after long exposure times. We could demonstrate that times to eye-opening and extubation were short and did not increase with increasing time of administration up to 24 hours in 32 postoperative patients.⁵³ Metabolization is minimal, and there is no concern with fluoride accumulation. Concerns about high cost⁵⁴ are unsubstantiated if low- or minimal-flow techniques are used. In our study with a fresh gas flow of 1 L/min, pure drug costs were €95/24 hours, which was half the price of propofol at the time.¹⁵ In the clinical evaluation of the Zeus for achieving an F_{et} of 3 vol% consumption of liquid desflurane was 10 mL every hour at a cost of €3/hour.³³

The introduction of the AnaConDa, a volatile anaesthetic reflection filter that can be used with isoflurane and sevoflurane, has focused attention on the latter. In one study 12 patients were sedated with 0.9–1.5 vol% sevoflurane for on average 70 hours and opened their eyes 17 ± 18 minutes after discontinuation.⁵⁵ In the absence of soda lime there is no concern about Compound A. It remains to be shown whether fluoride during prolonged administration will remain within acceptable limits. Currently experiments with pigs are under way, and preliminary results seem to be promising (personal communication, Professor Belda, Valencia, Spain).

The noble gas xenon seems to have ideal properties to become the inhalational agent of choice for ICU sedation. In the study of Bedi et al, 30 vol% xenon was sufficient, and patients were haemodynamically more stable than with propofol.¹⁴ There are only two

arguments against the use of xenon in the ICU: its price, and the need to apply high oxygen concentrations in some patients. Whether xenon will become widespread depends on the availability and handiness of closed breathing systems, methods of recycling, or discoveries of more natural resources that will lower the price.

PRACTICE OF INHALATIONAL SEDATION

If the technical prerequisites are met, inhalational anaesthesia can be used in any patients ventilated via endotracheal or tracheostomy tubes. Considerable air leakage—for instance by a bronchopleural fistula—may be a relative contraindication.

Most inhalational agents are poor analgesics, and there will be a need for analgesia especially in postoperative or trauma patients. Opioids, non-opioid drugs and regional analgesia techniques can be combined as appropriate. Obviously the need for analgesia is less than during surgery, and ideally when the volatile anaesthetic is stopped patients should wake up with continued analgesic medication and be in no pain. In the context of intravenous sedation opioids are often given in higher doses to profit from their sedative side-effects. Intensivists thereby try to reduce the dose of propofol and avoid PIS or to overcome the tolerance to benzodiazepines. As a rule of thumb, if a patient sedated intravenously is going to inhale a volatile anaesthetic, opioid requirements will be less than half, and it is wise to stop the opioid temporarily until the blood concentrations have fallen.

Low-dose opioids will allow reduction of the F_{et} of the volatile anaesthetic. By their action in the brainstem they promote tolerance to the endotracheal tube, and suppress the coughing reflex and the temporary vegetative excitation when the volatile anaesthetic is discontinued or administered in (too) low concentrations.

Because of its favourable pharmacokinetics, remifentanil⁵⁶ seems to be the ideal partner for inhalational sedation. Like the volatile anaesthetics, remifentanil will not accumulate even in patients with hepatic or renal insufficiency. Its use for ICU sedation has been described^{57–59}, and it has been licensed for ICU sedation for up to 3 days. If used as the sole agent, dose requirements are high and increase rapidly even up to 1.0 $\mu\text{g}/\text{kg}/\text{min}$.⁵⁷ Such high doses will lead to high cost and will cause peripheral side-effects such as intestinal paralysis. In spontaneously breathing patients sedated with desflurane we used 0.01–0.05 $\mu\text{g}/\text{kg}/\text{min}$ remifentanil at a cost of €5–25/24 hours.³³

Respiratory drive is influenced mainly by the arterial CO_2 partial pressure (chemical drive), but may be increased by psychological stress or anxiety (conscious drive) as well as hypoxia (hypoxic drive). The latter is completely abolished even at very low concentrations of volatile anaesthetic.^{60,61} A sufficient inspiratory oxygen fraction must be guaranteed and monitored together with pulse oximetry as is standard practice for ventilated ICU patients. Conscious drive may lead to hyperventilation. Therefore inhalational induction of anaesthesia often leads to breath-holding until PaCO_2 rises and chemical drive takes over. Chemical drive is usually well preserved. Volatile anaesthetics slightly decrease the slope of the CO_2 response curve. This means that there is a smaller increase in minute volume if the PaCO_2 rises—for example during rebreathing manoeuvres. In ten spontaneously breathing patients we did not see any influence of the F_{et} of desflurane varied between 1.5 and 5.0 vol% on minute ventilation, end-tidal CO_2 or breathing pattern.³³ Other investigators described an increased respiratory rate, a decreased tidal volume and CO_2 retention in volunteers inhaling desflurane via

a mask⁶², possibly because of decreased residual lung capacity and atelectasis in the absence of PEEP.

Spontaneous breathing (SB) has been shown to improve gas exchange in several animal models^{63,64}, and augmentation of SB is recommended for mechanically ventilated patients. In SB active movements of the diaphragm lead to ventilation and better aeration of the dorsobasal lung regions that usually become atelectatic during mechanical ventilation. Continued muscular activity may prevent muscular atrophy and shorten the weaning process. Additionally SB can be used to monitor the optimal dosage of opioids. With inhalational sedation SB is maintained and if necessary may be augmented by different ventilatory modes.

The clinical case below illustrates the development of tolerance to intravenous sedatives commonly seen in alcohol-addicted patients. The increase in the F_{et} of desflurane probably reflected the wearing off of the other sedatives' action. Synchronization with the ventilator and augmentation of SB are usually easily achieved with volatile anaesthetics, and intestinal motility will be much better if these high doses of opioids are avoided.

Clinical case: Mrs N, a 50-year-old lady weighing 60 kg, was transferred to our hospital with severe acute pancreatitis, liver cirrhosis and ascites resulting from alcohol abuse. She was sedated and ventilated via tracheostomy tube in our ICU for several weeks. On day 9 she received propofol 200 mg/h, sufentanil 160 μ g/h and clonidine 24 μ g/h. The day before midazolam 14.4 mg/h and S-(+)-ketamine 20 mg/h had been stopped for not being effective. She had been struggling with the ventilator and pulled out tubes and catheters several times. She was then ventilated with the Zeus and received desflurane for 3 days, 3 vol% later increased to 5 vol%. All other sedatives were stopped. Within the next hours she developed regular spontaneous breathing and was supported by the Zeus. On the next day her bowel sounds returned and the day after her bowels opened for the first time. The amount of enteral nutrition via an intestinal feeding tube could be increased. After a drug pause of 3 days, intravenous sedation was restarted with much lower doses. After several weeks she was transferred to the general ward and finally made a full recovery.

The F_{et} for inhalational sedation should be slightly above MAC_{awake} which for volatile anaesthetics is about one third of the MAC to avoid 'purposeful movement to a supramaximal stimulus'. MAC_{awake} for xenon, isoflurane and sevoflurane was determined in patients as 33, 0.4 and 0.6 vol%, respectively⁶⁵, and for desflurane as 2.4 vol% in young volunteers.⁶⁶ In the latter investigation, no volunteer recalled the painful tetanic stimulation applied until a concentration of 2.5 vol% desflurane. Our group determined MAC_{awake} of desflurane in ten spontaneously breathing ICU patients as 2.0 vol% (range: 1.5–2.6). Awakening was always brisk. No patient could guess the second half of the compound words that were played to them via earphones right up to awakening. We conclude that there is no implicit memory (unpublished data). Unlike the case with intravenous sedation the perception and integration of information seem to be possible only after patients become clearly awake and responsive.

From this it becomes clear that conscious sedation with the calm, cooperative and at best even oriented patient who tolerates ventilation and the endotracheal tube as a goal to minimize the dose, side-effects and accumulation of intravenous drugs, does not work well with inhalational sedation. In fact clinical scoring systems such as Ramsay's score or OAAS are of little help. Patients will react with unpurposeful movements, increased

heart rate and blood pressure, or with coughing when painful stimuli are applied or endotracheal suctioning is performed. Rarely will a patient open his eyes when spoken to.

When sedation is to be terminated, patients will wake up within minutes. In our study patients were responsive at 5 minutes, were extubated at 7.7 minutes, and could clearly state their date of birth at 10.5 minutes after stopping desflurane, each with a narrow statistical distribution.¹⁵ This means that awakening is predictable, and can be planned and organized. After 15 minutes almost all patients were completely orientated, had been reassured and could be left alone to recover.

After isoflurane sedation we observed a more prolonged vegetative agitation with an increase in heart rate and blood pressure. This will begin 10 minutes after discontinuation and may last several minutes to several hours depending on the duration of isoflurane sedation. This vegetative agitation is easily treated with clonidine. In patients sedated with isoflurane for more than a week, we recommend switching to intravenous sedation for another day, for instance with low-dose propofol combined with clonidine, if there is tachycardia.

THE ANACONDA

The AnaConDa is a very promising tool for inhalational sedation in the ICU because it enables the use of standard ICU ventilators. The only technical modification is connection to one form of AGS. If active AGS is applied with suction, the performance of the ventilator must be checked before a patient is connected.

Several points have to be considered:

- The volatile anaesthetics sevoflurane and isoflurane are drawn into a 50 mL syringe from the bottle with a specific adapter. Only special syringes and tubings may be used as unsuitable plastic materials may be dissolved by the volatile anaesthetics.
- Autopumping: care must be taken to avoid bubbles in the syringe. When volatile anaesthetics are stored in a refrigerator, other gases may dissolve and later may form bubbles when warming up. Due to their high vapour pressure, volatile anaesthetics will evaporate into these bubbles and make them grow. Additionally, because of their high density (1.5 g/mL), volatile anaesthetics may exert a negative pressure if the syringe pump is fixed high above the patient's head. This will lower the boiling point inside the syringe, which is 49 °C for isoflurane and 59 °C for sevoflurane at normal pressure. The growing bubbles may pump liquid volatile anaesthetics into the device, a mechanism referred to as autopumping. Autopumping may lead to a severe overdose. Therefore:
 - volatile anaesthetics should be stored at room temperature;
 - the syringe should be filled up without bubbles;
 - the syringe pump should be at the level of the patient's head or below; and obviously
 - heat sources must always be kept away from the syringe.

In the case where bubbles are detected the device should be disconnected from the patient and the reason investigated.

- Dosing: when starting the infusion, a rate of 25 mL/h is recommended until the volatile anaesthetic reaches the evaporator. This can be detected by carefully

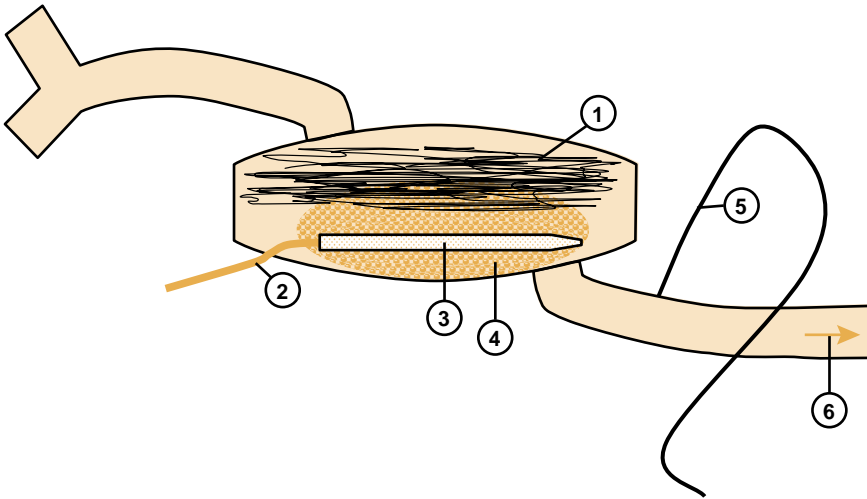


Figure 2. The anaesthetic conserving device (AnaConDa), a reflection filter for volatile anaesthetics. Volatile anaesthetic condenses on the surface of the activated carbon fibres (1) during expiration and evaporates again during the next inspiration. Thereby the AnaConDa reflects volatile anaesthetic like a heat and moisture exchanger reflects water vapour. Through the infusion line (2) liquid isoflurane is pumped to a porous rod called the evaporator (3). During the expiratory pause a 'cloud' of anaesthetic vapour (4) will form. During the next inspiration this cloud will pass by the sample line to the gas monitor (5). Because this cloud also contains a high carbon dioxide concentration from the last expiration, its high vapour concentration will be incorrectly interpreted as end-tidal fraction by most gas monitors. For a more detailed explanation see text.

watching the infusion line or by the first signal detected by the gas monitor. Depending on the minute volume and the desired concentration, the rate should then be selected according to a dosing table. After 1 hour the rate may be slightly lowered again. In our experience over up to 28 days, the rate of isoflurane very rarely needs to be modified. If sedation is not adequate, a bolus of 0.5 mL liquid isoflurane can be injected and onset of action will be more rapid than with any intravenous drug. Usually rates of 2–5 mL/hour at drug costs of €0.18–0.44 are enough to achieve an F_{et} of 0.3–0.5 vol%.

- Most standard gas monitors will not display inspiratory and end-tidal concentrations correctly. During the end-expiratory pause, the syringe pump will continue to administer volatile anaesthetic and a 'cloud' builds inside the device (Figure 2). During the next inspiration, this cloud will be pushed into the patient and pass the sample line to the gas monitor. There will be a peak concentration that will wrongly be classified by most monitors as F_{et} , because a high CO_2 concentration is measured simultaneously. Later during inspiration, this 'cloud' has passed and the activated carbon fibres deliver less and less volatile anaesthetic and there will be a dip. Therefore the inspiratory concentration is not constant. The dip will wrongly be interpreted as inspiratory concentration. During expiration there is a plateau representing the realistic value for F_{et} but this is not displayed as a numerical value. The mean of the displayed numbers represents a fair estimate of the true F_{et} (Figure 3). The difference between the displayed numbers is small, usually 0.2 vol% for isoflurane, making the estimate reliable enough. Monitors displaying the F_{et} course over time are

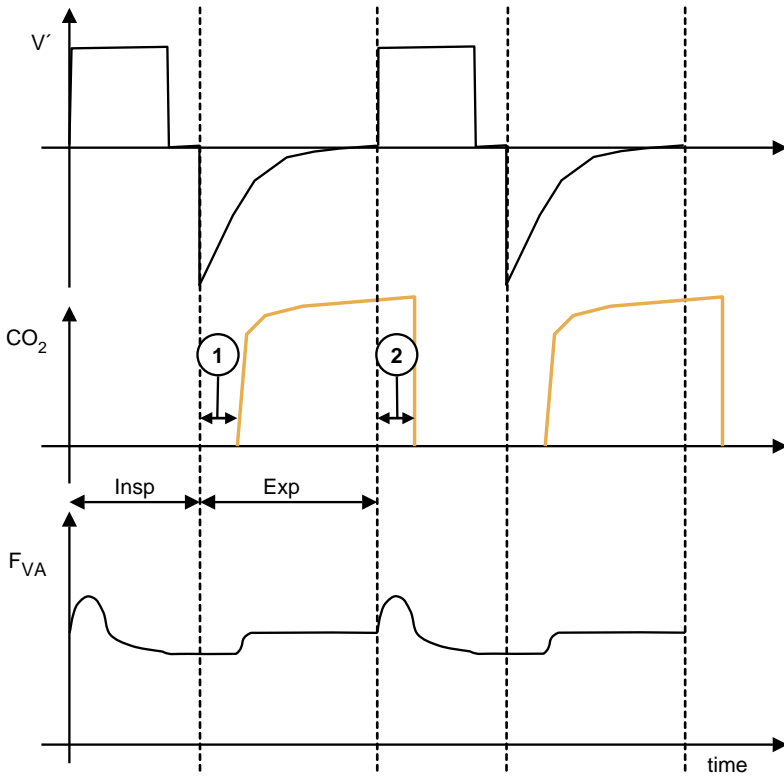


Figure 3. Ventilation cycle showing ventilatory flow (V'), carbon dioxide concentration (CO_2) and the fraction of the anaesthetic vapour (F_{VA}) as measured with a gas monitor connected to the AnaConDa. Due to the physiological dead space (1), CO_2 will only rise after the start of expiration (Exp). Due to the dead space inside the AnaConDa (2), CO_2 will continue to be sampled by the gas monitor during the start of inspiration (Insp). The peak F_{VA} , although occurring during inspiration, will be interpreted by most gas monitors as end-tidal fraction, because it is mixed with a high CO_2 . Later during inspiration, F_{VA} will fall as the activated carbon fibres are partially emptied. For a more detailed explanation see text.

preferable, and future monitors to be used with the AnaConDa should incorporate a different algorithm for detection of the end-tidal plateau value.

Practice points

- inhalational sedation in the ICU may be performed using anaesthesia ventilators, modified ICU ventilators connected to a vaporizer, or simply by using a volatile anaesthetic reflection filter (AnaConDa); for safety reasons the end-tidal concentrations should be monitored and some sort of AGS should be used
- regarding pharmacokinetics and haemodynamic stability, xenon would be the ideal inhalational agent, but its use is not economical; two decades of

experience in many countries make isoflurane the drug of first choice, while desflurane seems to be second best and is affordable but needs expensive equipment

- isoflurane and sevoflurane can be applied simply and efficiently via the AnaConDa connected to a normal ICU ventilator. Without soda lime, sevoflurane will not react to form Compound A, but fluoride levels may increase with long duration of application
- low concentrations of volatile anaesthetics around MAC_{awake} will suppress consciousness in the cerebral cortex but maintain control of temperature, blood pressure and respiration in the brain stem; even when used over weeks the concentrations do not have to be increased
- opioids will provide analgesia and promote tolerance to the endotracheal tube, but their dose can be much lower than with intravenous sedation, thereby facilitating intestinal motility and spontaneous breathing
- commonly used clinical sedation scales are of little help as most patients will not react to minor stimuli. Nevertheless awakening will be quick and predictable, and the patients will have to be watched closely only during a short time span; the vegetative excitation commonly seen when discontinuing the volatile anaesthetic can easily be treated with clonidine. When using the AnaConDa some technical points have to be considered
- Only special syringes and tubings may be used as volatile anaesthetics dissolve many plastic materials
- Volatile anaesthetics should be stored at room temperature, and care must be taken to fill up the syringe without bubbles. Bubbles increasing in size may lead to autopumping and to severe overdose. Heat sources must be avoided, and the syringe pump should *not* be placed above the level of the patient's head
- gas monitors will display the end-tidal concentration slightly incorrectly (too high), and the true F_{et} will be between the displayed values for the inspiratory and expiratory concentrations

Research agenda

The following questions should be addressed in carefully planned multicentre trials involving many patients:

- will inhalational sedation be beneficial for our patients?
- will it be possible to lower the rate of a poor psychological outcome in survivors of intensive care therapy, to improve lung function by maintaining spontaneous breathing, and to shorten the weaning phase and ICU stay?
- will inhalational sedation contribute to a better outcome for these severely ill ICU patients?

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