Inhaled sedation with isoflurane
in the Intensive Care Unit

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M.D

STOCKHOLM 2006
Believe those who are seeking the truth. Doubt in those who find it.

André Gide
ABSTRACT

Patients in the Intensive Care Unit (ICU) may experience distress and pain, for which they are often prescribed sedative and analgesic drugs, sometimes at the cost of clinically significant side effects, such as prolonged wake-up time, drug or solvent toxicity and withdrawal. The search for the ideal sedation regimen for these patients is ongoing.

Isoflurane – an inhaled anaesthetic – has sedative properties in subanaesthetic concentrations and is theoretically appealing as an ICU sedative but modern ICU ventilators are not compatible with currently available vaporizers. The Anesthetic Conserving Device / AnaConDa® (ACD) – a modified heat-moisture exchanger, with features permitting infusion of isoflurane from a standard syringe pump and rebreathing of exhaled isoflurane, has been developed for high-flow ventilation anaesthesia. This novel method has been studied in the anaesthesia setting but not for isoflurane sedation in the ICU.

The feasibility of isoflurane via the ACD for sedation in ICU patients was evaluated and sedation efficacy was compared with that of intravenous midazolam. Environmental aspects and agent-saving properties of the method were studied, as well as the potential benefit and limitations of ACD use in paediatric patients. The Bispectral index™ (BIS), a non-invasive EEG-derived numerical measure of anaesthetic and sedative depth, was evaluated as a predictor of clinically assessed sedation depth for isoflurane sedation and for midazolam sedation. Short-term recovery, long-term memories and psychological recovery in patients receiving isoflurane or midazolam were studied.

Wake-up times after isoflurane sedation via the ACD were significantly shorter than after midazolam. Few minor practical problems related to ACD use occurred and no adverse hepatic or renal effects related to either sedative were observed. Ambient isoflurane concentrations were low and well below recommended exposure limits. The novel method was useful in paediatric patients but required adapted placement in the breathing circuit to avoid increased dead-space in smaller children. BIS did not predict sedation depth well enough to replace clinical scoring during isoflurane or midazolam sedation. Patient follow-up did not reveal any differences in short-term recovery but significantly fewer patients reported delusions / hallucinations after isoflurane sedation than after midazolam sedation.

In conclusion, this thesis demonstrates that isoflurane via the ACD is efficacious for sedation of ICU patients, with shorter wake-up times than with midazolam. The use of the ACD for isoflurane delivery in the ICU is feasible, environmentally safe and reduces agent consumption compared with conventional vaporizer delivery. In paediatric ICU sedation, placement of the ACD in the inspiratory limb of the breathing circuit is necessary if the device is used in smaller children. BIS monitoring can not reliably replace clinical assessment of sedation depth in non-paralyzed ICU patients. Isoflurane sedation does not appear to have any serious negative psychological or cognitive effects compared to intravenous sedation and may possibly reduce the risk of delusions and hallucinations in the ICU.

Key words: vaporizer, ACD, AnaConDa®, BIS, follow-up
This thesis is based on the following papers that will be referred to by their roman numerals:

I. Sackey PV, Martling CR, Granath F, Radell PJ.  
**Prolonged isoflurane sedation of intensive care unit patients with the Anesthetic Conserving Device.**  

II. Sackey PV, Martling CR, Nise G, Radell PJ.  
**Ambient isoflurane pollution and isoflurane consumption during intensive care unit sedation with the Anesthetic Conserving Device.**  

III. Sackey PV, Martling CR, Radell PJ.  
**Three cases of PICU sedation with isoflurane delivered by the ‘AnaConDa’.**  

IV. Sackey PV, Granath F, Radell PJ, Martling CR.  
**Does the Bispectral Index predict sedation depth better during isoflurane than midazolam sedation in ICU patients?**  
*Submitted for publication.*

V. Sackey PV, Carlswärd C, Martling CR, Sundin Ö, Radell PJ,  
**Short- and long-term follow-up of ICU patients after sedation with isoflurane and midazolam – a pilot study.**  
*Manuscript.*
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<tr>
<td>ACD</td>
<td>Anesthetic Conserving Device / AnaConDa®</td>
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<tr>
<td>AEP</td>
<td>Auditory Evoked Potential</td>
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<td>APACHE</td>
<td>Acute Physiology And Chronic Health Evaluation</td>
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<td>APC</td>
<td>Anaesthetic Preconditioning</td>
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<td>ARDS</td>
<td>Acute respiratory distress syndrome</td>
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<tr>
<td>BIS</td>
<td>Bispectral Index™</td>
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<td>Bloomsbury</td>
<td>Bloomsbury Sedation Score</td>
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<tr>
<td>CNS</td>
<td>Central Nervous System</td>
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<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
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<tr>
<td>EMG</td>
<td>Electromyogram</td>
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<tr>
<td>E'T</td>
<td>End-tidal</td>
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<td>GABA</td>
<td>Gamma-aminobutyric acid</td>
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<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
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<td>HME</td>
<td>Heat Moisture Exchanger</td>
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<td>ICP</td>
<td>Intracranial Pressure</td>
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<td>ICU</td>
<td>Intensive Care Unit</td>
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<td>ICU-MT</td>
<td>Intensive Care Unit Memory Tool</td>
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<td>IES</td>
<td>Impact of Event Scale</td>
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<tr>
<td>MAC</td>
<td>Minimum Alveolar Concentration</td>
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<tr>
<td>MH</td>
<td>Malignant Hyperthermia</td>
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<td></td>
</tr>
<tr>
<td>MIN</td>
<td>minutes</td>
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<tr>
<td>mL</td>
<td>millilitres</td>
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<tr>
<td>NMBA</td>
<td>neuromuscular blocking agent</td>
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<tr>
<td>PPM</td>
<td>parts per million</td>
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<td>PTSD</td>
<td>Post-Traumatic Stress Disorder</td>
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<td>SQI</td>
<td>Signal Quality Index</td>
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Sedation in the ICU

The manifestations of critical illness, sleep deprivation and more or less invasive procedures in the intensive care unit (ICU), together with difficulties in communication and loss of control may all cause pain and distress\textsuperscript{112,158}. Besides good bedside care including information and reassurance from medical staff, there may be need for treatment with sedative and analgesic drugs\textsuperscript{57}. Particularly ventilator treatment may necessitate sedative and analgesic administration, to improve patient tolerance to the endotracheal tube, reduce autonomic stress and to increase ventilator synchrony.

Problems in ICU sedation and analgesia

Under- and oversedation:
Insufficient sedation and analgesia in non-paralyzed patients is usually easily observed, with the patient in discomfort, possibly agitated or in pain. Tachycardia and hypertension may be present as well as ventilator dysynchrony, with risk of hypoxia and hypercarbia. Agitation in ICU patients is associated with increased morbidity, longer ICU stay and greater risk of inadvertent removal of catheters and/or the endotracheal tube\textsuperscript{56,167}. Excessive sedation and analgesia may cause hypotension and bradycardia, as well as prolonged ventilator therapy and long wake-up times\textsuperscript{15,80}. High opiate doses may lead to gut immobility. Unless patients’ sedation depth is well monitored, deep sedation may pass unnoticed and later be confused with neurological injury, leading to investigations in order to rule out such injury\textsuperscript{80,97}.

Tolerance
There is often a need to increase dosage over time during intravenous sedation of ICU patients\textsuperscript{9,137}. Children may develop tolerance to sedative and analgesic drugs, sometimes neces-
sitting drug rotation or a polypharmacologic approach\(^1\)\(^3\). In clinical practice dosage may exceed recommended limits and lead to adverse effects or solvent toxicity, such as hyperlipidemia during propofol sedation\(^9\) and propylene glycol toxicity during lorazepam sedation\(^1\)\(^6\). \(^{153}\)

**Withdrawal**

Manifestations of benzodiazepine withdrawal include agitation, tachycardia, hypertension, tachypnea, hallucinations, seizures and gastrointestinal symptoms such as emesis, diarrhoea or stomach ache\(^3\). Tapering or termination of benzodiazepine infusions in critically ill patients may lead to withdrawal\(^2\)\(^2\),\(^4\). Benzodiazepine withdrawal in ICU sedation has been associated with high sedative doses and with long periods of sedation\(^1\)\(^8\),\(^3\)\(^3\),\(^4\)\(^0\),\(^1\)\(^5\). An association between the total dose and duration of fentanyl as well as the dose of midazolam for paediatric ICU sedation and the incidence of withdrawal has also been shown\(^6\). Withdrawal appears to be a significant problem after paediatric ICU sedation, with an incidence of 24-35 % after benzodiazepine sedation\(^3\)\(^9\),\(^4\)\(^0\).

**Delirium**

Delirium is defined as an acute state of altered consciousness and cognition and reduced attention, with a fluctuating course\(^3\). Delirium in ventilated ICU patients has been shown to predict increased ICU length of stay\(^1\)\(^5\)\(^1\) and increased mortality\(^3\)\(^7\). Suggested causes of delirium in ICU patients include septic encephalopathy, metabolic or electrolyte disturbances, as well as withdrawal syndromes\(^9\)\(^1\). The risk of delirium in ICU patients has been associated with increasing doses of intravenous sedatives\(^4\)\(^5\) and with anaemia\(^4\)\(^9\),\(^1\)\(^3\)\(^0\). In a recent study, lorazepam administration and dose were risk factors for later transition to delirium in ICU patients\(^1\)\(^1\)\(^8\).

### Drugs and regimens for ICU sedation

#### The ideal sedative agent

Some suggested qualities of the ideal sedative agent for patients in the ICU are the following:

- Rapid onset and offset of effect
- Easily controlled depth of sedation
- Amnesic effects
- Minimal side effects
- No active metabolites
- Elimination independent of normal organ function
- Compatible with other drugs
- Inexpensive

None of currently used ICU sedatives possess all the features described.

#### Benzodiazepines

The most commonly used sedatives in European and North American ICUs are the benzodiazepines\(^4\)\(^7\),\(^1\)\(^2\)\(^5\),\(^1\)\(^4\)\(^2\). They produce a state characterised by anxiolysis, hypnosis and anterograde amnesia, mainly by augmenting cerebral inhibitory GABA-ergic transmission\(^1\)\(^0\)\(^5\). Benzodiazepines also have anticonvulsive effects and reduce muscle tone. Diazepam (Valium), developed in the 1960s, was the first benzodiazepine used for sedation in the ICU. Newer and more short-acting benzodiazepines - lorazepam and midazolam - soon replaced diazepam for ICU sedation\(^1\)\(^4\)\(^2\).

Lorazepam, mainly used in ICUs in the United States (US) for long-term sedation\(^1\)\(^6\),\(^1\)\(^2\)\(^5\), has a relatively long onset of effect (5-20 minutes) and duration (8-15 hrs) and is administered intermittently or continuously\(^5\)\(^7\). Problems with prolonged wake-up times\(^8\) and metabolic acidosis due to propylene glycol toxicity\(^1\)\(^5\)\(^0\),\(^1\)\(^6\)\(^6\) have caused some reservation regarding its use for long-term sedation\(^1\)\(^2\)\(^7\). Midazolam, currently one of the most commonly used ICU sedatives in the US and Europe\(^4\)\(^7\),\(^1\)\(^2\)\(^5\),\(^1\)\(^4\)\(^2\), has a rapid onset (2-5 min) and has the shortest effect duration of the benzodiazepines in...
healthy volunteers. Prolonged infusions, particularly in elderly patients or in patients with renal and/or liver insufficiency, may however lead to accumulation of midazolam and its active metabolite $\alpha$-hydroxymidazolam. Prolonged wake-up times after midazolam infusions in ICU patients have been described by numerous authors. As previously stated, long-term use of benzodiazepines may also lead to tolerance and withdrawal at cessation of administration.

**Propofol**

Propofol, an intravenous anaesthetic agent introduced in 1989, acts mainly by potentiating cerebral GABA-ergic transmission. Metabolism is mainly hepatic to water-soluble inactive glucuronide metabolites. In the anaesthesia setting propofol has many useful features: fast induction, good titratability and a relatively rapid emergence from anaesthesia. Shortly after its introduction, propofol was adopted as an ICU sedative, with studies demonstrating good sedative properties and faster emergence from sedation than with midazolam. Other studies showed more modest or no advantage over midazolam.

Case reports soon accumulated of a condition involving fatty liver development, myocardial dysfunction, cardiovascular collapse and sudden death in paediatric and adult ICU patients receiving propofol for sedation. Higher doses (>5 mg/hour) and long-term use (>30-48 hours) appear to be risk factors for the development of what has been called the propofol infusion syndrome. Mitochondrial oxidative activity appears to be affected in propofol infusion syndrome. Since the latest published consensus recommendations on ICU sedation and analgesia from the Society of Critical Care Medicine in 2002, the authors recommend that it be used with caution for long-term sedation in adults. The US Food and Drugs Administration (FDA) recommend that propofol not be used for paediatric sedation in the ICU due to the risk of propofol infusion syndrome.

**Paediatric options**

Besides midazolam, lorazepam and clonidine, paediatric ICU sedatives include ketamine, droperidol, and occasionally oral chloral hydrate and pentobarbital.

**Haloperidol**

Haloperidol, an antipsychotic that reduces dopaminergic transmission in the brain, is recommended for the treatment of delirium in ICU patients. Haloperidol has sedative effects but is not recommended for ICU sedation as cumulative doses may increase the risk of prolonged QT-interval and cardiac dysrhythmias and cause extrapyrimidal symptoms. The use of haloperidol in ICU patients has, however, been associated with lower hospital mortality in a recent retrospective cohort analysis.
Opioid analgesics
Opioid analgesics, most frequently morphine and fentanyl, are commonly used as adjuncts to sedatives during mechanical ventilation\textsuperscript{125,142}. Besides providing analgesia, opioids have additive or synergistic sedative effects with benzodiazepines\textsuperscript{12,157}, propofol\textsuperscript{144,162} and inhaled anaesthetics\textsuperscript{85}.

ICU sedation strategies
Continuous infusion of sedatives offers the advantage of even administration, thereby reducing the probability of sudden arousal and of sedative-related hypotension compared with intermittent administration. While continuous administration is commonly used for long-term sedation in ICU patients\textsuperscript{125} it has been associated with prolonged duration of mechanical ventilation\textsuperscript{72} and requires frequent evaluation of sedation depth in order to avoid oversedation\textsuperscript{15}. Brook et al demonstrated the usefulness of titrating sedative administration to reach an interval on a sedation scale. A nurse-implemented sedation protocol was used in order to reach a prescribed sedation goal and significantly reduced the length of mechanical ventilation as well as ICU and hospital length of stay\textsuperscript{15}.

In a series of well-cited studies, Kress et al demonstrated that daily interruption of intravenous sedative administration until patients were responsive shortened the duration of mechanical ventilation and length of stay in the ICU\textsuperscript{79}, and also reduced the incidence of complications to critical illness\textsuperscript{79} without increasing long-term psychological sequelae\textsuperscript{133}. Current sedation guidelines recommend this strategy\textsuperscript{97}. Benefits of drug rotation for reducing drug accumulation and prolonged wake-up times have also been demonstrated\textsuperscript{130}.

Assessment of ICU sedation
Monitoring of sedation depth is essential for evaluating and titrating sedative treatment in ICU patients\textsuperscript{15,57}. Numerous sedation scales are used in clinical practice\textsuperscript{20}, of which few are appropriately tested for validity or reliability\textsuperscript{31}. Examples of used sedation scales include the Ramsay Sedation Scale (Table 1)\textsuperscript{121}, the Bloomsbury Sedation Score (Bloomsbury) (Table 2)\textsuperscript{7} and the Motor and Activity Assessment Scale (Table 3)\textsuperscript{152}. Most sedation scales used in adult ICUs are based on observations of patient response to increasing stimuli\textsuperscript{20}. This implies potential disturbance of the patient at almost every occasion of sedation monitoring. While the significance of such disturbances for patient recovery is unknown, many patients in the ICU complain of insufficient sleep and sleep disruption\textsuperscript{62,129}.

Different “objective” electroencephalographic measures of level of cerebral activity or arousability have been proposed for sedation depth monitoring, including auditory evoked potentials (AEP)\textsuperscript{132} and the Bispectral index™ (BIS)\textsuperscript{66,141}.

AEP is a method of monitoring electrophysiological CNS responses to standardized auditory stimuli. With increasing sedation or anaesthesia the latency of AEP response increases and

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<tr>
<td>1 Anxious, agitated or restless or both</td>
</tr>
<tr>
<td>2 Cooperative, oriented and tranquil</td>
</tr>
<tr>
<td>3 Responding to commands only</td>
</tr>
<tr>
<td>4 Brisk response to glabellar tap</td>
</tr>
<tr>
<td>5 Sluggish response to light glabellar tap</td>
</tr>
<tr>
<td>6 No response to light glabellar tap</td>
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<tr>
<td><strong>Bloomsbury Sedation Score</strong></td>
</tr>
<tr>
<td>3 Agitated and restless</td>
</tr>
<tr>
<td>2 Awake and uncomfortable</td>
</tr>
<tr>
<td>1 Aware but calm</td>
</tr>
<tr>
<td>0 Roused by voice, remains calm</td>
</tr>
<tr>
<td>-1 Roused by movement or suction</td>
</tr>
<tr>
<td>-2 Roused by painful stimuli</td>
</tr>
<tr>
<td>-3 Unrousable</td>
</tr>
<tr>
<td>A Natural sleep</td>
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Table 3. The Motor and Activity Assessment Scale.

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<thead>
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<th>Score</th>
<th>Description</th>
<th>Definition</th>
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<tr>
<td>0</td>
<td>Unresponsive</td>
<td>Does not move with noxious stimulus*</td>
</tr>
<tr>
<td>1</td>
<td>Responsive only to noxious stimuli</td>
<td>Opens eyes OR raises eyebrows OR turns head toward stimulus OR moves limbs with noxious stimulus*</td>
</tr>
<tr>
<td>2</td>
<td>Responsive to touch or name</td>
<td>Opens eyes OR raises eyebrows OR turns head toward stimulus OR moves limbs when touched or name is loudly spoken</td>
</tr>
<tr>
<td>3</td>
<td>Calm and cooperative</td>
<td>No external stimulus is required to elicit movement AND patient is adjusting sheets or clothes purposefully and follows commands</td>
</tr>
<tr>
<td>4</td>
<td>Restless and cooperative</td>
<td>No external stimulus is required to elicit movement AND patient is picking at sheets or tubes OR uncovering self and follows commands</td>
</tr>
<tr>
<td>5</td>
<td>Agitated</td>
<td>No external stimulus is required to elicit movement AND attempting to sit up OR moves limbs out of bed AND does not consistently follow commands (e.g., will lie down when asked but soon reverts back to attempts to sit up or move limb out of bed)</td>
</tr>
<tr>
<td>6</td>
<td>Dangerously agitated, uncooperative</td>
<td>No external stimulus is required to elicit movement AND patient is pulling at tubes or catheters OR thrashing side to side OR striking at staff OR trying to climb out of bed AND does not calm down when asked</td>
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</table>

* Noxious stimulus, suctioning OR 5 secs. of vigorous orbital, sternal, or nail bed pressure

the amplitude decreases. AEP shows poor correlation with sedation depth at lighter sedation levels, making it questionable for clinical use in the ICU. BIS is a non-invasive processed measure of raw frontal electroencephalogram (EEG). EEG power and frequency are analysed continuously and converted to a numerical scale between 0 and 100. A BIS value of 0 equals an isoelectric EEG and a value of 100 indicates a fully awake patient. Studies have shown good correlation between BIS and clinical depth of sedation and anaesthesia in healthy volunteers and the use of BIS in the anaesthesia setting appears to reduce the risk of awareness. Correlation studies of BIS and clinical assessment in intravenously sedated, critically ill patients in the ICU have shown varying results. The FDA approved BIS monitoring in 1996 for assessing the hypnotic effects of general anaesthetics and sedatives.

Memories and long-term psychological sequelae of ICU experience

Many patients remember the ICU as stressful or confusing, sometimes to an extent that may be underestimated by caregivers. Memories may be fragmentary both in critical illness and with the use of sedatives, and delusional memories are not uncommon. Psychological morbidity after ICU treatment ap-
pears to be substantial, with clinically significant depressive or anxiety disorders including post-traumatic stress disorder (PTSD) being found in as many as 20-30% of ICU patients.

Symptoms of post-traumatic stress have been described by different authors for centuries, but PTSD was not recognized as a psychiatric diagnosis until after the Vietnam war, when many veterans experienced similar long-standing psychological symptoms leading to a formal definition.

PTSD is defined as:

- the person experienced a traumatic event involving actual or threatened death or serious injury, or a threat to physical integrity
- the person's response involved intense fear, helplessness, or horror
- the traumatic event is persistently re-experienced and stimuli associated with the trauma are avoided
- numbing of general responsiveness
- the person has persistent symptoms of increased arousal
- the disorder causes clinically significant distress or impairment in social, occupational or other important areas of functioning

PTSD has been identified as a common disorder after ICU care, occurring in as many as 28% of patients with acute respiratory distress syndrome (ARDS). It is not surprising that this disorder may occur after ICU stay, the reason for ICU admission commonly being a life-threatening illness or trauma.

With growing interest in ICU outcomes, possible risk factors for long-term psychological sequelae after intensive care are being increasingly evaluated. The risk for developing PTSD after ICU stay appears to be increased with physical trauma prior to ICU admission, previous need for professional help for psychological symptoms and younger age. In a study by Schelling and co-workers, the number of adverse experiences from the ICU increased the risk of PTSD significantly. Jones et al concluded in another study that delusional memories from the ICU were associated with later development of PTSD, while factual memories from the ICU were found to have a protective effect.

In yet another study, prolonged sedation, but not initial severity of illness, was associated with later PTSD and depression after ICU treatment for acute lung injury.

**Inhaled anaesthetics**

Inhaled anaesthetics have been used to achieve anaesthesia and analgesia for surgery since the middle of the 19th century, when nitrous oxide and ether were demonstrated to possess analgesic properties. The first halogenated ether, halothane, was presented by Charles Suckling in 1954. Halothane was followed by among others enflurane and its isomer isoflurane. Desflurane and sevoflurane are the latest contributions to the family of halogenated inhaled anaesthetics, (hereafter referred to as inhaled anaesthetics).

**Pharmacokinetics**

After administration of an inhaled anaesthetic via the airways, rapid diffusion over the alveolar membrane facilitates blood-borne transport to all perfused organs, including the brain. For all inhaled anaesthetics, the rate at which the alveolar (end-tidal) anaesthetic concentration rises to approach the inspired concentration is mainly determined by the individual blood/gas coefficient (the anaesthetic’s relative solubility in blood). In clinical practice, the onset of anaesthetic effect of a poorly soluble agent with a low blood / gas coefficient (e.g. sevoflurane) is much faster than that of a highly soluble agent with a high blood/gas coefficient (e.g. halothane). Other important factors influencing the speed of equilibration are lung ventilation (hyperventilation increases the speed), rate of uptake in various organs (high uptake rate slows the speed of blood / gas equilibrium) and lung ventilation/perfusion (mismatch slows the speed of equilibration).

The tissue / blood solubility coefficient, tissue volume, blood perfusion rate (% of cardiac output), and the arterial to tissue partial pressure difference determine the uptake rate of anaes-
thetic agent to a specific tissue. Concentrations in tissues with high blood flow (e.g. brain, kidney) approach equilibrium with blood concentrations within hours, while concentrations in tissues with low blood flow (e.g. fat) take several days to reach equilibrium. In the elimination phase after terminated administration, the elimination of inhaled anaesthetic from these “slow tissues” may take a long time and contribute to prolonged emergence from anaesthesia, especially in obese patients.\(^6_3\)

Elimination of inhaled anaesthetics can be said to be independent of organ metabolism, as they potentially can be cleared via the lungs after terminated administration. While pulmonary elimination of inhaled anaesthetics is the only needed route of elimination, all inhaled anaesthetics, with the exception of the inert gas Xenon, are metabolised to varying degrees.\(^10_3\)

Approximately 15-20 % of inhaled halothane is metabolised, while sevoflurane is metabolised to approximately 5 %, and isoflurane to 0.2 %. Desflurane metabolism is merely 0.02 %. Modern inhaled halogenated anaesthetics undergo mainly hepatic metabolism (cytochrome P450) with liberation of different metabolites and inorganic fluorides, which are excreted in urine.\(^10_3,12_3\)

Pharmacodynamics

CNS effects

The mechanisms of action of inhaled anaesthetics on the central nervous system (CNS) are understood only in part. The Meyer-Overton rule, implying that the lipid-solubility of anaesthetic agents is the determinant of anaesthetic potency, is only true in part and does not specifically explain how inhaled anaesthetics exert their effect. An obvious exception to the Meyer-Overton rule is the different potency of the isomers enflurane and isoflurane despite similar lipid solubility. The unitary theory of narcosis, implying a common target site of action for all inhaled anaesthetics, has been abandoned as more is being learned about specific receptor modulation by different anaesthetic agents in different CNS regions. Analgesia appears to be mediated primarily via receptor modulation in the spinal cord, while hypnosis and amnesia effects are currently believed to be mediated mainly by enhancement of inhibitory transmission (Gamma-aminobutyric acid [GABA], glycine) and inhibition of excitatory transmission (glutamate) in the brain.\(^19\)

The Minimum Alveolar Concentration (MAC) is a common measure for describing the anaesthetic effect of all currently used inhaled anaesthetics.\(^19,10_3\) 1 MAC is defined as the end-tidal (\(E_T\)) concentration of a given inhaled anaesthetic - when administered alone - at which a surgical stimulus elicits a motor response in 50 % of subjects. MAC values vary for different inhaled anaesthetics and are age-dependent, with 1 MAC for isoflurane at age 40-50 being approximately 1.15 % and lower in older patients.\(^10_3\)

As all other halogenated anaesthetics, isoflurane reduces cerebral metabolic rate and increases cerebral blood flow.\(^10_3\) In concentrations above 1 MAC there may be cerebrovasodilation and subsequent increase in intracranial pressure (ICP) in patients with reduced intracranial compliance or increased ICP.\(^4_6\) Isoflurane can reduce or abolish CNS epileptogenic activity, a property that has led to its occasional use in therapy-resistant status epilepticus.\(^7_4,10_4\)

Cardiovascular effects

Isoflurane, dose-dependently reduces blood pressure, primarily via reduced systemic vascular resistance and to a lesser extent via myocardial depression.\(^10_3\) Heart rate is dose-dependently increased. Coronary vasodilator effects of isoflurane have caused some concern for “coronary steal” - redistribution of coronary blood flow from myocardium supplied by atherosclerotic vessels during anaesthesia.\(^10_3\) There has, however, been little evidence of isoflurane-induced coronary blood flow redistribution leading to myocardial ischemia in clinical practice. Instead, recent data imply a myocardial protective effect of inhaled anaesthetics, including isoflurane.\(^3_0,8_3,14_7\) Exposure to inhaled anaesthetics has been shown to lead to reduced
myocardial cell necrosis after an ischemic insult, the phenomenon being named anaesthetic preconditioning (APC). The mechanism is not fully understood, but APC appears to be mediated via activation of myocardial cell $K_{\text{ATP}}$ channels.

**Respiratory effects**

Isoflurane causes a reduction in tidal volume, thereby reducing minute ventilation. The apneic threshold is not affected by isoflurane but the response to hypercarbia is attenuated. Hypoxic drive is dose-dependently attenuated by all inhaled halogenated anaesthetics, with pronounced effects already in subanaesthetic concentrations. Isoflurane dose-dependently attenuates hypoxic pulmonary vasoconstriction, with a 50% reduction at 0.6 MAC. Bronchomotor tone is not significantly influenced by isoflurane under normal conditions, but powerful attenuation of histamine- or ascaris antigen induced bronchoconstriction has been shown. Numerous case reports describe successful treatment of difficult cases of status asthmaticus with isoflurane.

**Isoflurane metabolism and related risk for toxicity**

There has been some concern about prolonged isoflurane or sevoflurane anaesthesia / sedation leading to high levels of inorganic fluorides, considered toxic. In studies of isoflurane sedation, inorganic fluoride levels during several days sedation in some cases reached the postulated threshold values for subclinical (50 µM) and clinical (100µM) polyuric renal failure seen with methoxyflurane anaesthesia. However to date, there have been no reports of fluoride-mediated renal insufficiency after isoflurane administration or after sevoflurane anaesthesia, despite elevated inorganic fluoride levels.

Halothane, also a halogenated inhaled anaesthetic, has been implicated in cases of hepatic necrosis after anaesthesia, with an estimated occurrence of 1 in 35 000 halothane anaesthetics. Rare case reports of hepatic dysfunction after isoflurane anaesthesia have been published, and despite lack of definite evidence, a risk for hepatotoxicity after isoflurane exposure can not be completely excluded. The few cases of hepatotoxicity possibly associated with isoflurane and the millions of isoflurane anaesthetics performed since its introduction indicate that such risk would be much smaller than after halothane, possibly due to a considerably lesser degree of metabolism.

**Inhaled anaesthetics and Malignant Hyperthermia**

Malignant hyperthermia (MH) is a familial pharmacogenetic reaction occurring in individuals exposed to inhaled halogenated anaesthetic agents or to succinylcholine. The incidence of MH in general anaesthesia practice has been estimated to 1/62000 anaesthetics. The pathophysiology includes triggering a pathological ryanodine receptor - of abnormal $Ca^{2+}$ release from the sarcoplasmic reticulum with subsequent muscle rigidity, tachycardia, hypertension, hypercarbia, acidosis and potentially lethal hyperthermia and arrhythmias. Vigilance and early treatment by withdrawal of the causative agent, cooling and administration of the antidote dantrolene sodium has reduced mortality rates to < 10% in this condition.

**Isoflurane for ICU sedation**

Experiences of prolonged isoflurane sedation

Inhalational sedation in the ICU was first described in the 1950s, when nitrous oxide was used for sedation of polio patients undergoing mechanical ventilation, until side effects (megaloblastic anaemia, neurological dysfunction) of long-term use were revealed. Since then different inhaled anaesthetics have been used,
including desflurane\textsuperscript{99} and isoflurane\textsuperscript{4,78,101,143}. Isoflurane has been studied for prolonged ICU sedation since the 1980s. Kong et al described potential benefits when isoflurane was compared with midazolam, with better sedation efficacy and shorter weaning time\textsuperscript{78}. In a crossover study of mechanically ventilated patients, isoflurane equaled with propofol for sedation quality and wake-up times\textsuperscript{101}. Postoperative isoflurane sedation after cardiac surgery has also been demonstrated to be efficacious without tachyphylaxis and adverse hepatic or renal effects\textsuperscript{148}. Recently, desflurane was compared with propofol for postoperative sedation. Weaning was faster with desflurane and the authors concluded that awakening was more predictable with desflurane than with propofol\textsuperscript{99}.

Besides studies demonstrating favourable sedative effects of inhaled anaesthetics, isoflurane has been used successfully in the ICU for treatment of severe treatment-refractory status asthmaticus\textsuperscript{59,138} and status epilepticus\textsuperscript{74,98,104}.

Environmental aspects of isoflurane sedation in the ICU

Concerns of staff exposure to isoflurane during administration in the ICU and the need to address such concerns has been mentioned by authors advocating more widespread ICU use of inhaled anaesthetics\textsuperscript{76,99,101}.

Historically, the ICU environment has – in contrast to the operating room environment – not received much attention regarding potential risks of inhaled anaesthetic agent exposure and ventilation standards have not been as rigorous as in the operating room. ICU ventilators traditionally use high flow with advanced ventilator modes for the sake of effective treatment of lung injured patients. High-flow ventilator use has implied that there is no recycling of any given inhaled anaesthetic and that all exhaled anaesthetic from the patient leaves the ventilator’s expiratory outlet, potentially contaminating the ICU. Most studies of inhaled sedation in the ICU setting describe active or passive scavenging as part of the protocol\textsuperscript{142,78,101}. Measurements of ambient isoflurane concentration when using scavenging devices have shown acceptable levels of isoflurane\textsuperscript{23,52}.

Figure 1. Isoflurane

Delivery of isoflurane in the ICU

In the early days of intensive care, ventilators in the operating room and ICU were identical and interchangeable. Over the past decades, ventilators for ICU use have been developed and become more advanced than anaesthesia ventilators with regard to respiratory modes. The trend in ICU ventilation therapy towards augmenting spontaneous breathing and enabling lung recruitment has made anaesthesia ventilators less suitable for ICU use. With modern ICU ventilators, the only option to bringing an anaesthesia machine from the operating room for isoflurane treatment in the ICU is to connect a vaporizer to the ICU ventilator. Adaptation of the ICU ventilator or breathing circuit is necessary. Adaptations described by different investigators include connecting a vaporizer in parallel between the oxygen blender and the inspiratory limb of a Servo-B ventilator\textsuperscript{101}, connecting a vaporizer to the low-pressure port of a Servo 900 ventilator\textsuperscript{13} or incorporating an Oxford Miniature Vaporizer inside the circuit when using a Servo 300 ventilator\textsuperscript{96}. 

Background 21
The Anesthetic Conserving Device / AnaConDa® (ACD)

In the late 1990s, a device for administering and rebreathing of isoflurane or sevoflurane was developed, primarily for reducing agent consumption with high-flow ventilation during anaesthesia\textsuperscript{39,149}. The Anesthetic Conserving Device / AnaConDa\textsuperscript{TM} (ACD) is a modified heat and moisture exchanger (HME)(Figure 2). As with HMEs the ACD is placed between the Y-piece and the endotracheal tube. The dead-space is approximately 100 ml and airway resistance is 2.5 cm H\textsubscript{2}O at 60 l/min air flow. The moisture exchanging efficacy is 30 mg H\textsubscript{2}O/l air at tidal volumes of 750 ml, which is similar to the efficacy of other currently available HMEs (personal communication, Leif Held). The ACD also contains a viral and bacterial filter. Besides standard HME features, the ACD has an infusion line for delivery of isoflurane / sevoflurane via a syringe pump to the ACD. In the ACD, the anaesthetic agent is delivered to a porous "evaporator rod". During inspiration the fresh gas flow passing the ACD vaporizes 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 an active carbon filter in the ACD. At the next breath delivered to the patient, the anaesthetic agent is desorbed and inhaled. Potential benefits of the ACD are that it is compatible with all modern ICU ventilators without further adaptation, that agent requirement should be reduced due to the rebreathing of inhaled anaesthetic and that isoflurane content in exhaled air should be lowered due to adsorption of isoflurane to the active carbon in the ACD.

![Cross-sectional view of the Anesthetic Conserving Device/AnaConDa® (ACD).](Fig 2)
The principal objective of this thesis was to evaluate if isoflurane at subanaesthetic levels, delivered via the ACD, is a feasible alternative to current methods of sedation.

The specific aims were:

1) To investigate the sedation efficacy and practical feasibility of prolonged isoflurane administration via the ACD in critically ill patients.

2) To evaluate the environmental safety of isoflurane via the ACD for ICU sedation and to measure isoflurane consumption during sedation with isoflurane via the ACD.

3) To evaluate and describe the ACD for isoflurane sedation of pediatric ICU patients.

4) To test the concept and possible benefit of the latest available version of the Bispectral index™ (BIS) as a predictor of clinically measured sedation depth in critically ill patients during isoflurane or midazolam sedation.

5) To examine if there were major differences in memories from the ICU and in short- and long-term psychological recovery between critically ill patients sedated with isoflurane and midazolam.
MATERIALS AND METHODS

Patients/Subjects

Paper I
Forty ventilator-dependent general ICU patients aged 18-80, receiving sedatives or anaesthetics for less than 18 hours prior to inclusion and expected to need more than 12 hours sedation were studied. Patients with MH susceptibility, intracranial pathology or in need of dialysis were excluded, as were pregnant women. As patients were sedated when eligible for inclusion, the nearest of kin gave informed consent to participation in the study.

Paper II
Fifteen isoflurane sedated patients from paper I were followed with regard to ambient isoflurane concentrations near the patient. Ten ICU nurses caring for four of these patients were individually monitored.

Paper III
Three patients in the pediatric intensive care unit, aged 4-12 years were treated with isoflurane delivered via the ACD. In two patients, sedative treatment with conventional intravenous sedatives was not satisfactory despite a polypharmacological approach and in one patient status epilepticus was not well controlled with several antiepileptic drugs and sedatives.

Paper IV
A subgroup of ten consecutive isoflurane sedated and ten consecutive midazolam sedated patients from paper I were studied.

Paper V
All survivors from paper I were included for paper V. For short-term evaluation 18 patients in the isoflurane group and 18 patients in the midazolam group were eligible. At the time for long-term follow up 16 isoflurane sedated patients and 13 midazolam sedated patients were eligible.

Interventions

Papers I-II, IV-V
Patients were mechanically ventilated with the Siemens Servo 300 (Siemens-Elema/Maquet, Solna, Sweden) or the Dräger Evita 4 (Dräger Medical AG & Co.KgaA, Lübeck, Germany)
ventilator. Patients were randomized to sedation with isoflurane via the ACD for study subjects and intravenous midazolam for controls. After randomization, other sedatives were terminated and the study sedative administered. Isoflurane was infused to the ACD according to the manufacturer’s recommended infusion rate to obtain an end-tidal concentration of 0.5% (1.0-3.5 ml/hour). Midazolam was initially infused in the dose range 0.02-0.05 mg/kg/hour. Infusion rates were thereafter adjusted by the patient’s nurse in order achieve a target sedation scale interval (Bloomsbury –1 - +1), unless the attending ICU physician considered a different interval desirable.

When needed, a bolus dose of sedative was given. In the isoflurane group a bolus was given by increasing the infusion rate to 10 ml/hour for 2 minutes, while a bolus of midazolam 0.02-0.05 mg/kg was given in the control group. If these bolus doses were not sufficient and the patient needed an increase of sedation propofol 0.5 mg/kg was given. Opioids for analgesia were given by infusion or intermittently according to the ICU physician orders.

Study duration was 96 hours or until extubation, whichever was first. If a patient was considered ready for extubation by the ICU physician during the study period, sedation was terminated. Midazolam sedation was terminated by termination of the infusion. Isoflurane sedation was terminated by disconnection of the ACD from the breathing circuit.

**Paper II**
During isoflurane sedation, standardized changing of the ACD, isoflurane syringe and opening of the respiratory circuit was performed according to written investigator instructions. Active scavenging of waste gas from the respirator was performed in ten patients with an open ejector suction connected between the ventilator expiratory outlet and the hospital’s waste gas system. In the remaining five patients no active scavenging was to be performed unless bedside ambient isoflurane concentrations rose above half the Swedish recommended long-term exposure limit.

**Paper III**
In the paediatric patients receiving isoflurane for sedation, isoflurane dosage was targeted at achieving a depth of sedation at which patients were arousable and not agitated (Et concentrations of 0.3-0.4%). The patient with refractory status epilepticus required higher isoflurane Et concentrations (0.9%) in order to achieve suppression of epileptic EEG activity.

**Paper IV**
At the outset of study sedative administration, the patient’s forehead was wiped with alcohol and four-lead BIS QUATRO electrodes were attached according to instructions. After approved automatic impedance testing the BIS monitor screen was covered. BIS monitoring was terminated after extubation or at 96 hours.

**Paper V**
Patients were sedated with isoflurane or midazolam according to the sedation protocol in paper I for up to 96 hours or extubation, whichever was first. Patients in need of continued sedation after 96 hours received intravenous sedation according to unit practice.

**Monitoring/Measurements**

**Paper I**

**Sedation efficacy:**
Sedation depth was assessed hourly with Bloomsbury and adequate sedation was defined as Bloomsbury –1 - +1. Nurses’ subjective opinion of whether sedation over the past hour had been adequate was noted. Time from termination of sedative administration until extubation and until patients could follow a verbal command was noted in all patients ready for extubation during the study period. Opioid dosage and bolus sedative administration were noted.

**Feasibility and complications**
Daily Sepsis-related Organ Failure Assessment (SOFA) Score was calculated. Practical and patient-related complications with the ACD were noted by attending staff, as well as episodes of overt agitation or self-extubation attempts.
Haemodynamic and respiratory values were monitored continuously. In isoflurane sedated patients, inspired and end-tidal isoflurane concentrations were monitored continuously (Datex-Ohmeda AS 3 Compact, Datex-Ohmeda, Helsingfors, Finland). Hepatic function was measured daily with serum alanine transferase, aspartate transferase and bilirubine and renal function was measured daily with creatinine and urine output and with creatinine clearance at the start and end of the study. Blood samples were analysed at the Karolinska Hospital Chemistry Laboratory. Daily serum inorganic fluoride samples were drawn from the isoflurane sedated patients up to the day after terminated isoflurane sedation and later analysed with an ion-selective electrode method at the Department of Occupational and Environmental Medicine, Örebro University Hospital.

Paper II
Isoflurane concentrations measurement at the bedside:
Ambient isoflurane concentration in parts per million (ppm) was measured continuously at 0.5 m from the patient’s head with the MIRAN 1 B mass spectrophotometer, calibrated for isoflurane at the Department of Occupational and Environmental Medicine, Karolinska Hospital, Stockholm. Ambient isoflurane concentration trends were printed and all interventions potentially affecting concentrations, such as ACD and isoflurane syringe changes or suctioning, were noted on the printer sheet for later analysis of the impact of interventions on isoflurane peaks.

Long-term staff exposure measurement:
Passive lapel dosimeter sampling was performed (SKC Passive sampler 575-002, Eighty Four, PA, USA) for ten staff nurses over eight-hour shifts. Dosimeter analysis was performed at the Laboratory of Occupational and Environmental Medicine, Sahlgrenska University Hospital, Göteborg.

Isoflurane requirement:
Isoflurane requirement was obtained with downloaded infusion pump data (P6002 / TIVA, Alaris Medical Systems, Sollentuna Sweden) in all patients.

Paper III
Patients’ haemodynamic and respiratory variables during sedation were monitored continuously. Daily hepatic function tests (serum alanine transferase, aspartate transferase and bilirubine) and serum creatinine were analysed at the Karolinska Hospital Chemistry Laboratory. Creatinine clearance was measured before and after isoflurane sedation. Concomitant intravenous sedative and opioid analgesic administration were noted.
Serum inorganic fluoride samples were analysed with an ion-selective electrode method at the Department of Occupational and Environmental Medicine, Örebro University Hospital.

Paper IV
Patients were continuously monitored for up to 96 hours of sedation with the latest available BIS monitor BIS A-2000 XP, version 3.12 with four-lead BIS QUATRO electrodes. Hourly clinical evaluation with Bloomsbury was performed by the attending ICU nurse with the BIS monitor covered. Median BIS values over ten minutes prior to clinical evaluation were used in correlation analysis. Electromyogram (EMG) activity and Signal Quality Index (SQI) were measured continuously with the BIS monitor and downloaded together with BIS data.

Paper V
Short-term follow-up:
Follow-up started at the termination of study sedative in study I. Short-term psychological and cognitive recovery after sedative exposure in the patients was evaluated retrospectively by scrutiny of all doctor, nurse and physiotherapist notes from the entry of the follow-up and the next four days. The ICU doctors and staff caring for the patients were not aware of the follow-up. Terms indicating pathological or adequate psy-
chological or cognitive recovery were sought for with the aid of a list of terms defined by the investigators. The co-author screening for key words in the charts was blinded for which treatment patients had received. Patient’s cognitive / psychological recovery was thereafter classified by two of the co-authors in consensus as:

1) Overt pathology in cognitive / psychological recovery
2) Adequate cognitive / psychological recovery
3) Uninformative / equivocal notes

Long-term follow-up:
Long-term psychological outcome was evaluated with questionnaires sent to all survivors at 6-9 months after the ICU stay. Memories from the ICU were assessed with the ICU Memory Tool (ICU-MT). Anxiety or depression symptoms were assessed with the Hospital Anxiety and Depression Scale (HADS). Symptoms of posttraumatic stress were assessed with the Impact of Event Scale (IES) and the Well-Being Index (WB) was used to evaluate patient’s global well-being the past week. A questionnaire screening for traumatic experiences and PTSD symptoms prior to the ICU stay was included.

Statistics

Paper I:
Differences between group in proportion of time within the predefined Bloomsbury interval and time with adequate sedation were compared with Student’s t-test, as well as sedative bolus administration and opiate dosage. Differences in time to extubation and to following verbal commands after terminated sedation were analysed with both Student’s t-test and with Wilcoxon’s test. Logarithmic transformation was necessary to yield approximate normal distribution of wake-up times prior to the Student’s t-test. Multiple regression analysis was used for wake-up data in order to evaluate possible confounding of the following variables: APACHE II, age, duration of sedation, sedative prior to study inclusion, opiate requirement and proportion of time with oversedation.

Paper II-III:
Descriptive data.

Paper IV:
Correlation between Bloomsbury and median BIS was analysed with Spearman’s rho. Individual correlation coefficients were calculated in order to respect multiple observations in each individual. Correlation between EMG and BIS were analysed with Spearman’s rho, as well as correlation between Bloomsbury and end-tidal isoflurane. Differences in proportions of BIS values over 60 during clinically deep sedation (Bloomsbury –2 and – 3) between groups were analysed with Pearson’s Chi-square test. Morphine requirement in groups was compared with Student’s t-test.

Paper V:
Dichotomous outcomes were compared with Fisher’s exact test. Student’s two-tailed test was used for demographic data with expected normal distribution. Correlation coefficients for number of memories and HAD/IES scores were calculated with Spearman’s rho.
**RESULTS**

**Paper I:**

**Sedation efficacy:**

Proportion of time within the targeted sedation interval did not differ between groups; proportion of time (mean ± SD) in the interval was 54 ± 26 % for isoflurane versus 59 ± 31 % for midazolam. Nurses’ rating of adequacy of sedation was higher in both groups, with proportion of time (mean ± SD) with sedation considered adequate 89 ± 16 % for isoflurane versus 87 ± 13 % for midazolam. Wake-up times after termination of sedative was significantly shorter in the isoflurane group than in the midazolam group; time (mean±SD) to extubation was 10 ± 5 min versus 252 ± 270 min and to follow verbal command was 10 ± 8 min versus 110 ± 130 min after terminated sedation (Figures 3 and 4). Differences in wake-up times between groups were not affected by potential confounders in the multiple regression analysis.

![Fig 3](image1.png)

*Fig 3*

*Box-plot of time from terminated sedation to extubation (logarithmic time scale).*

![Fig 4](image2.png)

*Fig 4*

*Time from terminated sedation until patients followed a verbal command (logarithmic time scale).*
Feasibility and complications:
No serious complications related to either sedative drug occurred. No haemodynamic, hepatic or renal adverse effects related to either sedative drug were found. Few practical problems related to the use of the ACD were encountered.

Paper II:
Isoflurane concentrations measurement at the bedside:
Continuous spectrophotometer readings (0.1 ± 0.2 ppm) were low and below internationally recommended long-term exposure limits (Table 4) in all patients. Isoflurane peaks during nursing procedures were brief, infrequent and of low amplitude. There was no clinically significant difference between isoflurane trace levels with or without an active scavenging system.

Long-term staff exposure:
Passive dosimeter values were low, ranging from undetectable to 0.16 ppm. There was a trend to higher values measured during daytime nursing shifts compared with night dosimeter measurements.

Isoflurane requirement:
Mean $E_T$ isoflurane concentration for sedation was 0.3% (range 0.1-0.8%). Mean isoflurane consumption with the ACD was 2.2 ±1.0 ml per hour, approximately one fourth of predicted and previously reported consumption of isoflurane with vaporizer-administered sedation in the ICU setting.

Table 4. Recommended exposure limits (in parts per million) for isoflurane in the US, Sweden and England.

<table>
<thead>
<tr>
<th>Country</th>
<th>Long term exposure limit</th>
<th>Short term exposure limit</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden</td>
<td>10</td>
<td>20</td>
<td>Swedish Work Environment Authority, Occupational Exposure Limit Values and Measures against Air Contaminents, AFS 2000:</td>
</tr>
</tbody>
</table>

Paper III
ACD feasibility and function:
Patients weighing 40 and 30 kg were treated with the ACD placed at the Y-piece, while the patient weighing 20 kg was treated with the ACD in the inspiratory limb of the respiratory circuit, due to excessive dead space with the ACD at the Y-piece (Figure 5).

Isoflurane sedation efficacy and side-effects
Adequate sedation was achieved with $E_T$ isoflurane concentrations of 0.3-0.4 %, while antiepileptic effect was achieved at $E_T$ isoflurane 0.9%. Intravenous sedatives could be reduced or discontinued during isoflurane sedation. None of the patients deteriorated in renal function after isoflurane sedation. Highest inorganic fluoride concentration was 41 umol/l in one patient. One patient had reversible clonus in one foot after seven days isoflurane sedation that resolved within 48 hours. One patient had involuntary movements and ataxia after weaning of sedatives that resolved after 4-5 days.

Paper IV:
Correlation was poor between BIS and Bloomsbury in both groups (Spearman’s rho 0.012 in the isoflurane group and -0.057 in the midazolam group) despite high SQI (Figure 6). The proportion of median BIS values >60 during clinically assessed deep sedation was 16%.
Fig 5
**ACD in the breathing circuit.**

a) Conventional connection at the Y-piece

b) Connection in the inspiratory limb for smaller paediatric patients in order to avoid dead-space.

Fig 6
**Box-plot of median BIS values at different Bloomsbury sedation scores.**

$I =$ isoflurane  $M =$ midazolam

$N =$ number of observations at each sedation level.

Fig 7
**Box-plot of end-tidal isoflurane concentration at different Bloomsbury sedation scores.**

$N =$ number of observations at each sedation level.

in the isoflurane group and 43 % in the midazolam group. Significant correlation was found between end-tidal isoflurane concentration and Bloomsbury (Spearman’s rho 0.47) (Figure 7). Strong correlation was found between BIS and EMG (Spearman’s rho 0.74) (Figure 8).
Linear regression lines of mean BIS index and EMG activity for the entire cohort

Bold black line: Both groups
Grey line: Isoflurane group
Thin black line: Midazolam group

Paper V

Short-term follow-up:
Eight of 18 isoflurane sedated patients versus six of 18 midazolam sedated patients had an adequate recovery in the four day follow-up (Fisher’s exact test, p=0.4) and 4/18 isoflurane sedated versus 3/18 midazolam sedated patients had an overtly pathological recovery (Fisher’s exact test, p=0.5).

Long-term follow-up:
Memories of delusions/hallucinations were significantly less common in the isoflurane group than in the midazolam group (two of ten isoflurane patients versus five of seven midazolam patients (Fisher’s exact test, p=0.05). Memories of negative feelings did not differ between groups.
There was a trend towards a greater proportion of patients with pathological short-term recovery among questionnaire non-responders; five of 12 questionnaire non-responders had overtly pathological recovery in the short-term follow-up while only two of 17 responders had been classified as overtly pathological (p=0.08).
There was no difference in groups in long-term psychological morbidity as measured with HADS and IES. Six of ten isoflurane patients and two of six midazolam patients had HADS scores indicating impairment (depression, anxiety) or IES scores indicating moderate to severe impact (Fisher’s exact test, p=0.3).
In the entire cohort, memories of negative feelings from the ICU (ICU-MT) were associated with and positively correlated with high HADS and IES scores (Fisher’s exact test, p=0.005 and p=0.018 respectively, Spearman’s rho 0.82, [p<0.001] and 0.82, [p<0.001] respectively).
In papers I-III of this thesis, it is demonstrated that inhaled isoflurane in subanaesthetic doses via the ACD to mechanically ventilated ICU patients is feasible and effective for achieving sedation. Paper III shows the potential benefit and limitations of isoflurane sedation via the ACD in the paediatric ICU population. In paper IV BIS is studied during isoflurane and midazolam sedation in critically ill patients and its usefulness in the ICU setting discussed. The results of Paper V indicate that isoflurane sedation may promote less memories of hallucinations or delusions from the ICU than midazolam.

**Feasibility and environmental aspects of ACD-delivered isoflurane in the ICU**

In papers I-III, the ACD was demonstrated to be a feasible alternative to conventional vaporizer delivery of inhaled isoflurane. Besides changing of the ACD and filling isoflurane syringes, all practical handling of the ACD was performed by nursing staff previously unfamiliar to the method. The ICU is a high-technology environment with constant evolution of equipment, software and with many potent drugs and invasive treatments. Isoflurane sedation via the ACD requires some basic knowledge of isoflurane pharmacodynamics, dosage range and gas monitoring, as well as comprehensive training before use. No serious adverse events occurred during the study; nursing staff managed the device and sedation proficiently after an in-service training session and written investigator instructions, despite the novelty of both sedative agent and technique of administration. Ambient concentrations of isoflurane when using the ACD were low in relation to Swedish and international recommended exposure limits. With current knowledge of potential carcinogenic or teratogenic effects of trace concentrations of isoflurane, our data indicate that this method of sedation is unlikely to pose a health risk if appropriate, standardized measures are taken in handling the ACD and isoflurane. During manufacturing of isoflurane, an 8-hour time-weighted average isoflurane concentration of 50 ppm is considered the permissible exposure limit for staff compared to the mean ambient concentration of 0.1 ppm reported in paper II. While earlier studies of ambient isoflurane concentrations during ICU sedation with a conventional vaporizer demonstrated levels below recommended exposure
limits\textsuperscript{23,52}, levels in these reports were somewhat higher than what we found with the ACD. One explanation for this difference may be that the active carbon filter in the ACD not only facilitates rebreathing of isoflurane but also contributes to lower concentrations of isoflurane in the exhaled air leaving the ventilator. Results of environmental measurements may also vary somewhat depending on physical layout, room ventilation, number of patients sedated simultaneously and scavenging system. 

During isoflurane sedation in paper II open airway suctioning was performed. Using a closed suctioning technique may further reduce ambient isoflurane concentrations. Conversely, ambient isoflurane concentrations may be higher than in our study if uncuffed endotracheal tubes are used such as in smaller pediatric patients. Such patients may also be of such a size that the ACD may need to be placed in the inspiratory limb of the breathing circuit, leading to a higher isoflurane content in exhaled air leaving the ventilator as the rebreathing function of the ACD is lost. 

Despite the low values found even without active scavenging, good practice includes active scavenging or an isoflurane adsorbing device\textsuperscript{160}.

**Sedation efficacy of isoflurane - clinical implications**

The short and predictable wake-up time after prolonged isoflurane sedation demonstrated in paper I is a valuable feature of an ICU sedative. Previous studies of isoflurane sedation in ICU patients\textsuperscript{4,78,101} and of postoperative sedation with desflurane\textsuperscript{99} have shown similar results. Extubation in patients receiving inhaled isoflurane can be predicted and planned with the attending physician present. Emergence may not be as predictable after prolonged intravenous sedation\textsuperscript{115,140}. Residual sedation will likely hamper neurological assessment less after isoflurane sedation than midazolam sedation\textsuperscript{80,97}. Prompt patient cooperation after termination of sedation may be of value, facilitating earlier extubation, ability to follow instructions and interact during nursing and physiotherapy interventions, e.g. coughing, deep breathing. 

A suggested and commonly used measure of sedation quality is the proportion of time within a predefined interval on a sedation scale\textsuperscript{20}. In paper I the proportion of successful sedation was 54 % during isoflurane sedation and 59 % during midazolam sedation. These proportions may appear to be low. However, in earlier studies with similar end-points success rates were comparable for midazolam and slightly higher for isoflurane\textsuperscript{4,78,104}. The lower success rate for isoflurane in paper I may reflect nurses being less familiar with the new technique of sedation. Nurses’ subjective satisfaction with sedation was higher, with 89% of time during isoflurane sedation and 87 % during midazolam sedation, possibly reflecting nurses acceptance of slightly deeper sedation than the set target interval permitted. 

One reason for titrating sedative administration according to a sedation scale interval is to avoid oversedation\textsuperscript{15}. The effect of oversedation on wake-up times with intravenous agents is well-recognized. Considering the short wake-up times seen with isoflurane, it is unlikely that isoflurane oversedation in a reasonable dosage range, eg. $E_T$ isoflurane concentrations<$1\%$, would result in long wake-up times as may occur with intravenous sedatives. 

There was a non-significant trend towards lower opioid requirement in the isoflurane sedated patients compared to the midazolam group, 2.7 mg/hour vs 4.2 mg/hour. The patient populations were heterogeneous, including medical, surgical and trauma patients with a wide range of opioid doses, making interpretation difficult. Synergistic sedative effects exist between opioids and anaesthetic agents\textsuperscript{44,95,157}. In the multiple regression analysis of wake-up times, opioid dosage did not change the differences between isoflurane and midazolam significantly.
Isoflurane sedation and hepatic/renal function

In the patient in papers I and III, isoflurane sedation did not adversely affect hepatic or renal function. This supports the results of other studies of prolonged isoflurane sedation. Serum inorganic fluoride levels were moderately elevated in some patients, mainly those exposed to inhaled anaesthesia for surgery prior to or during their ICU stay, but there was no evidence of renal deterioration in these patients. There has been some debate regarding serum inorganic fluoride level as an indicator of related nephrotoxic potential. Degree of intrarenal metabolism rather than serum fluoride levels appear to determine the risk of nephrotoxicity, eg. methoxyflurane exhibits significant renal metabolism. Metabolic products exclusive for methoxyflurane in presence of inorganic fluorides appear to contribute to methoxyflurane nephrotoxicity (personal communication, ED Kharasch). In our patient series there was no case of overt renal failure in the isoflurane group compared with three midazolam patients that received continuous renal replacement therapy. To our knowledge isoflurane has not been implicated in the development of renal dysfunction. In fact, isoflurane is considered one of the safest anaesthetics for organ transplantation and for patients with renal dysfunction. Isoflurane sedation makes it an attractive alternative in cases when conventional intravenous sedation is unsatisfactory.

We observed reversible neurological symptoms in two of the patients after several days’ sedation. This finding is of some interest, as involuntary movements and ataxia have been previously described during or after isoflurane sedation in paediatric ICU patients as “emergence phenomena”. It is poorly elucidated to what extent these findings occur after prolonged intravenous agent use. While it is uncertain whether withdrawal in a more classical sense occurs after isoflurane sedation in pediatric patients, withdrawal after prolonged intravenous sedation is not uncommon.

The Bispectral index™ for ICU sedation monitoring

In paper III, poor correlation was found between the median BIS value over ten minutes prior to stimulation and clinical evaluation in isoflurane sedated patients as well as in midazolam sedated patients. BIS correlated strongly with facial EMG. One potential benefit of BIS would be the ability to effectively discriminate between adequate and deep sedation, without frequent and at times disruptive clinical assessments. The proportion of time with BIS index values above 60 despite deep sedation was relatively high; 16% of observations in the isoflurane group and 43% in the midazolam group. This finding is of some concern, as midazolam oversedation likely contributes to long wake-up times. If the BIS monitor reports high values when patients in fact are deeply sedated, relying on BIS may lead to oversedation.

Another important potential benefit of reliable BIS monitoring would be accurate monitoring of sedation depth in patients receiving neuromuscular blocking agents (NMBAs). The fact that BIS values in early versions were more or less affected by EMG led to updated versions.
and an additional electrode in order to reduce artifactual disturbances. In a study using the previous version of BIS (A-1000), BIS values were as lowered to 33-64 in healthy, awake volunteers receiving a NMBA. In another study using the latest version, mean BIS XP values were lowered by 23% when NMBAs were administered to sedated ICU patients. In a recent study of BIS XP during intravenous sedation, correlation between BIS and EMG was found. Our and other investigators' findings indicate that EMG contributes significantly to BIS values. Whether BIS accurately reflects sedation depth in critically ill patients receiving NMBAs has not been assessed in the present studies and remains unclear.

End-tidal isoflurane concentrations during sedation correlated better than BIS with clinical sedation depth and may be a better indicator of sedation depth than BIS in critically ill patients receiving isoflurane for sedation.

**Psychological and cognitive recovery after critical illness and possible implications of sedative agent use**

Results of paper V indicate that isoflurane sedation may promote less delusional memories than with midazolam sedation. Two of ten isoflurane sedated questionnaire responders and five of seven midazolam sedated questionnaire responders remembered delusions / hallucinations from the ICU (p=0.05). In fact, none of the six exclusively isoflurane sedated questionnaire responders had delusional memories. A possible explanation of these findings would be a more clear-cut intercept between sedation and the awake state with isoflurane, with less time spent in a transitional state, in which there may be room for misinterpretation of sensory input, so called source confusion. Withdrawal, not uncommon after prolonged benzodiazepine administration, may include delusions or hallucinations. Withdrawal was, however, not systematically assessed in paper V.

High dosage of intravenous sedatives in ICU patients has been associated with adverse psychological outcome, including withdrawal and delirium in numerous studies. However, in paper V we did not find evidence that the reduced incidence of hallucinations and/or delusions in the isoflurane group led to a better long-term outcome. The lack of reduced long-term psychological morbidity despite a lower rate of delusional memories stands in contrast to findings by Jones et al of an association between delusional memories from the ICU and late psychological morbidity. As previously stated, various other risk factors, of which only some have been identified, may contribute to the development of psychological problems after critical illness.

Identifying potential long-term benefits of isoflurane sedation will likely require a greater number of patients and minimal loss to follow-up, in order to assess the true long-term morbidity. The importance of and difficulty in obtaining a high response rate in traumatic stress research becomes clear when considering the cluster of symptoms in PTSD, which include avoidance of stimuli (e.g. an envelope from the hospital) reminding of the traumatic event (e.g. life-threatening illness or ICU stay). The trend towards a greater proportion of patients with overtly pathological short-term recovery not responding to the questionnaires gives rise to the speculation that patients with an overtly pathological short-term recovery may have had more post-traumatic symptoms, including avoidance behaviour.

Memories of negative feelings were associated with high HADS and IES scores in the entire cohort, a finding that is consistent with previous findings of Schelling et al, who found an association between number of adverse experiences from the ICU and PTSD. It would be attractive to infer that early detection of negative memories from the ICU predict psychological morbidity. Unfortunately in our study ICU memories and indicators of PTSD or depression were measured simultaneously at 6 months. Even if there is evidence of well preserved memory...
of events from the ICU over time\textsuperscript{46}, our study design does not allow us to conclude that early memories predict later depressive or post-traumatic symptoms.

The results of paper V support the use of isoflurane for ICU sedation and indicate that there may be other potential benefits, besides good sedation efficacy, with long-term isoflurane sedation over intravenous sedation.

**Future perspectives**

While isoflurane appears to be beneficial as a sedative for critically ill patients, some other potential positive and negative effects of isoflurane as a long-term sedative need to be assessed.

Anaesthetic preconditioning (APC) of the myocardium with inhaled anaesthetics is now recognized as a clinically important phenomenon in the cardiothoracic anaesthesia setting\textsuperscript{29,30,68,147}. In a recent study, isoflurane exposure prior to coronary bypass surgery led to better postoperative cardiac index, stroke volume and lower troponine-I release compared with controls\textsuperscript{84}.

Isoflurane appears to exert neuroprotection\textsuperscript{106,145,146} and protection against renal ischemia-reperfusion in vivo\textsuperscript{83}. Pulmonary anti-inflammatory effects of isoflurane, with lowered release of inflammatory mediators in endotoxin-induced lung injury, have also been demonstrated\textsuperscript{124}.

Whether cardiac or other organ protective effects of inhaled anaesthetics are of clinical significance for critically ill ICU patients sedated with inhaled anaesthetics in subanaesthetic concentrations is unknown. APC studies generally have used higher concentrations (end-tidal concentration of 1 MAC and above) of inhaled anaesthetic than is needed for sedation. Moreover the effects of prolonged exposure on possible protection need to be elucidated.

In neurosurgical ICU patients isoflurane sedation could potentially be an attractive method, promoting haemodynamic stability and short wake-up times for reliable evaluation of neurological status. Experimental data indicate that isoflurane has neuroprotective properties to an extent that isoflurane is stated to be unsuitable as an anaesthetic in traumatic brain injury models, due to confounding protective effects\textsuperscript{146}. Interestingly, a recent study of severe forebrain ischemia in the rat showed that exposure to concentrations as low as 0.5-1.0 MAC isoflurane were more protective than >1 MAC\textsuperscript{110}.

Isoflurane in higher doses (E\textsubscript{T} concentration >1%) dose-dependently causes cerebrovasodilation, potentially increasing intracranial pressure. Whether sedative concentrations of isoflurane (E\textsubscript{T} concentrations of 0.2 -0.6 %) have clinically significant effects on intracranial pressure in patients with elevated intracranial pressure needs evaluation. With potential benefits of short wake-up times and possible neuroprotection, further study of the implications of low-dose isoflurane in neurosurgical patients with complete monitoring is warranted.

Prospective studies of paediatric ICU sedation focusing on sedative effects and side effects, including the occurrence and consequence of withdrawal symptoms or emergence phenomena using different sedation methods (inhaled versus intravenous) may give valuable information regarding isoflurane sedation in the paediatric population. It is also essential to better elucidate the consequence of prolonged exposure to inhaled anaesthetics for neurodevelopment and relate possible findings to other available options\textsuperscript{58}.

Follow-up data in paper V need to be confirmed in larger trials with prospective short-term follow-up and possibly including standardized measures of psychological and cognitive recovery.

The ICU patient population is heterogeneous, with varying patterns and extent of organ dysfunction and numerous treatment modalities, invariably impacting on disease process and outcome. Well-designed studies assessing psychological and cognitive function after isoflurane sedation, as well as possible toxic or organ protective effects of long-term isoflurane exposure are a challenge for the future.
1) Prolonged isoflurane administration via the ACD for sedation of intensive care patients is feasible and efficacious, with short wake-up times compared to the most commonly used intravenous sedative midazolam.

2) Isoflurane sedation via the ACD in the ICU setting is environmentally safe, with ambient isoflurane levels well below recommended exposure limits, provided instructions for routines in handling equipment and isoflurane are followed. The use of the ACD reduces isoflurane requirements when compared with calculated and reported consumption of isoflurane with vaporizer and high-flow ventilator use.

3) Inhaled sedation with the ACD provides a potential alternative to current sedative regimens in pediatric ICU patients. In its present construction and placement, the ACD creates an increase in dead-space unacceptable for use in small children.

4) BIS A-2000 XP is not effective as a preditor of sedation depth as measured clinically with Bloomsbury in non-paralysed ICU patients receiving isoflurane or midazolam. End-tidal isoflurane concentration correlates better to sedation depth than BIS. BIS correlates strongly to facial EMG.

5) Prolonged isoflurane sedation may promote less delusional memories / hallucinations from the ICU and does not appear to have significant negative effects on long-term psychological recovery compared with midazolam sedation.
Ideas are like rabbits. You get a couple and learn how to handle them, and pretty soon you have a dozen.

John Steinbeck
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