

# Inhalational sedation in intensive care

Scientific Symposium  
and Workshop on  
AnaConDa® set-up

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Klinikum Ludwigshafen,  
Department of  
Anaesthesiology and  
Intensive Care Medicine

## Editorial

### Paradigm shift in intensive care sedation?

Adequate analgosedation is an integral part of modern concepts in intensive care medicine. Targets are an individually adjustable and controlled attenuation of patients' pain and consciousness, optimised ventilation patterns, a short weaning process, and programmed extubation. During the past years, sedation management has changed due to the introduction of short-acting drugs such as propofol and remifentanyl. Nevertheless, given the risk of propofol infusion syndrome and due to pharmaco-economic pressure, midazolam has maintained its position as the most frequently used sedative drug, particularly in critically ill patients.

Based on their pharmacological properties, volatile anaesthetics represent almost the "ideal" sedative agents and have proven their efficiency and safety in general anaesthesia over decades. Until recently, complex technical equipment (vaporizer technology) was a crucial reason for the restriction of anaesthetic gases to be used in the operating room. Anaesthesia machines – the last option in the case of status asthmaticus – cannot perform modern ventilation modes, and moreover, have not been approved for intensive care indications. A few years ago, AnaConDa® (Anesthetic Conserving Device), an innovative system for the administration of volatile anaesthetics, was introduced. The specific benefits of AnaConDa® are the easy set-up between the endotracheal tube and the Y-piece of any intensive care ventilator, and the low consumption of anaesthetics due to the reflection of up to 90% of the anaesthetic gas by the integrated carbon storage filter.

First clinical reports about the use of the AnaConDa® device have been published since 2001. The results of randomised studies of isoflurane vs. midazolam for sedation in intensive care units (ICU) have been promising, particularly with regard to significantly reduce wake-up and extubation times after sedation periods of up to 96 hours.

Our working group has gathered experience with inhalational sedation over a period of 18 months. Approximately 150 patients in our ICU have been sedated using AnaConDa® during this period. In a randomised study comparing sevoflurane vs. propofol sedation, sevoflurane was found to significantly reduce wake-up and extubation times, while the quality of sedation was similar. In long-term ventilation up to 192 hours, the use of volatile anaesthetics, particularly for deep sedation in acute lung failure related with extensive kinetic therapy (e.g. Rotorest bed), was well titratable.

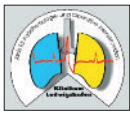
The future will show if the application of volatile anaesthetics using AnaConDa® is capable of replacing current sedation concepts in intensive care. In fact, our experience shows that the system represents a viable and safe alternative for the sedation of critical care patients, already today.

All measures were taken to ensure correctness of the dosages and instructions mentioned in this article.

Nevertheless, every physician has the sole responsibility for treatment procedures and dosages.

Dr. K. D. Röhm

PD Dr. S. N. Piper



Following the welcome address of Prof. Dr. J. Boldt, Director of the Department of Anaesthesiology and Intensive Care Medicine, Klinikum Ludwigshafen, Germany, Dr. S. N. Piper (Ph.D.) gave a lecture on standards and trends in analgo-sedation.

Targets of analgo-sedation are to prevent the patient from unpleasant experiences during her/his ICU stay, to provide efficient analgesia and sufficient anxiolysis, and to ensure a stress-free weaning off the ventilator. Dr. Piper pointed out that often sedative drugs are given too early, even before patients have had the possibility to show any pain. Therefore, analgesics should principally be administered prior to sedative drugs and the onset of analgetic action should be verified.

For the measurement of the sedation depth, several options are available, such as clinical and neurophysiological parameters, scoring

systems and plasma concentration measurements.

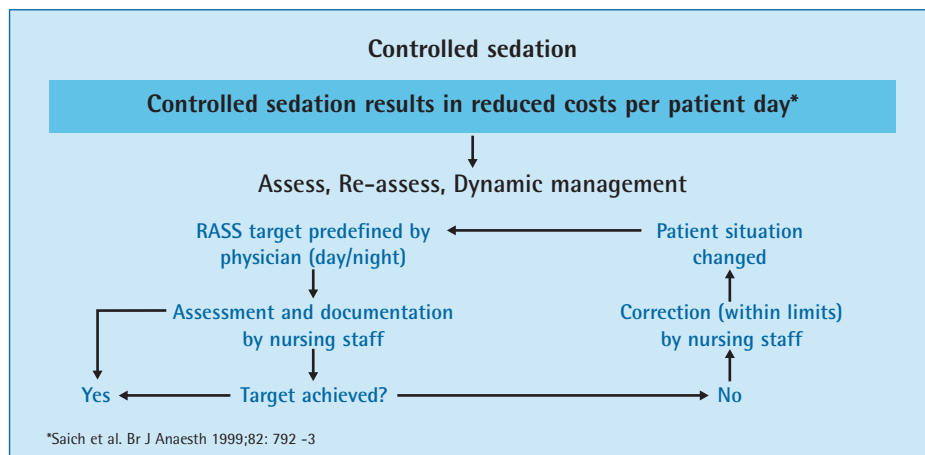
The depth of analgo-sedation should be thoroughly balanced between too deep and too superficial – if sedation is too superficial the patient is potentially threatened by sleeplessness, anxiety, and stress to myocardial ischaemia. If analgo-sedation is too deep the patient may risk hypotension, bradycardia, delayed weaning, immunosuppression, reduced organ perfusion and development of paralytic ileus. Therefore, internal clinical ICU sedation protocols should be implemented with nursing staff support. The physician determines the desired depth of sedation, taking into account the day-night rhythm, and the nurses may autonomously evaluate the patients' status and adjust doses if required (fig. 1). Studies showed a reduction in ventilation times up to 50% if such protocols were implemented.

Which drugs are available for analgo-sedation? It is useful to consider the context-sensitive half-time when comparing different agents (fig. 2). The values of hypnotic drugs differ considerably, with pronounced accumulation of benzodiazepines – but even with propofol half-time increases with duration of exposure. Commonly used opioids such as fentanyl and sufentanil also accumulate, except for remifentanyl which is completely independent of duration of administration. In a survey by Soliman et al., the use of sedative drugs and analgetic drugs in 13 European countries were evaluated. Midazolam is still the drug of 1st choice for sedation followed by propofol; while morphine and fentanyl are the preferred analgesics (fig. 3). PD Dr. Piper commented upon the propofol infusion syndrome (PRIS), which is rare but has a high mortality rate. It is strongly recommended not to exceed a maximum dose of 4 mg/kg BW/h propofol and an application time of 72 h.

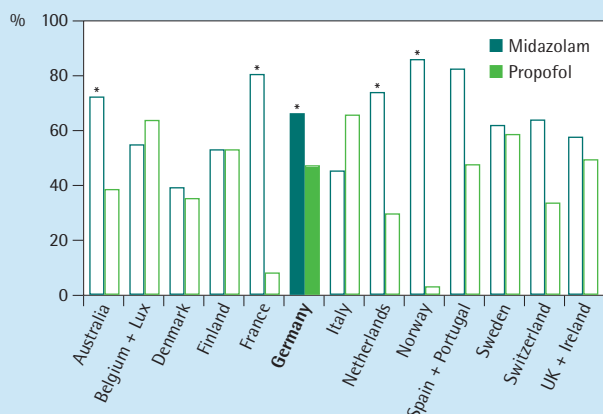
Dr. Piper finished his lecture with the presentation of an individual sedation scheme used in Ludwigshafen considering expected duration of sedation, the level of pain and the underlying diseases of the patient.

The new AnaConDa® system may be implemented according to the SeSAM-concept introduced by Martin et al., using 4 different categories (fig. 4). Taking into account the increase in the number of multi-morbid patients in the future and parallel shortage of ICU beds, inhalational sedation in the ICU may represent an alternative to conventional sedation methods.

Thereafter, Dr. A. Schellhaaß discussed pharmacological and clinical aspects of the volatile anaesthetic isoflurane. Since this agent was clinically introduced in 1984 in Germany, there is considerable experience with its use.



### Sedation in intensive care units in Europe



<b>Sedation:</b>	
Midazolam:	63,0 %
Propofol:	35,0 %
Haloperidol:	9,0 %
Clonidine:	1,8 %
Ketamine:	1,2 %
Flunitrazepam:	0,9 %
Droperidol:	0,7 %
Diazepam:	0,3 %
<b>Analgesia:</b>	
Morphine:	33,0 %
Fentanyl:	33,0 %
Sufentanil:	24,0 %
Piritramid:	0,7 %

Soliman et al. BJA 2001; 87: 186-9

Figure 3

### SESAM Categories

Sequential sedation and analgesia management

#### 1<sup>st</sup> category:

Sedation time < 24 h:

e.g. postoperative ventilation in hypothermia

Regimen:

- Sedation: Propofol or AnaConDa®
- Analgesia: Piritramide (bolus) or Remifentanyl + NSAID and metamizol

#### 2<sup>nd</sup> category:

Sedation time 24 – 72 h:

Underlying disease does not permit rapid weaning (e.g. cardiocirculatory instability, severe swelling of the throat)

Regimen:

- Sedation: Propofol or AnaConDa®
- Analgesia: Fentanyl or sufentanil perfusor + NSAID and metamizol

#### 3<sup>rd</sup> category:

Sedation time > 72 h:

Sepsis, ARDS, second look planned; peritonitis, open abdominal treatment

Regimen:

- Sedation: Midazolam or AnaConDa® + (if required) clonidine, promethazine
- Analgesia: fentanyl, sufentanil, ketanest

#### 4<sup>th</sup> category:

Short-term sedation with requirement of short, deep sedation and rapid onset of spontaneous breathing; e.g. stable cardiothoracic patient; lung surgery patient; COPD patients

Regimen:

- Sedation: Propofol or AnaConDa®
- Analgesia: Piritramid (bolus) or remifentanyl + NSAID and metamizol

Figure 4

Isoflurane can be used regardless of renal or hepatic function. Hepatic damage (auto-immune hepatitis) after isoflurane administration has rarely been reported. In the context of inhalational sedation in the ICU, the pharmacokinetic differences between different volatile anaesthetics known from the operating theatre regarding wake-up conditions have little clinical relevance.

Dr. Schellhaab concluded that isoflurane in combination with AnaConDa® represents a cost-effective and safe option for sedation in the ICU.

In the following lecture, Dr. J. Mayer presented the volatile anaesthetic agent sevoflurane that was introduced in Germany in 1996.

The chemical structure of this agent does not include a chloride atom, therefore, sevoflurane has no effect on the ozone layer. Sevoflurane does not induce airway irritation and is particularly suited for mask induction of children. Easy control of action due to a rapid on- and offset ensures short induction and wake-up times. Equivalent to desflurane and isoflurane, sevoflurane also shows cardioprotective effects and is increasingly used in cardiac anaesthesia. Sevoflurane is almost exclusively metabolised in the liver to hexafluoroisopropanol (HFIP), inorganic fluoride and carbon dioxide. HFIP is excreted via the urine after glucuronidation. The consequences of inorganic fluoride ions in long-term applications for sedation have not yet been established. To date, no effects on renal function have been attributed to sevoflurane exposure.

For the manufacturing company, Mr. vom Dorp informed about the technical properties of the Anaesthetic Conserving Device and the set-up. Since 2005, AnaConDa® has been manufactured and distributed by Sedana Medical (Uppsala, Sweden). The system includes a miniature vaporizer, a highly efficient storage (conserving) medium for anaesthetic gas with an additional heat and moisture function (HME), and a bacterial/viral filter. Although an open ventilator circuit is used, efficiency is equivalent to "low-flow" anaesthesia (Abb. 5) which makes it more cost-effective.

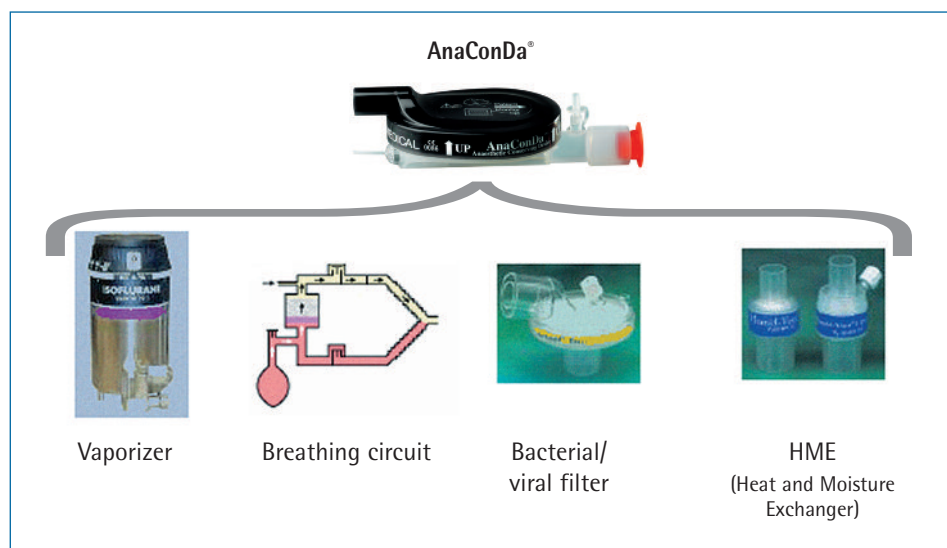


Figure 5

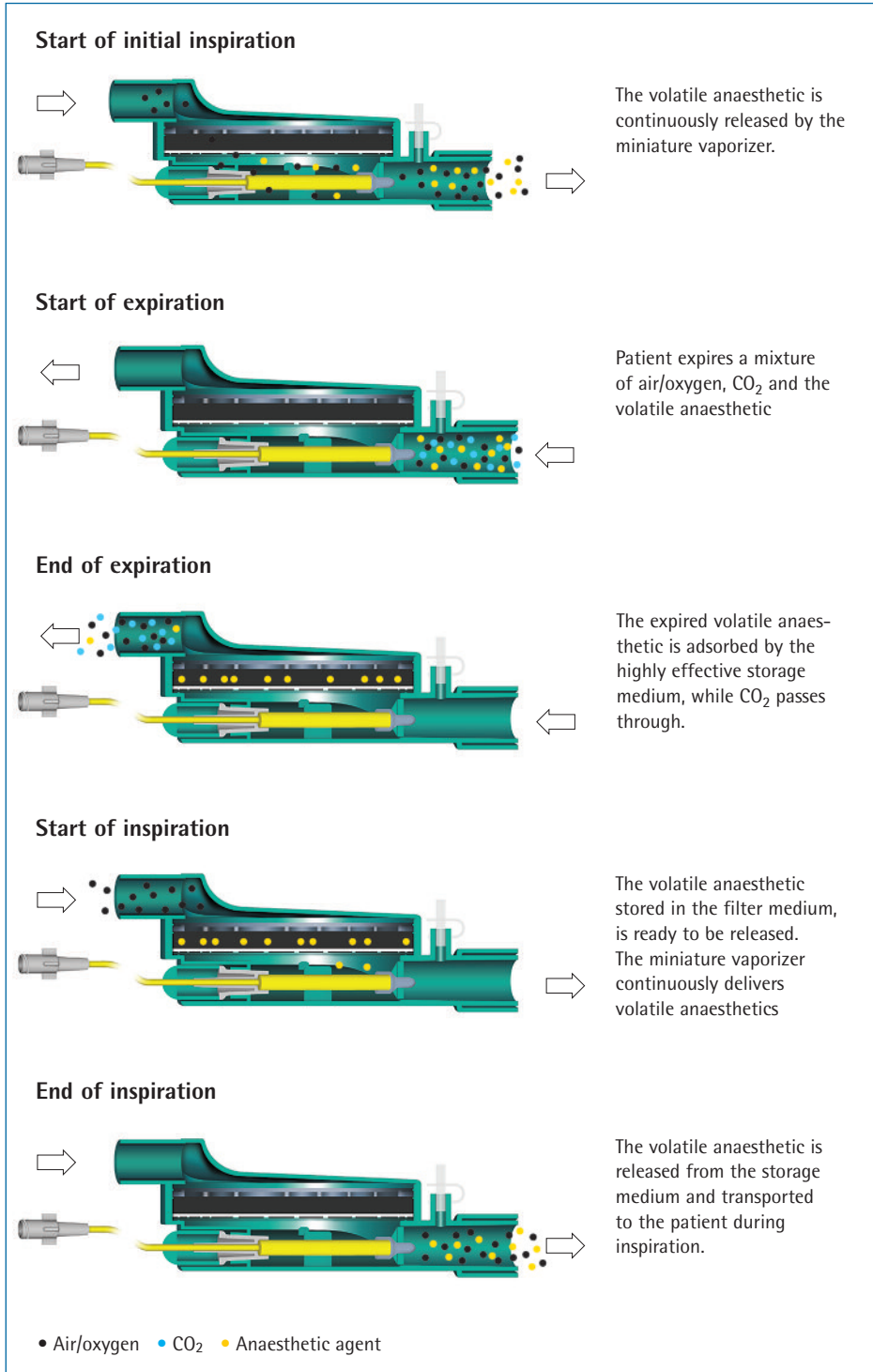
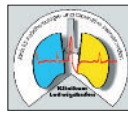
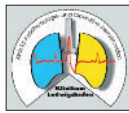


Figure 6

The function of the AnaConDa® system is shown schematically in fig. 6: During the inspiration phase the volatile anaesthetic is delivered via the miniature vaporizer into the system through the endotracheal tube (ET) into the patient. During the expiration phase, 90% of the expired volatile anaesthetic is adsorbed by the carbon filter within the AnaConDa® device and then re-delivered to the patient again during the next inspiration phase (recycling effect).

The AnaConDa® device is integrated into the breathing circuit between the ET and the Y-piece. Liquid volatile anaesthetic is administered into the AnaConDa® device using an AnaConDa® syringe in a standard syringe pump.

A gas monitor ensures simple bedside monitoring of gas concentrations in inspired and expired air.



As 10% of the administered anaesthetic gas is lost via expiration through the intensive care ventilator, Sedana Medical recommends the use of either an active anaesthetic gas scavenging system or a passive activated charcoal/zeolite-based gas filter. Thus, possible contaminations of the workplace by inhalational anaesthetics can be avoided. For staff safety, maximum exposure limits have been set and recommended for general anaesthesia in the operation room: Nitrous oxide 100 ppm, Halothane 5 ppm and isoflurane 10 ppm. For sevoflurane and desflurane, values have still not been set, although their intraoperative use has become quite common. Measurements of ambient air in ICUs during AnaConDa® use have shown that room air exposure was far below recommended maximum limits (< 0.5 ppm isoflurane or sevoflurane), even without the use of residual gas filters, but at standard ICU air change rate alone.

In her first lecture, Dr. K. D. Röhm focused on the historical development of inhalational anaesthetics and the initial use of these agents in the ICU in 1985. Primarily, anaesthetic equipment with commercially available vaporizer technology was used as last resort for sedation in ICU patients.

This type of application was associated with high expenditure of anaesthetic gas and led to high workplace exposure in absence of

central scavenging systems. In 2001, the Swedish anaesthesiologist Dr. Enlund described the utilisation of an Anaesthetic Conserving Device for the administration of inhalational anaesthetics for the first time. Intraoperatively, the system showed anaesthetic gas savings of 40%, thus, the gas expenditure was similar to "low-flow" anaesthesia (1 - 1.5 l/min fresh gas supply), as also demonstrated by Prof. Belda (Valencia, Spain) later on. The first randomised study was published by Sackey et al. (Stockholm, Sweden) in 2004. His study results (fig. 7) were promising with regard to significantly reduced wake-up time with isoflurane vs. midazolam (10 vs. 100 min). Recent studies describe the use of AnaConDa® as a last therapeutic option for patients in status asthmaticus, and for sedation of critically ill patients using sevoflurane. Weaning and extubation as well as neurologic assessment were shorter and more predictable.

The prolonged use of inhalational anaesthetics is commonly related to an increase of inorganic fluoride concentrations. Particularly intraoperative sevoflurane application led to a significant elevation of fluoride levels that exceeded the postulated 50 µmol/l nephrotoxic threshold, as shown by Obata et al. in 2000 and by Conzen et al. in 2002. However, no clinical deterioration of the kidney was ever observed.

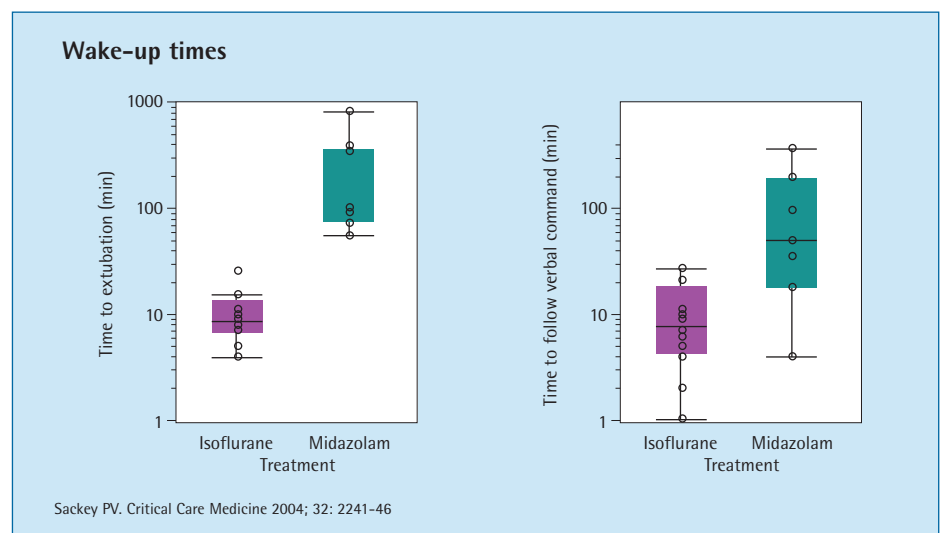


Figure 7

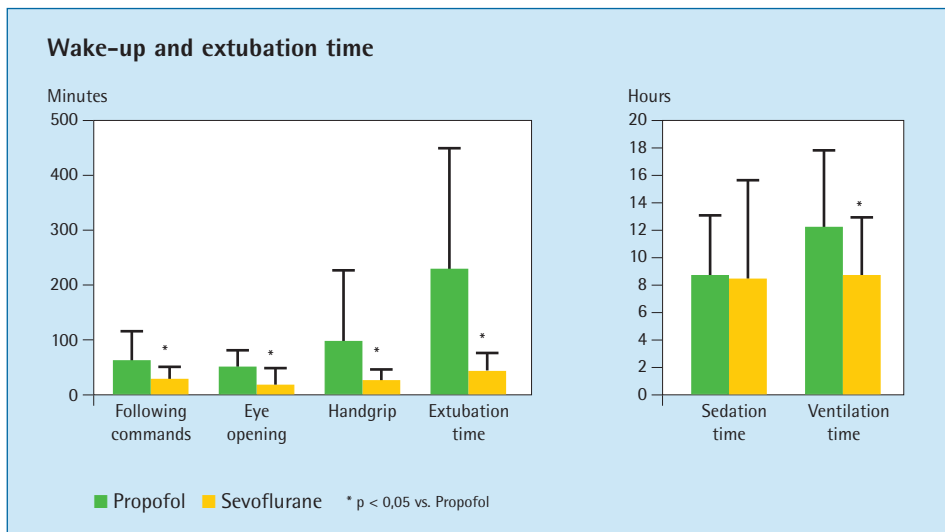


Figure 8

Also, the study group in Ludwigshafen has observed significant elevations of fluoride concentrations under short-term sevoflurane sedation; however, these increases did not lead to any impairment in renal function with regard to the clinical situation or to laboratory targets. During long-term use of sevoflurane, measured fluoride values were again markedly increased and exceeded the postulated renal threshold by far, but no long-term negative effects were observed.

In her second presentation, Dr. Röhm showed results of a randomised, prospective study with 70 cardiac surgery patients regarding sevoflurane administration with the AnaConDa® device in ICU compared to propofol. Patients of the sevoflurane group showed significantly reduced wake-up and extubation times, and the ventilation period could be reduced by 3 h in total (fig. 8). While the quality of sedation (RASS-score) was similar, mean sevoflurane consumption was 3.4 ml/h at endtidal concentrations of 0.5 to 1 Vol%. The frequency of side effects, particularly cardiac arrhythmia, nausea and vomiting, and postoperative delirium was similar in both groups. Cost-comparison analysis of both groups showed similar drug costs, though the AnaConDa® device presents an additional cost factor.

The use of the AnaConDa® device in long-term ventilated critically ill patients at the Klinikum Ludwigshafen demonstrated a safe administration and good performance under invasive ventilation with high PEEP values

(15 mmHg) and peak inspiration pressures of 35 mmHg.

It was particularly possible to sedate patients with acute lung failure and extensive kinetic therapy (e.g. Rotorest bed) using sevoflurane as a monotherapy (concomitantly with an opioid). The average sevoflurane consumption was 6.7 ml/h at end-tidal gas concentrations of 0.8 to 1.5 Vol%. In total, 12 patients were sedated over periods of 50 to 192 hours. It was possible to extubate 4 patients within 30 min to 6 h after removal of the AnaConDa® device. In Ludwigshafen, the AnaConDa® device is used in invasively ventilated patients over a period of 48 hours.

Dr. Röhm indicated that from the clinical point of view, sedation with the AnaConDa® device is an excellent alternative to conventional intravenous sedation. The system is characterised by a simple and safe handling, and for the first time ever in critical care, direct monitoring of the "sedation depth" via anaesthetic gas monitors is possible. Principally, it must be emphasised in this context that the use of anaesthetic gases in the ICU has not been licensed. However, with regard to free therapy, every physician has the option to use volatile anaesthetics.

## Conclusion:

- Based on pharmacological and pharmacodynamic properties, volatile anaesthetics represent almost ideal sedative agents
- With the AnaConDa® device, technical means are provided to enable safe and efficient administration of volatile anaesthetics in the ICU
- For the first time ever, an alternative sedation method is available for the ICU that does not use the I.V. administration route.
- Randomised studies have shown significant reduction in ventilation times with isoflurane and sevoflurane sedation over i.v. sedation.
- Impairment in renal function following sevoflurane exposure has not been reported; effects on long-term exposure still have to be determined.
- Reduction in ICU and hospital stay may compensate and even out-weight additional treatment costs caused by the AnaConDa® device

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