

CLINICAL INVESTIGATIONS

Desflurane compared with propofol for postoperative sedation in the intensive care unit^{†‡}

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Background. We hypothesized that emergence from sedation in postoperative patients in the intensive care unit would be faster and more predictable after sedation with desflurane than with propofol.

Methods. Sixty patients after major operations were allocated randomly to receive either desflurane or propofol. The target level of sedation was defined by a bispectral indexTM (BISTM) of 60. All patients were receiving mechanical ventilation of the lungs for 10.6 (SD 5.5) h depending on their clinical state. The study drugs were stopped abruptly in a calm atmosphere with the fresh gas flow set to 6 litres min⁻¹, and the time until the BIS increased above 75 was measured (t_{BIS75} , the main objective measure). After extubation of the trachea, when the patients could state their birth date, they were asked to memorize five words.

Results. Emergence times were shorter ($P < 0.001$) after desflurane than after propofol (25th, 50th and 75th percentiles): t_{BIS75} , 3.0, 4.5 and 5.8 vs 5.2, 7.7 and 10.3 min; time to first response, 3.7, 5.0 and 5.7 vs 6.9, 8.6 and 10.7 min; time to eyes open, 4.7, 5.7 and 8.0 vs 7.3, 10.5 and 20.8 min; time to squeeze hand, 5.1, 6.5 and 10.2 vs 9.2, 11.1 and 21.1 min; time to tracheal extubation, 5.8, 7.7 and 10.0 vs 9.7, 13.5 and 18.9 min; time to saying their birth date, 7.7, 10.5 and 15.5 vs 13.0, 19.4 and 31.8 min. Patients who received desflurane recalled significantly more of the five words. We did not observe major side-effects and there were no haemodynamic or laboratory changes except for a more marked increase in systolic blood pressure after stopping desflurane. Using a low fresh gas flow (air/oxygen 1 litre min⁻¹), pure drug costs were lower for desflurane than for propofol (95 vs 171 Euros day⁻¹).

Conclusions. We found shorter and more predictable emergence times and quicker mental recovery after short-term postoperative sedation with desflurane compared with propofol. Desflurane allows precise timing of extubation, shortening the time during which the patient needs very close attention.

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The use of isoflurane for sedation of ventilated patients in intensive care units (ICU) has been described repeatedly in the literature. Several randomized controlled studies compared the use of isoflurane with midazolam^{1,2} or with propofol³ for ICU sedation. There are many reports about sedation with isoflurane for special indications^{4–9} and from

paediatric ICUs.^{10–11} In spite of this favourable literature, isoflurane has not gained widespread use as a sedative agent.

[†]This paper contains data that will become part of the doctoral theses of Martin Bellgardt, Susanne Lohmann and Andreas Garthoff.

[‡]This article is accompanied by Editorial I.

This may be attributable to concerns about atmospheric contamination, concerns about (slightly) elevated plasma fluoride concentrations,¹² the high cost if used without a rebreathing system and lack of technical equipment (vaporizer, scavenging).

Because of its much greater stability, desflurane is even less toxic than isoflurane in humans.¹³ Its very low blood–gas and tissue–blood partition coefficients lead to a small distribution volume and to favourable pharmacokinetics. After extensively investigating isoflurane sedation,^{1 14–16} Kong concluded his review article¹⁷ thus: ‘Whether desflurane can fulfil the promise of a better inhalational agent for intensive care sedation remains to be seen, although its cost is likely to be prohibitive.’

The technology available in modern anaesthesia ventilators has improved and some offer ventilatory modes such as synchronized intermittent mandatory ventilation and pressure-controlled ventilation. This permits their use for ventilating ICU patients without restricting the standard quality of respiratory care. Therefore, we decided to evaluate the efficacy and safety of desflurane for ICU sedation as well as the practicability of using a modern anaesthesia ventilator with a low rate of fresh gas flow in the intensive care setting.

In a pilot study in 32 postoperative patients sedated with desflurane in our ICU, we found short emergence times that did not correlate with age, duration of sedation, chronic alcohol intake, end-tidal concentration of desflurane or body mass index.¹⁸ We then hypothesized that emergence times after sedation with desflurane would be shorter and more predictable than with propofol. This would allow precise timing of extubation and more efficient use of ICU resources.

Patients and methods

The study procedure was approved by the local institutional review board. All adult patients undergoing major operations with a likelihood of postoperative sedation and ventilation in the ICU and who gave informed consent could be included. Exclusion criteria were possible pregnancy, severe organ insufficiency (e.g. serum creatinine >2 mg dl⁻¹; $Pa_{O_2} <60$ mm Hg; $Pa_{CO_2} >60$ mm Hg), preoperative breathlessness on physical exercise (one staircase), alcohol or drug dependency, any central nervous system disease, and severe haemodynamic instability or high oxygen requirement ($F_{I_{O_2}}$ 1.0) at the end of the operation. On the day before surgery, patients were asked to complete a five-word memory test, Trieger’s dot test (TT) and the digit symbol substitution test (DSST) to obtain baseline scores.

If at the end of the operation the anaesthetist decided to continue the mechanical ventilation, patients were allocated for sedation with either desflurane (Suprane®; Baxter, Erlangen, Germany; Group D) or propofol (Disoprivan® 2%; Astra-Zeneca, Wedel, Germany; Group P) by telephone

call to the hospital pharmacy department, where a randomization list was stored.

The study observation period was from arrival at the ICU to 2 h after tracheal extubation. Patients were treated by the nurses and doctors (one surgeon, one anaesthetist) in charge, the principal investigator was present at the start and the end of administration of the study drugs, and at least one of three study observers was present at all times to ensure adherence to the study procedure, to assess the sedation status according to the Ramsay scale¹⁹ at least hourly, and to record data. Neither researchers nor staff involved was blinded to the study drug.

The lungs of all patients were ventilated with an anaesthesia ventilator (Cicero™, kindly provided by Dräger Medical, Lübeck, Germany) with the nitrous oxide port disengaged and the gas outlet connected to the central gas scavenging system. The Cicero ventilator offers synchronized intermittent mandatory ventilation, which would seem ideal for intensive care patients. However, with the current model a simultaneous application of PEEP is not possible. Therefore, the lungs of all patients were ventilated mechanically, using the pressure-controlled mode in most cases. Fresh soda lime was used for each patient and PEEP was set to 5 cm H₂O. Desflurane was delivered by a modified TEC-6 vaporizer (Dräger Medical). Fresh gas flow, regulated by an oxygen and an air rotameter, was set to air/oxygen 6 litres min⁻¹ initially, reduced to 1 litre min⁻¹ after 5 min, and increased to pure oxygen 6 litres min⁻¹ after stopping the study drugs. For the adjustment of desflurane concentration, the gas flow could be increased. End-tidal desflurane and carbon dioxide concentrations were monitored by side-stream infrared spectroscopy. Ventilation was first set up by an anaesthetist and later controlled by qualified nursing staff to maintain the Pa_{CO_2} between 35 and 45 mm Hg and the Pa_{O_2} between 100 and 150 mm Hg. Arterial blood gases, including carboxyhaemoglobin concentrations, were determined at 2 h intervals, at the start and immediately before the end of the study sedation and 2 h after tracheal extubation.

After gently rubbing the skin with 70% ethanol on a cotton swab, Zipprepp® electrodes (Spacelabs Medical, Kaarst, Germany) were placed on the left and right temples (midway between eye and ear), and on lateral (ground) and mid-forehead (reference), and these electrodes were connected to an Aspect A 1000™ (Spacelabs Medical) for bilateral monitoring of the bispectral index™ (BIS™, version 3.1). The electrode impedance had to be <5000 kΩ. The BIS was stored electronically on a computer hard disk and the average of the bilateral measurements was analysed.

During transport to the ICU, patients were sedated with propofol. On arrival, the study drugs were adjusted to achieve a target BIS of 60. For desflurane, an end-tidal concentration of 3 vol % was used initially, and this could be changed in steps of up to 0.5 vol %. Propofol infusions were started at the rate of 4 mg kg⁻¹ h⁻¹ and changed in steps

of up to 40 mg h⁻¹ every 15 min. Bolus doses of propofol 40 mg were allowed in Group P. At times when BIS monitoring was not available (artefacts, poor signal quality, disconnection for nursing care) we aimed at a Ramsay score of 4–5 instead.

Because of the heterogeneous patient population, a single analgesic regimen was not practicable. The following guidelines were adhered to. The only opioid allowed was piritramide (15 mg are equivalent to morphine 10 mg) at a low to moderate rate (≤ 3.6 mg h⁻¹) by continuous i.v. infusion, as is our standard practice for short-term sedation. Patients with epidural catheters could receive ropivacaine 2 mg ml⁻¹ epidurally at up to 6 ml h⁻¹. In addition, metamizol 1 or 2.5 g could be given i.v. as a bolus up to a maximum daily dose of 6 g. Metamizol is our standard non-opioid analgesic drug; it does not have sedative effects. Other analgesic drugs were not allowed. Analgesia was determined and assessed regularly by the doctors in charge (not the investigators). Piritramide and ropivacaine were continued unchanged when the study drugs were stopped.

Sedation and ventilation were continued as long as clinically indicated. In a calm atmosphere with as little noise as possible, dimmed light and with the BIS below 65, the study drugs were stopped abruptly. The BIS was allowed to increase spontaneously above 75 [the time to BIS 75 (t_{BIS75}) was the main objective measure]. After this, patients were addressed by their last name, asked to open their eyes and to squeeze the hand of an observer, each repeated once every 20 s. The tracheal tubes were removed according to our clinical criteria (responsiveness, cough reflex, sufficient spontaneous ventilation). After saying their birth date, asked once every minute, the patients had to repeat five spoken words one by one and they were asked to recall these words after 1, 5 and 10 min (five-word memory test). TTs were performed 30 and 60 min and DSSTs 60 and 120 min after removal of the tracheal tubes.

All data available from the anaesthesia procedures were entered into case report forms. The Acute Physiology and Chronic Health Evaluation II score (APACHE II) for admission to the ICU was calculated as specified by Knaus and colleagues,²⁰ except that no points were given for the Glasgow coma scale. At the end of the observation period patients were asked about nausea, vomiting and other complaints.

For comparison of groups, the χ^2 -test, Mann–Whitney *U*-test or *t*-test was used as appropriate. $P < 0.05$ was considered significant. In the pilot study we noticed that a BIS of 75 [midway between 60 (target level of sedation) and 90 (responsiveness)] corresponded to the steep part of the S-shaped BIS curve, when emergence was monitored with the BIS. For this reason and to improve objectivity, t_{BIS75} was chosen as the main objective measure. In a planned interim analysis after 10 patients, we calculated a probability of 90% (power) to detect a difference of 5 min or more with a standard deviation of 5 min if 22 patients were included per group. To compensate for possible dropouts,

Table 1 Details of patients and of the surgery and anaesthesia preceding the study. Data are mean (SD), median [interquartile range], mean (range) or absolute number

	Desflurane (n=28)	Propofol (n=28)
Age (yr)	65.0 (37–83)	59.9 (33–77)
Sex (F/M)	9/19	11/17
Height (cm)	171.8 (9.3)	169.4 (8.3)
BMI (kg m ⁻²)	24.6 (3.9)	25.9 (3.3)
APACHE II	12 [10–15]	11 [9–12]
Surgery		
Duration (h)	4.92 (1.73)	4.73 (1.43)
Blood loss (litres)	2.03 (1.56)	2.01 (1.42)
Type [DT (OE)/AA/MO]	18 (4)/3/7	14 (1)/2/12
Anaesthesia		
Duration (h)	6.08 (1.78)	6.02 (1.48)
Volatile anaesthetic (D/S/I)	18/9/1	21/5/2
Sufentanil (μ g)	168 (141)	129 (54)
Final temperature ($^{\circ}$ C)	35.0 (1.1)	35.4 (1.4)
Red blood cells (units)	2 [2–4]	2 [2–3]

BMI=body mass index; APACHE II=Acute Physiology and Chronic Health Evaluation II score; DT=digestive tract malignancy; OE=oesophagectomy; AA=abdominal aortic surgery; MO=major orthopaedic surgery (replacement of hip arthroplasty, spinal surgery); D/S/I=desflurane/sevoflurane/isoflurane.

because we also looked at other variables (side-effects, laboratory and haemodynamic data) and in accordance with published clinical trials on ICU sedation,^{1–3} we determined that 30 patients in each Group should be allocated to the treatments and analysed.

Results

Study profile

One hundred and seven patients consented to participate. Prolonged ventilation was indicated in 60 patients who were allocated to one of the treatment groups. Four patients were excluded. In two, ventilation was discontinued in the operating theatre (one in Group D, one in Group P); two other patients became haemodynamically unstable before arriving in the ICU (one experienced a cardiac arrest and the other had severe uncontrollable blood loss; both were in Group D). Thus, 56 patients were treated with the study drugs; 28 received desflurane for 2.8–21.6 h and 28 received propofol for 3.8–17.1 h. In three patients after oesophagectomy (Group D), continued sedation and ventilation was necessary for reasons of postsurgical care for more than 24 h. In these patients the study drug was stopped the next morning, t_{BIS75} and times to first response and to eye opening were measured, then bolus injections of midazolam and sufentanil were given and sedation was continued using these drugs.

Table 1 shows the details of patients and of the surgery and anaesthesia preceding the study. Patients in Group D were on average 5 yr older than patients in Group P. In Group D there were more patients who had surgery for digestive tract malignancies (including oesophagectomies;

Table 2 Dosages of analgesic and study drugs. All patients received i.v. piritramide or epidural ropivacaine 2 mg ml⁻¹ or both. Additionally i.v. metamizol, a non-opioid analgesic, was given to some patients during the study sedation as part of their analgesic regime (metamizol 1) or after study drugs had been stopped, when patients complained of pain (metamizol 2). Data are mean (SD). ***Significant difference between initial and mean F_{ET}(DES) (paired *t*-test, *P*<0.001); **significant difference between mean and last F_{ET}(DES) (paired *t*-test, *P*=0.004); †significant difference between T4 and last propofol (paired *t*-test, *P*=0.012)

	Desflurane (<i>n</i> =28)	Propofol (<i>n</i> =28)
Dosage of analgesic drugs		
Piritramide (µg kg ⁻¹ h ⁻¹)	26.1 (12.1) (<i>n</i> =23)	25.4 (11.7) (<i>n</i> =24)
Ropivacaine (mg h ⁻¹)	7.1 (3.6) (<i>n</i> =14)	7.3 (1.5) (<i>n</i> = 8)
Metamizol 1 (mg)	1.9 (0.8) (<i>n</i> = 7)	2.3 (1.1) (<i>n</i> = 6)
Metamizol 2 (mg)	1.9 (0.8) (<i>n</i> = 8)	1.9 (0.8) (<i>n</i> =10)
Dosage of study drugs		
Initial F _{ET} (DES) (vol %)	3.0 (0.5)***	–
Mean F _{ET} (DES) (vol %)	3.5 (0.5)**	–
Last F _{ET} (DES) (vol %)	3.9 (0.7)	–
Initial propofol (mg kg ⁻¹ h ⁻¹)	–	4.2 (1.4)
Mean propofol (mg kg ⁻¹ h ⁻¹)	–	4.4 (1.1)
T4 propofol (mg kg ⁻¹ h ⁻¹)	–	4.7 (1.5)†
Last propofol (mg kg ⁻¹ h ⁻¹)	–	4.2 (1.1)

F_{ET}(DES)=end-tidal concentration of desflurane; T4 propofol=propofol infusion rate after 4 h study sedation (maximal).

4 vs 1) than in Group P. For the general anaesthesia preceding the study period, the same drugs had been used in similar dosages in the two groups (sufentanil, volatile anaesthetics mostly in nitrous oxide/oxygen). Blood loss, duration of surgery and anaesthesia, number of blood transfusions and final temperatures were also similar (Table 1).

Table 2 shows the dosages of analgesic and study drugs used. All patients had received i.v. opioid or epidural analgesia or both, as determined by the intensive care physicians. End-tidal concentrations of desflurane between 2.0 and 5.0 vol % were applied. The dosage of desflurane had to be increased gradually during the study period to meet the target BIS of 60. In contrast, the dosage of propofol, after a peak at 4 h, could be reduced significantly (Table 2). Dosages between 2.8 and 6.0 mg kg⁻¹ h⁻¹ were needed.

Patients in both groups were rather deeply sedated, some patients not responding to moderately painful stimuli (Ramsay score 6). Ramsay scores during the sedation and before stopping the study drugs were higher (more deeply sedated) in Group D than in Group P. The BIS could be recorded with good signal quality during 87% of total sedation time. During the rewarming phase we noticed falsely high BIS values (>90) in deeply sedated patients (Ramsay score ≥4), coinciding with high power (>40 dB) in the 70–110 Hz frequency band ('low EMG' displayed by the Aspect A 1000). This was the case during 15% of sedation time in both study groups. These values were considered as artefacts and omitted from the analysis. Thus, the BIS could be used for adjusting the study drugs during 72% of the study period. BIS values during the sedation and before stopping the study drugs were not significantly different

Table 3 Study sedation. Data are mean (SD) or median [interquartile range]. ^PCalculated from pooled data; ***significant difference between study groups (*U*-test, *P*<0.001); **significant difference between study groups (*U*-test, *P*=0.006); †††significant difference between study groups (χ^2 -test, *P*<0.001); ‡significant difference between study groups (*t*-test, *P*=0.049); †significant difference between before and after extubation (paired *t*-test, *P*=0.035); ††significant difference between before and after extubation (paired *t*-test, *P*=0.002)

	Desflurane (<i>n</i> =28)	Propofol (<i>n</i> =28)
Duration (h)	11.53 (5.72)	9.68 (5.27)
RA (1/2/3/4/5/6; % of time) ^{P***}	0.3/0.6/4.5/9.1/1 41.7/43.7	0.4/0.8/10.4/12.3/ 54.6/21.5
Last RA (1/2/3/4/5/6)**	0/0/1/1/13/13	0/1/3/5/14/5
BIS (median of each patient)	53 [46–59]	59 [50–63]
Last BIS [44–59]	54 [46–59]	–
HR (beats min ⁻¹) ^P	75.6 (12.7)	76.0 (16.1)
HR _{60–100} (L/N/H; % of time) ^{P†††}	7.8/86.7/5.5	17.2/72.4/10.3
MAP (mm Hg) ^P	68.6 (10.3)	70.1 (11.5)
MAP _{65–90} (L/N/H; % of time) ^P	34.6/62.6/2.8	25.5/67.7/6.8
SAP _{max} after extubation (mm Hg) [‡]	152.3 (22.0)	138.3 (26.9)
O ₂ index 1 (mm Hg)	365.3 (80.7)†	359.5 (91.3)††
O ₂ index 2 (mm Hg)	325.1 (113.0)	290.1 (100.1)

RA=Ramsay score; BIS=bispectral index™; HR=heart rate; MAP=mean arterial pressure; HR_{60–100} and MAP_{65–90}=percentage of total sedation time when these values were below (low, L), within (normal, N) or above (high, H) the normal ranges (HR, 60–100 min⁻¹; MAP, 65–90 mm Hg); SAP_{max}=maximal systolic arterial pressure after stopping the study drugs to 2 h after extubation; O₂ index 1=oxygation index (Pa_{O₂}/F_IO₂) before extubation; O₂ index 2=2 h after extubation.

(Table 3) and there was no difference in BIS at any time point (Fig. 1).

Heart rate was similar in the two groups, with less variation in Group D. Heart rate was in the normal range during 87% of the total sedation time with desflurane but only during 72% of time with propofol (χ^2 -test, *P*<0.001; Table 3). Mean arterial pressures were similar in the two groups during the sedation, but there was a significantly greater increase in systolic pressures after stopping desflurane than after stopping propofol (Table 3). In Group D, 11 patients had systolic arterial pressures above 160 mm Hg, and six of these were treated with antihypertensive drugs; in Group P the numbers were five and four respectively. The oxygenation index was not different between the study groups and decreased to a similar extent after discontinuation of mechanical ventilation (Table 3). There were no significant differences in the routine laboratory profile, additional drugs given or total fluid balance.

Emergence was faster and more predictable after desflurane than after propofol. The *t*_{BIS75} and the times to first response, eye opening, hand squeeze, removal of the tracheal tube and saying the birth date were all considerably and significantly shorter after desflurane (*U*-test, all *P*<0.001; Fig. 2). There was a broad distribution of values after propofol but not after desflurane. The range in the time to first response was 1.8–11 min after desflurane (median 5.0 min) but 2.7–25 min after propofol (median 8.6 min).

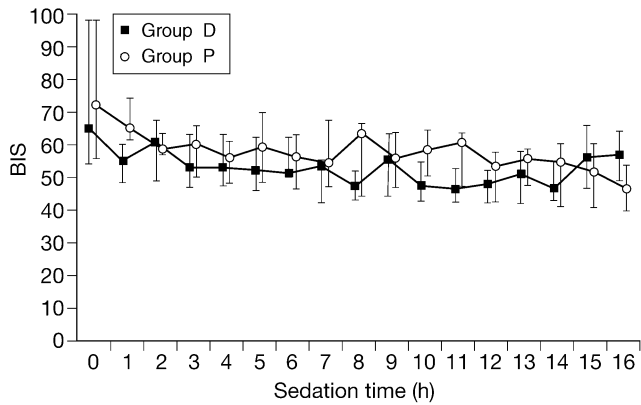


Fig 1 Time course of the bispectral index (BIS) during the study sedation with desflurane and propofol. Median values (vertical bars show interquartile ranges) representing more than three patients are shown. There were no significant differences between the study groups at any time point.

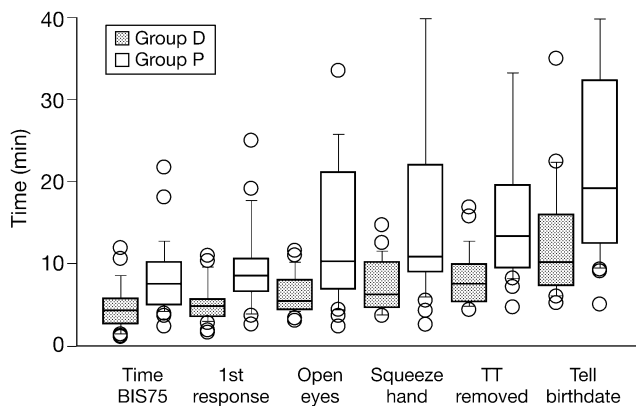


Fig 2 Emergence times after sedation with desflurane or propofol. All times were measured from stopping the study drugs until the bispectral index (BIS) increased above 75 (time to BIS 75 was the main objective measure), until the patients first responded when addressed with their names, until they first opened their eyes completely and squeezed the hand of an observer, until the tracheal tubes (TT) were removed and until they stated their birth date correctly. Box plots show 50th, 25th and 75th (boxes), 10th and 90th percentiles (whiskers) and individual outliers (open circles). All emergence times were significantly different between the two study groups (U -test, $P < 0.001$). There is a broad distribution of values after propofol but not after desflurane.

In the five word memory test, patients in Group D recalled significantly more words, although they were asked to do this test earlier than patients in Group P (i.e. after saying their birth date) (Table 4). In contrast, TT and DSST did not detect differences in psychometric performance.

Very few patients were considered to be agitated after using the study drugs. No patient vomited and no patient who received desflurane complained of nausea. Some reported other complaints, including dry mouth, dizziness, headache and shivering, when asked 2 h after tracheal extubation (Table 4).

Table 4 Patient recovery and psychometric tests. Baseline tests were performed the day before surgery with different test kits. The number of patients able to perform each test (n) is given in parentheses. Data for side-effects are numbers of patients. *Patients after sedation with desflurane recalled significantly more words after 1, 5 and 10 min than patients after propofol (U -test, all $P < 0.05$)

	Desflurane ($n=25$)	Propofol ($n=28$)
Psychometric tests		
WT _{baseline} (1, 5, 10 min)	3.7, 3.7, 3.6	4.1, 3.9, 3.9
WT (1, 5, 10 min)*	2.0, 1.6, 1.4	1.2, 0.9, 0.6
TT _{baseline}	41 [41–42]	42 [41–42]
TT _{30 min}	16 [8–27] ($n=15$)	20 [5–34] ($n=15$)
TT _{60 min}	22 [8–28] ($n=15$)	21 [10–38] ($n=20$)
DSST _{baseline}	29 [25–39]	36 [21–40]
DSST _{60 min}	14 [10–16] ($n=10$)	14 [9–20] ($n=15$)
DSST _{120 min}	18 [9–22] ($n=14$)	19 [11–25] ($n=16$)
Side-effects		
Agitation	2	4
Nausea	0	2
Vomiting	0	0
Other complaints	7	6

WT=five-word memory test (mean number of words after 1, 5 and 10 min), performed after the patients could state their birth date; TT=Trieger's dot test (median [interquartile range]), performed 30 and 60 min after removal of the tracheal tube; DSST=digit symbol substitution test (median [interquartile range]), performed 60 and 120 min after removal of the tracheal tube.

Drug costs

For 271 h of propofol sedation, 109 bottles containing 50 ml of propofol 2% were used. Partially empty bottles were discarded. For 323 h of desflurane sedation, 18 bottles containing 240 ml liquid desflurane were used. This resulted in pure drug costs for 24 h of sedation of 171 Euros for propofol and 95 Euros for desflurane.

Discussion

Our present report describes the use of desflurane for the intensive care sedation of mechanically ventilated patients and compares this with propofol sedation. All six measured emergence times were significantly shorter after desflurane than after propofol. It is of note that the distribution of emergence times after propofol was much wider (Fig. 2): in Group D the range in extubation time was 4.5–17 min (median 7.7 min), whereas in Group P it was 4.75–102 min (median 13.5 min). The same was true for the times until the patients were awake, cooperative (squeeze hand on command) and orientated (say birth date). In the ICU, rapid and reliably predictable emergence is itself a considerable advantage. It allows precise timing of extubation. Rapid emergence shortens the time during which the patient needs very close attention, thereby saving the time of staff.

In addition, quick emergence times are indicators of greater control of sedation. If the level of sedation needs to be increased to perform unpleasant or painful procedures, this can be achieved quickly. After the procedure, the previous level of sedation may be restored immediately. For example, in spinal fusion patients the assessment of

neurological function may be of primary importance. Using desflurane, we could adjust the level of sedation easily to communicate to the patients a request to move their toes, after which we increased the level again. In our view, sedation with desflurane could be of benefit in ventilated patients when repeated neurological evaluation is indicated.

Apart from the quicker emergence, we found better cognitive function after sedation with desflurane, although these patients were 5 yr older and had been sedated more deeply according to the Ramsay score: patients in Group D correctly stated their birth date on average 26 min earlier and were able to recall significantly more words at this time than patients in Group P. The TT and DSST did not detect differences in psychometric performance. However, many patients, in spite of being mentally competent, were not able to execute the tests because of weakness, tremor, swollen hands, impaired vision (oedema of the conjunctiva or upper eye lids) and inability to sit up.

We did not observe major side-effects of a 3–22 h application of desflurane. There were no significant differences in liver and kidney function tests between groups (data not shown). Only a few patients in both groups complained of side-effects when asked 2 h after extubation. Interestingly, no patient receiving desflurane complained of nausea, a finding that contrasts with common experience from the postanaesthesia care unit where up to 30 or even 50% of patients after inhalational anaesthesia will complain of nausea or vomiting. Possible explanations are that we used low concentrations of desflurane, only small doses of opioids and no nitrous oxide, and the patients were normothermic more comfortable and in less pain than patients in a postanaesthesia care unit because more time had passed since the operation.

A frequently discussed adverse reaction to desflurane is sympathetic hyperactivity.²¹ This is blunted in humans by opioids.²² In a comprehensive study in human volunteers, Ebert and colleagues²³ demonstrated that sympathetic activation only occurs when abruptly increasing the desflurane concentration from 1 MAC (minimum alveolar concentration) (7.25 vol %) to 1.5 MAC (11 vol %), but not from 0.5 to 1 MAC. We did not notice any episode of tachycardia or hypertension attributable to an increase in desflurane concentration, probably because we never used more than 5 vol % desflurane and all patients had received opioid drugs. Indeed, heart rate was significantly more often in the normal range during sedation with desflurane than with propofol. Arterial pressures were not different between groups during the sedation, but we noticed a more pronounced increase in systolic arterial pressures after stopping desflurane than after propofol. Antihypertensive drugs were given to six and four patients respectively. These patients were not in pain. One possible explanation would be quicker restoration of arterial vascular tone to (or above?) normal after desflurane.

Other adverse reactions of desflurane are very rare. Toxicity caused by metabolites or fluoride would be even

less than with any other volatile anaesthetic,¹⁷ although one case of desflurane hepatotoxicity after previous sensitization to halothane has been reported.²⁴ There is a small risk of malignant hyperthermia after desflurane.²⁵ Desflurane may react with desiccated soda lime to form carbon monoxide.^{26–27} Therefore, we used fresh soda lime for each patient to minimize the risk. Carboxyhaemoglobin concentrations were measured several times in all patients and were always within acceptable limits (data not shown).

Because blinding of the medical staff did not seem possible and because clinical assessment of depth of sedation and of emergence may not be observer-independent, we decided to use the BIS, firstly to define objectively the target depth of sedation and secondly to measure the velocity of emergence. The BIS has been shown to measure the depth of anaesthesia or sedation reliably with different hypnotic drugs.²⁸ For several reasons, we chose a rather low target BIS, of around 60. The patients in our study were sedated and ventilated after major surgery (in many cases surgery for malignant tumours) for a short time because of high blood loss, for expected high fluid shifts and for rewarming. Inadequate sedation may carry the risks of the patient pulling out tubes and catheters, and of shivering and discomfort, whereas pulmonary function and discontinuation of ventilation is usually not a problem in these patients. Second, a BIS of 60 during intensive care sedation is not comparable to the same BIS during surgery, when strong painful stimuli continuously arouse the brain. As Shapiro puts it: ‘The bispectral index measures the state of the brain, not a concentration of a drug.’²⁹ Sleigh and colleagues³⁰ recorded BIS values between 20 and 70 during normal delta-wave sleep. Third, neurophysiological monitoring would not work well with half-awake, sometimes agitated patients. In the pilot study we found it difficult to target BIS values around 80 because the values were unstable and would either increase, with patients struggling against the ventilator, or decrease.

Reliable BIS monitoring was available during 72% of sedation time. In both groups, we found falsely high BIS values (often above 95) during 15% of time, mainly at the beginning of the study sedation, while the patients were deeply sedated, with a Ramsay score of 4–6. This coincided with a rise in body temperature and high EMG activity, as displayed by the Aspect A 1000, although frank muscle shivering was never observed. During these periods the study drugs were adjusted according to the Ramsay score.

After eliminating these falsely high BIS values, we did not find differences in BIS values between groups at any time point (Fig. 1). In contrast, Ramsay scores were higher (more deeply sedated) in Group D than in Group P. As an explanation, we assume that volatile anaesthetics may act like an on-off switch for consciousness, whereas with propofol it may be easier to achieve intermediate levels of sedation.

We also used the BIS to define our main objective measure: the time from stopping the study drugs until the

BIS increased spontaneously from below 65 to above 75. We did not find any difficulty in monitoring BIS during emergence, and t_{BIS75} turned out to correlate well with all other clinical emergence times measured in this study.

In this study, a heterogeneous patient population admitted to a mixed operative ICU was included after major abdominal, orthopaedic or aortic surgery. This precluded a single analgesic regimen. As expected, many patients consenting to participate did not take part because prolonged sedation and ventilation in the ICU were not indicated. For these reasons, we did not standardize the anaesthesia preceding the study. To prevent a large number of dropouts, the patients were allocated randomly only at the end of the operation. After randomization, only four patients had to be excluded.

The time course of the dosage of the study drugs was different. The gradual increase in the end-tidal concentration of desflurane during the whole sedation period and the initial increase in the infusion rate of propofol may be explained by the subsiding effect of strong opioids from the preceding anaesthesia. After a peak at 4 h of study sedation, propofol infusion rates could be significantly decreased while maintaining a BIS around 60. This time course in our study parallels the target-controlled infusion algorithm and indicates redistribution of the drug.

We did not find technical difficulties or problems in the use of the anaesthesia ventilator or of the desflurane vaporizer in the environment of our operative ICU, which is equipped with a central gas scavenging system. Generally, after instruction in the use of the anaesthesia ventilator had been given, the new sedation method was well accepted by our nurses.

Contamination of room air with inhalation anaesthetics should be controlled just as strictly in the ICU as in the operating theatre. High workplace concentrations may occur in postanesthesia and intensive care units as a result of patients exhaling older volatile anaesthetics after long-lasting anaesthesia. Frequently, the turnover of room air is inadequate and gas scavenging is not used with intensive care respirators.³¹ Hoerauf and colleagues³² and Coleman and colleagues,³³ however, measured workplace concentrations during sedation with isoflurane in the ICU and did not find high exposure levels when using gas scavenging.

Contrary to Kong's apprehension, our cost analysis showed that the pure drug costs for sedation with desflurane were lower than those for propofol (95 vs 171 Euros per 24 h). This was made possible by reducing the initially high fresh gas flow after <15 min and by using a low gas flow of 1 litre min^{-1} for maintenance of sedation. Additional costs were about 5 Euros for the soda lime, as opposed to 2.5 Euros for infusion tubing for propofol. Cheap scavenging systems that can be connected to the suction vacuum are available commercially. Our calculation does not take into account the (additional?) costs for an anaesthesia ventilator with vaporizer and gas monitor.

To conclude, we found postoperative sedation of adult ICU patients with desflurane to be feasible and easy to perform. Awakening was pleasant and emergence times were shorter than after equivalent sedation with propofol. This provides safety for the patient, saves time for staff and indicates good control of the level of sedation. A gas scavenging system and sufficient turnover of ambient air by an air-conditioning system are prerequisites. Using a low fresh gas flow rate, the costs of desflurane are similar to or less than those of propofol. Taking all facts together, desflurane seems a promising new alternative to i.v. sedatives for postoperative short-term sedation of ventilated adult patients in the ICU.

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