Feasibility and Potential Cost/Benefit of Routine Isoflurane Sedation Using an Anesthetic-Conserving Device: a Prospective Observational Study

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BACKGROUND: Inhaled sedation is efficient and easily controllable; in low concentrations it causes minimal changes in the patient and very little interference with hemodynamics. Awakening after inhaled sedation is quick and predictable. The major reason inhaled sedation has not become widely used in intensive care is that no commercially available administration device has been available. METHODS: In our intensive care unit we conducted a prospective observational study to assess the feasibility, benefits, and costs of routine isoflurane sedation via the AnaConDa anesthetic-administration device. We included 15 adult patients who required > 24 hours of deep sedation. Conventional intravenous sedation (benzodiazepine and opioid) had been administered according to a sedation protocol that included a predetermined target Ramsay-scale sedation score. We then switched to inhaled isoflurane via the AnaConDa, and measured sedation efficacy, cumulative dose, and daily cost of sedation. Adverse events were prospectively defined and monitored. RESULTS: The sedation goal was reached with isoflurane in all 15 patients ($P < .01$, compared to the conventional sedation protocol). Hemodynamic changes were nonsignificant, and no renal or hepatic dysfunctions were observed. The frequency of meeting the sedation goal was significantly better with isoflurane than with our usual sedation protocol. With isoflurane, awakening from sedation was always ≤ 4 hours, despite some long-duration sedations (up to 14.5 d). The overall daily cost of the 2 sedation protocols was not different in the whole group of 15 patients, but in the subgroup of 7 patients who required a mean midazolam infusion larger than the average dose, the cost difference was very significant (€218 ± 111 vs €110 ± 19, $P < .01$). CONCLUSIONS: Routine ICU isoflurane sedation with the AnaConDa is easily feasible, effective, safe, and has a relatively short awakening period. In some patients with sedation difficulties, this sedation method may significantly decrease sedation cost and enhance sedation efficacy. *Key words: sedation, AnaConDa, isoflurane, midazolam, costs, hemodynamics, intensive care*. [Respir Care 2008;53(10):1295–1303. © 2008 Daedalus Enterprises]

Introduction

If sedation is frequently required in the intensive care unit (ICU), it is known to induce several problems. The clinician should first avoid the hazards of under-sedation and over-sedation.[1-3] The main adverse effect of sedation is interference with hemodynamic regulation, which causes vasodilation, myocardial depression, and bradycardia. The incidence of post-traumatic stress disorder after long-term sedation is high. There is often a need to increase the sedation dosage during intravenous sedation of ICU patients.[4]

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The ideal ICU sedative would be effective, easily controllable, have rapid onset and offset, would not accumulate or have active metabolites, would have few adverse effects, would be cost-effective, would improve the qual-

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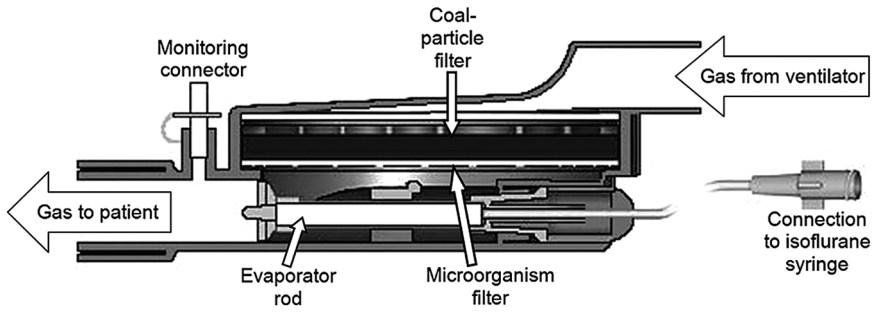

Fig. 1. The AnaConDa is a modified heat-and-moisture exchanger, and is connected between the patient and a standard intensive-care ventilator. The anesthetic infuses through the evaporator rod. A lipophilic coal-particle filter captures (via adsorption-desorption) approximately 90% of exhaled anesthetic, so only a small amount of anesthetic gas escapes the system, which minimizes ambient-air pollution. The isoflurane consumption is similar to that with a low-flow circle system.

ity of care, and would reduce the duration of mechanical ventilation and ICU stay.[5]

Volatile anesthetics selectively suppress consciousness while leaving many autonomic functions intact. Awakening after inhaled sedation is usually quick and predictable, even after prolonged use, and inhaled sedatives can be said to act like an "on/off switch" for consciousness. In low concentrations, volatile anesthetics interfere very little with hemodynamics, and some are potent bronchodilators.[6] The major reason inhaled sedation has not become more widely used in intensive care is that no commercially available administration device or ventilator had all the desired properties. The recent introduction of a volatile-anesthetic reflection filter anesthetic-conserving device (AnaConDa, Sedana Medical, Sundbyberg, Sweden) enables inhaled sedation in most ICUs.[7] Interest in the device was described in a preliminary study.[8]

The aims of this prospective observational study were to assess the feasibility, costs, and benefits of routine isoflurane sedation via the AnaConDa in the ICU.

Methods

Our institution's ethics committee approved this study.

Patients

We studied 15 adult patients admitted to our 15-bed ICU during a 3-month period. Patients who required $>$ 0.05 mg/kg/h midazolam and 0.2 μg/kg/h sufentanyl to meet the predetermined Ramsay-sedation-scale goal were eligible to receive isoflurane sedation. All patients were mechanically ventilated and were expected to require $>$ 24 hours of deep sedation, according to a predetermined routine protocol. All the subjects were enrolled within 48 hours of ICU admission.

Exclusion criteria for isoflurane sedation were pregnancy, hemodynamic instability (mean arterial pressure $<$ 70 mm Hg despite adequate fluid resuscitation and vasopressors), neuromuscular disease, personal or familial history of malignant hyperthermia and/or eosinophilia after inhaled sedation, intracranial pressure increase $>$ 20 mm Hg, and acute and/or chronic liver or renal disease.

Conventional Sedation Protocol

Our conventional ICU intravenous sedation protocol uses midazolam plus sufentanyl. Dosage is adjusted hourly by the nursing staff, to reach the predetermined target Ramsay sedation score, depending on the patient's pathology and status. For example, a patient with cerebral trauma or acute respiratory distress would be sedated to a mean Ramsay score of 5 during the first 24 hours of medical care and/or until stabilization.

Isoflurane Administration

Inhaled sedation was administered with the AnaConDa (Fig. 1),[7] which is a disposable device connected between the patient and a normal ICU ventilator, like a standard heat-and-moisture exchanger (Fig. 2). The manufacturer indicates that moisture output is up to 30 mg H_2O/L. The device's approximate inner volume (dead space) is 100 mL. Resistance to gas flow at 60 L/min is 2.5 cm H_2O/L/s, which is comparable to a standard heat-and-moisture exchanger. The isoflurane is injected via a standard ICU syringe pump (Orchestra module, Fresenius Vial, Brezins, France, flow range 0.1–1,200 mL/h, flow accuracy $\pm$ 1% on drive mechanism) into the porous "evaporator rod" (see

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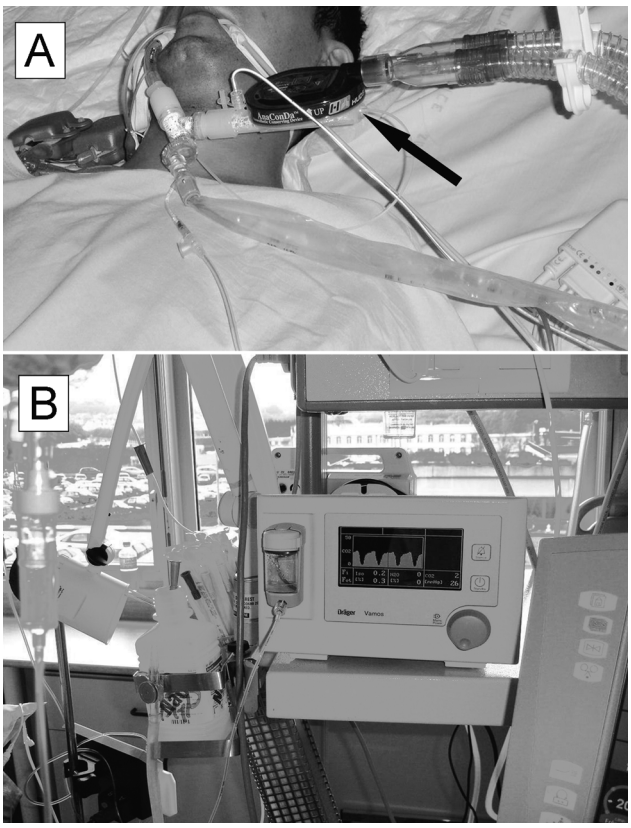

Fig. 2. Connection of the AnaConDa (arrow) to the ventilator circuit. A closed suctioning system is always used, to avoid ambient-air pollution by anesthetic. The monitoring line is at the proximal end of the AnaConDa. Gas monitoring is performed sequentially, especially during the initiation phase. The isoflurane expiratory concentration is always to be set below 1%. In this patient, who had major sedation difficulty under our conventional sedation protocol, adequate sedation (Ramsay score 6) was obtained with an isoflurane expiratory concentration of only 0.3%.

Fig. 1) from which the sedative is delivered during each inspiration. Ninety percent of the exhaled anesthetic condenses on the coal-particle filter and is released during the next inspiration, so only a small amount of anesthetic escapes the system, which, theoretically, provides low ambient pollution and gas consumption similar to that with a low-flow circle system.[9,10] Each disposable AnaConDa comes with a device-specific 50-mL keyed syringe and a 22-cm anesthetic supply line. The syringe barrel and plunger are made of polypropylene, and the piston is made of rubber. A prefilled syringe is guaranteed to stay stable for a 7-day storage time in darkness and at room temperature.

Gas-scavenging was performed with a commercially available canister (Cardiff Aldasorber, Shirley Aldred and Company, Worksop, Nottinghamshire, United Kingdom) connected to the ventilator output. The canister contains 1 kg of activated charcoal and removes isoflurane from the expired air up to a weight increase of 300 g, which provides > 48 hours with the AnaConDa.

The isoflurane infusion rate was initially set to 5 mL/h and then adjusted to reach adequate sedation depth by changing the rate in steps of 0.1 mL/h, according to our routine sedation protocol. Isoflurane expiratory concentration was measured (Vamos, Dräger, Antony, France) (see Fig. 2) at least each 8 hours, and was kept at or below 1%. Our standardized procedure involved daily change of the AnaConDa, closed suctioning, and management of the scavenging system to limit ambient air pollution.

Measurements

All data were prospectively collected and recorded on a specific daily chart by an independent physician. Sedation efficacy was assessed hourly per our sedation protocol, based on the Ramsay sedation scale, and sedative dosage was adjusted to reach the sedation goal. Success/failure in meeting the sedation goal was considered the difference between the measured Ramsay score and the predetermined Ramsey goal. For example, if the measured Ramsay score was 6 but the target score was 4, the sedation-success/failure value would be +2 (over-sedation). If the measured Ramsay score was 2 but the target score was 3, the sedation-success/failure value would be −1 (under-sedation).

Table 1. Subjects

Subject	Age (y)	Sex	Admission Diagnosis	SAPS II	ICU Stay (d)
1	77	Female	Community-acquired pneumonia	31	35
2	69	Male	Community-acquired pneumonia	44	18
3	73	Male	Cerebral trauma	62	9
4	50	Male	Status epilepticus	44	5
5	44	Male	Community-acquired pneumonia	27	23
6	32	Female	Status asthmaticus	15	11
7	68	Male	Community-acquired pneumonia	48	33
8	46	Male	Community-acquired pneumonia	67	19
9	58	Female	COPD	35	18
10	58	Male	COPD	38	21
11	57	Female	Sepsis	52	31
12	30	Female	Community-acquired pneumonia	23	22
13	25	Male	Community-acquired pneumonia	27	26
14	42	Female	COPD	36	47
15	43	Male	Cerebral trauma	28	25

SAPS II = Simplified Acute Physiology Score II, measured within 24 h of admission
ICU = intensive care unit
COPD = chronic obstructive pulmonary disease exacerbation

Table 2. Sedation Before and After Isoflurane Initiation

Subject	24-Hour Period Before Initiating Isoflurane (Day –1)				24-Hour Period After Initiating Isoflurane (Day +1)*				
	Midazolam (mean mg/kg/h)	Sufentanyl (mean μg/kg/h)	Ramsay Score Immediately Prior to Isoflurane Initiation	Measured vs Target Ramsay Score	Isoflurane Consumption (mL/h)	Isoflurane Expiratory Concentration (%)	Sufentanyl (μg/kg/h)	Ramsay Score After 24 h of Isoflurane Sedation	Measured vs Target Ramsay Score
1	0.06	0.3	4	–1	4.4	0.7	0.2	6	1
2	0.06	0.3	6	0	5.5	0.6	0.1	6	0
3	0.4	0.4	4	–2	4.4	0.5	0.1	ND	ND
4	0.3	0.4	5	0	5.8	0.4	0.2	6	1
5	0.2	0.2	6	0	5	0.4	0.05	6	0
6	0.4	0.4	ND	ND	7.3	0.7	0.1	6	0
7	0.5	0.5	6	0	3	0.5	0.1	6	0
8	0.3	0.3	6	0	8.6	0.6	0.05	6	0
9	0.5	0.8	6	0	4.6	0.6	0.1	6	0
10	0.5	0.5	3	–1	4.4	0.7	0.4	4	0
11	0.3	0.3	4	0	4.1	0.7	0.1	6	2
12	0.3	0.3	4	0	2.2	0.3	0.1	5	1
13	0.8	1.6	3	–2	4.3	0.8	0.5	5	0
14	0.5	0.5	2	–1	2.9	0.2	0.2	6	3
15	0.2	0.2	5	0	2.1	0.5	0.1	6	1
Mean ± SD	0.4 ± 0.2	0.5 ± 0.1	NA	–0.5 ± 0.8	4.6 ± 1.8	0.5 ± 0.2	0.2 ± 0.1†	NA	+0.6 ± 0.9‡

* Midazolam was switched to isoflurane at the beginning Day +1.
† There was a significant decrease ($P < .005$) in sufentanyl infusion on Day +1.
‡ Success in meeting the Ramsey-score goal was significantly greater ($P < .005$) on Day +1 than on Day –1.
NA = not applicable
ND = no data available

The cumulative dose of sedative was assessed with the infusion system's data-collection software (Base Intensive, Orchestra, Fresenius Vial, Brezins, France). The baseline daily cost of sedation was calculated as the overall cost of sedation during the 24-hour period before initiation of isoflurane (day –1) (ie, the total of the costs of midazolam, sufentanyl, other drugs, and all administration devices). The daily cost of isoflurane sedation included all those variables, plus the cost of the isoflurane, AnaConDa, gas-scavenging system, and fluid resuscitation and vasopressors in the 24 hours following isoflurane initiation.

Adverse events were defined as death, bradycardia (≤ 45 beats/min), persistent hypotension despite adequate medical management (mean arterial pressure ≤ 70 mm Hg), and acute renal-function alteration (creatinine-clearance decrease ≥ 25%), acute liver failure (≥ 25% increase in aspartate aminotransferase, alanine aminotransferase, or bilirubin, or a ≥ 25% decrease in prothrombin time). Renal and hepatic function were measured at least every 48 hours during isoflurane administration.

Statistical Analysis

Results are given as mean ± SD. We used 2-way analysis of variance for most comparisons. We used analysis of variance for repeated measures to compare the arterial pressure values. P values ≤ .05 were considered significant.

Results

Table 1 shows the subjects' ages, admission diagnoses, Simplified Acute Physiologic Score II (measured within 24-h of admission), and duration of ICU stay. Five patients were receiving norepinephrine infusion (mean dose < 0.01 mg/kg/h) before initiation of isoflurane.

Baseline Response to Our Standard Sedation Protocol

Because of the severity of their illness, 4 patients (patients 5, 6, 9, and 13) required addition of cisatracurium (mean dosage 0.2 ± 0.2 mg/kg/h). Patient 13 required addition of 3 mg/kg/h propofol plus 0.3 mg/kg/h ketamine to reach the target Ramsay score. With our standard sedation protocol the target Ramsay score was not reached in 5 of the 15 patients (Table 2).

Response to Our Isoflurane Sedation Protocol

After 24 hours of isoflurane, success in meeting the sedation goal was significantly improved (Table 3). The

Table 3. Isoflurane Sedation Data

Subject	Isoflurane Consumption (mL/h)	Sufentanyl Dosage (μg/kg/h)	Duration of Isoflurane Sedation (h)	Isoflurane Expiratory Concentration (median %)
1	2.6	0.1	138	0.6
2	4.7	0.1	49	0.6
3	4.4	0.2	11	0.8
4	5.8	0.2	21	0.8
5	5.8	0.1	35	0.5
6	3.5	0.1	72	0.6
7	3.4	0.1	48	0.7
8	9.9	0.05	15	0.5
9	6.4	0.2	65	0.8
10	5.9	0.4	336	0.6
11	4.2	0.1	69	0.6
12	2.1	0.1	28	0.7
13	6.5	0.7	348	1
14	3.6	0.2	98	0.8
15	3.2	0.1	56	0.5
Mean ± SD	4.8 ± 2.0	0.2 ± 0.2	93 ± 107	NA

NA = not applicable

predetermined target Ramsay score was reached in all 15 patients ($P < .01$, compared to the conventional sedation protocol). In 6 of the 15 patients the isoflurane Ramsay score was higher than the target.

During the first day of isoflurane, midazolam sedation was stopped and sufentanyl infusion was reduced by half in all 15 patients. Two patients still received cisatracurium. The overall mean isoflurane sedation duration was approximately 4 days (range 11 h to 15 d). There were no important adverse events. Hemodynamic changes were nonsignificant (Fig. 3), and no vascular fluid load or vasopressor increase/initiation was necessary after isoflurane initiation. No renal or hepatic dysfunctions were observed, despite some long-term isoflurane administrations. Isoflurane consumption remained constant during the overall sedation course. Post-isoflurane awakening was always within 4 hours.

Sedation Cost

Initial daily sedation cost ranged widely (Table 4), so the overall daily cost of the 2 sedation protocols was not different. However, among the 7 patients who had an above-average midazolam requirement (0.4 mg/kg/h), isoflurane allowed either achievement of the sedation goal (in all cases) or lower daily sedation cost (€218 ± 111 vs €110 ± 19, $P < .01$).

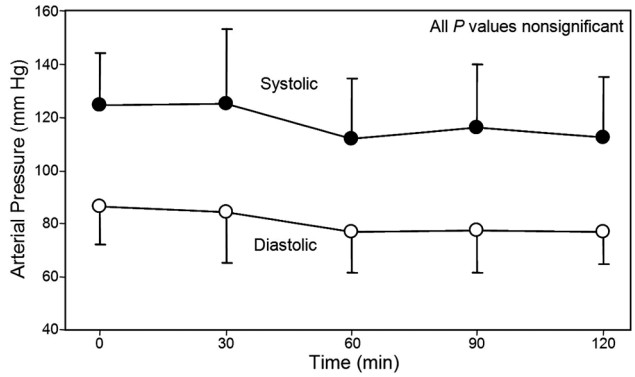

Fig. 3. Mean systolic (dots) and diastolic (circles) arterial pressure during the first 2 hours of inhaled isoflurane. There were no significant arterial pressure changes.

Discussion

The present study confirms the feasibility, efficacy, and safety of inhaled isoflurane sedation with the AnaConDa in the ICU. The AnaConDa allows easy isoflurane sedation in most ICU patients and with all types of ventilators. Isoflurane sedation via the AnaConDa lowers sedation cost in patients who require prolonged sedation and patients in whom it is difficult to reach the sedation goal with standard sedation doses.

Feasibility and Efficacy of Isoflurane Sedation With the AnaConDa in the ICU

Though the efficacy of inhaled sedation is well known, it is rarely used in the ICU, mainly because of technological problems. The feasibility of the AnaConDa as an anesthetic delivery system was confirmed in studies in the operating room.[9,10] In a randomized study in an ICU, isoflurane sedation via the AnaConDa was compared to midazolam sedation for up to 96 hours in 40 patients.[8] Awakening was faster after isoflurane sedation, and there were no serious adverse effects in either group. They concluded that the AnaConDa could easily be managed by the nursing staff.

Several studies have indicated more rapid emergence after prolonged ICU sedation with inhaled anesthetic administered via vaporizer, compared to common intravenous anesthetic.[11-13] However, inhaled sedation was not yet routinely possible.

Our results clearly confirm the feasibility and efficacy of prolonged (up to 348 h) routine inhaled sedation via the AnaConDa in a standard ICU population. In all 15 of our patients isoflurane achieved the sedation goal without needing to add midazolam, and with less sufentanyl. Awakening was rapid, even after long-duration sedation. Rapid awakening may provide other important benefits that we

Table 4. Cost of Sedation*

Subject	Cost (€/d)		
	24-Hour Period Before Initiating Isoflurane (conventional sedation)	First 24 Hours of Isoflurane Sedation	Mean Isoflurane Sedation Cost
1	45	109	91
2	54	100	95
3	140	95	104
4	151	225	251
5	272	183	174
6	246	120	116
7	140	95	90
8	187	100	120
9	426	99	107
10	140	117	121
11	117	98	99
12	140	107	105
13	292	145	170
14	140	98	97
15	70	92	96
Mean ± SD	171 ± 101	119 ± 38	122 ± 44

* The sedation cost includes drugs, drug-administration devices, closed-suctioning system, and gas-scavenging device.

did not monitor, such as shorter weaning time and ICU stay. Isoflurane administration duration was highly variable, depending on the patient's clinical status, as the proportion of time spent under isoflurane with respect to the duration of ICU stay. After initiation of isoflurane, isoflurane was the main anesthetic used, and in most patients isoflurane was infused until weaning or death. Only a few patients (< 10%) were returned to intravenous sedation after weaning failure.

Anesthesia Gas Scavenging and Ambient Air Pollution

Anesthesia gas scavenging is suggested for inhaled sedation with ICU ventilators that have open circuits, to limit ambient air pollution. We used a commercially available activated-charcoal canister that removes isoflurane from the expired air for > 48 hours. A similar procedure was evaluated by Coleman et al during isoflurane sedation in 3 ICUs. In that study the mean ambient-air isoflurane level was < 1 ppm while using such scavenging units.[14] Those results were confirmed in a study by Sackey et al, which supported the environmental safety of isoflurane sedation in the ICU.[15] Moreover, they confirmed that the use of the charcoal canister may be prolonged while using the AnaConDa, because the AnaConDa contains a charcoal filter that reduces both pollution and isoflurane consumption. More than 90% of the anesthetic is recirculated, and mean isoflurane consumption was reported to be approximately one fourth of previously reported consumption of isoflurane with vaporizer-administered sedation in the ICU setting.

We monitored ambient-air pollution in our ICU rooms with the first 5 patients (data not shown). We used a turbine ventilator that drew ambient air into a 2-L canister, and measurements were performed continuously for at least 2-hour periods with the Vamos device. The ambient isoflurane level was always < 1 ppm with our isoflurane administration and scavenging protocols.

Patient-Safety Concerns About Prolonged Isoflurane Sedation

Up until now no inhaled sedative has been licensed for ICU sedation. On the other hand, there is no time limit for the duration of anesthesia, and there is vast experience with prolonged use of isoflurane in the literature. Common indications for inhaled sedation in the ICU include acute severe asthma[16-18] and status epilepticus.[19,20]

Inhaled anesthetics produce dose-dependent circulatory effects.[21] One minimum alveolar concentration of isoflurane can produce up to a 30% reduction in arterial pressure, mostly mediated by a decrease in systemic vascular resistance. Given the low isoflurane expiratory concentration with our protocol, and the fact that hemodynamically unstable patients were excluded, no fluid load or vasopressor increase was required immediately following isoflurane initiation or during the subsequent hours.

Halothane and nitrous oxide use must now be discouraged because of potential hepatic, neurologic, and red-blood-cell toxicity. Prolonged sedation with isoflurane has, however, been used for almost 2 decades without important adverse events. In our study there were no important adverse events, despite some long-duration administration. Theoretical concerns about prolonged use of isoflurane in patients with hypoxemia and the risk of hepatocyte toxicity were taken into account, even though only a few cases have been reported. Patients with a previous history of liver disease and/or biological hepatic-function abnormalities were not included. Daily hepatic-function measurements remained stable during the entire patient stay. Because of concerns about potential deleterious effects in head-trauma patients, isoflurane was not used unless intracranial pressure was stable. We included 2 patients with cerebral trauma; in both cases, intracranial pressure remained stable and continuously below 10 mm Hg.

Plasma fluoride concentration is known to increase up to 50 mmol/L during long-duration sedation with volatile anesthetics, which is related to renal dysfunction.[22,23] That fact is, however, no longer a matter of concern,[24,25] so plasma fluoride concentration was not monitored. No sig-

nificant creatinine-clearance variation was observed, even in patients sedated for 5–15 days.

A United Kingdom safety alert was published in August 2006 due to a case of anesthetic overdose while using the AnaConDa, which in the United Kingdom is now to be used only by "clinicians specifically trained in the use of anaesthetic drugs" and "with the correct level of monitoring and respiratory support."[26] That adverse event was considered to be related to a combination of user error and inconsistencies in the device's instructions, which were pointed out in a recent bench study.[27] The device design was changed (eliminated the Luer-Lok connection between the anesthetic supply line and the syringe; added a specific keyed syringe) and the instructions were modified. To our knowledge, and based on our current clinical practice, no more such incidents should occur.

Potential Costs and Benefits of Inhaled Sedation in the ICU

Overall, in our 15-patient group there was no significant difference in daily sedation cost between the 2 sedation protocols, but in a selected subgroup inhaled sedation cost less. Moreover, our cost evaluation included daily change of both the AnaConDa and the gas-scavenging setup, whereas in routine practice in our ICU both these devices may be used for a mean of 48 hours, with constant efficacy, which may double the cost benefit. We did not measure indirect cost benefits such as shorter weaning or ICU stay, from faster awakening with isoflurane.

Practical Issues About Routine Prolonged Isoflurane Sedation

The use of the AnaConDa is conceptually simpler than an anesthesia machine for non-anesthesia-trained physicians and nursing staff. Sedative dosage is adjusted simply by changing the infusion rate, which is analogous to the method with intravenous sedatives. If contraindications (the most important being hemodynamic instability) are absent, inhaled anesthesia can be delivered via the AnaConDa to any ventilated patient.

Discussion about other sedatives with shorter-duration effect (eg, propofol, remifentanyl) would have been interesting, but those are not conventional sedatives in most European and French ICUs.[28,29]

Another major concern is our Ramsay-score goals, which can be considered particularly deep, and the effective Ramsay score for patients who received isoflurane, which was usually 6, whereas the greatest difference in awakening time was clearly observed with deep sedation (Ramsay scores ≥ 4).[30] If a common sedation target is a calm patient who can be easily awoken,[31] then the appropriate target sedation depends primarily on the patient's acute disease process. Some patients require deeper sedation during the initial phase of treatment to facilitate mechanical ventilation, decrease oxygen consumption, and avoid inadvertent removal of devices and catheters.[32,33] For that reason our routine protocol recommends deep sedation during the initial medical management of selected patients (eg, cerebral trauma, acute respiratory distress). Per protocol, our subjects all received deep sedation at isoflurane initiation.

In most cases, patients under isoflurane sedation could be considered over-sedated, whereas we found that level of sedation was considered greater success in meeting the sedation goal. Such potential over-sedation was already pointed out in a previous study. The percent of time above the target sedation score (over-sedation) was $44 \pm 26\%$, as compared to $37 \pm 33\%$ under midazolam (difference not significant).[8] However, even in those cases, as in patients who required the longest sedation (up to 15 d), awakening from isoflurane was < 4 hours.

Because of their severity of illness at inclusion, no daily sedation-cessation (as advocated by Kress et al[3]) was initially performed. However, after stabilization and decrease in Ramsay score, daily sedation-cessation was performed until weaning. This sedation-cessation strategy is facilitated by isoflurane's rapid offset and onset.

Limitations

This study was designed as an open pragmatic evaluation of a new device that is not routinely used in most ICUs but could be promising, according to previous studies. The open nature of the study may have induced several biases, and we did not have a comparison group, so we must be cautious about inferences about efficacy and safety.

The Ramsay score has been criticized for its lack of clear discrimination between the various levels of sedation.[31] Nevertheless, given the facts that it has acceptable inter-rater reliability (compared to other scales), it has been used in many comparative trials, and it is widely used in ICUs, we choose the Ramsay scale as our evaluation tool for our routine sedation protocol.

Adequate cost and efficacy evaluations would require a prospective randomized trial. Without a wash-out period or random assignments, a carry-over effect may have been responsible for the seemingly greater efficacy of isoflurane sedation during the initial isoflurane period. However, the sedation goal was reached during the overall sedation period with isoflurane, whereas the sedation goal was not reached in all patients with midazolam. For the same reason, the duration of isoflurane administration was highly variable in our study, depending on the patient's clinical status and the proportion of total ICU time on isoflurane. After initiating isoflurane, isoflurane was the main anesthetic used and was continued in most of the

patients until weaning or death. Only a few patients (< 10%) were returned to intravenous sedation after weaning failure and re-intubation. Subgroup analysis must be considered with great caution, but clearly reflects the "real-life" situation: when a patient is very difficult to sedate, isoflurane easily and cost-effectively attains the sedation goal.

Four of the 15 patients were receiving neuromuscular blockers before initiation of isoflurane, and in those patients sedation-depth evaluation could be considered not feasible. However, in those patients the decision to initiate isoflurane was based on failure of sedation and neuromuscular blockade. After isoflurane initiation, neuromuscular blockers were stopped in 2 patients and maintained in 2 others, according to individual practitioner preference.

Conclusions

Routine ICU isoflurane sedation with the AnaConDa is easily feasible, efficacious, safe, and provides rapid onset and offset. Isoflurane is highly effective, and in this study it succeeded in sedating certain patients who failed our conventional sedation protocol. Isoflurane significantly decreases sedation cost in some patients. In our ICU we now use isoflurane as a standard sedation tool in certain cases, especially when deep sedation is required during the initial phase of care.

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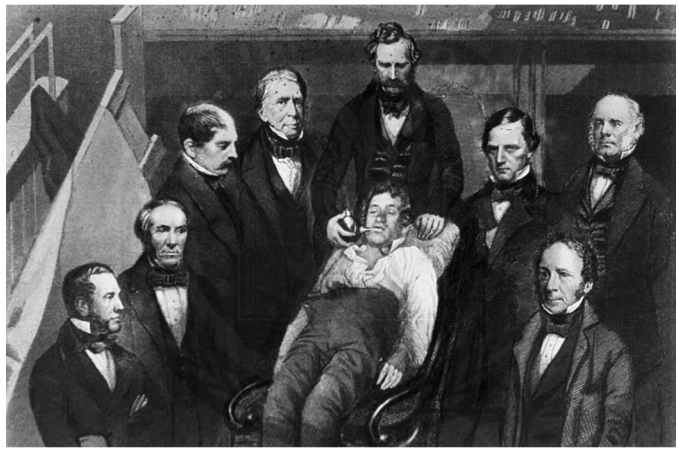

Morton demonstrating the administration of ether
at Massachusetts General Hospital, Boston, Massachusetts
October 16, 1846
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