LEADING ARTICLE

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Inhalation Anaesthetics as Sedatives in the Intensive Care Unit

Do They Have a Role?

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Abstract

Many different drugs are used for sedation of patients in the intensive care unit (ICU). The vast majority of the agents used are administered intravenously; however, for the purposes of sedation, inhalational anaesthetic agents have some advantages, and potential disadvantages, over intravenous drugs. There has been some published work on the use of isoflurane as a sedative agent in this situation, with favourable comparisons with the currently used intravenous drugs. Ultimately, the role of inhalational agents as sedatives in the ICU will depend on the development of appropriate equipment and the enthusiasm of the clinicians involved.

Most critically ill patients who are mechanically ventilated in intensive care units (ICUs) require sedation to minimise the perception of, and the stress responses to, noxious stimuli. Sedative drugs used for these patients must be well tolerated with no adverse effects on any organ system. Ideally, they should sedate patients to a desired level for the required duration and have a short recovery period to facilitate weaning and early extubation or to enable regular neurological assessment. Traditionally, a variety of intravenous agents are used,[1] but each agent has some unwanted effects and other disadvantages. However, it is unrealistic to expect a single sedative agent to meet the different requirements of the multitude of critically ill patients.

For many years, inhalational anaesthetic agents have been used intermittently to provide analgesia and sedation in mechanically ventilated patients in the ICU. These drugs have the distinct advantage of being administered and almost exclusively excreted through the lungs. Unlike intravenous sedatives, which depend on liver metabolism or renal excretion for elimination, the cumulative effects after prolonged administration of inhalational agents are minimal, and recovery from inhalational sedation is both rapid and predictable. Any adverse effects arising from an overdose of an inhalational anaesthetic agent can be rapidly reversed by a reduction of its inspired concentration. Furthermore, the muscle relaxant effects of inhalational agents such as isoflurane may reduce the need for intravenous neuromuscular blocking agents during mechanical ventilation. Many inhalational agents have specific advantages in patients with asthma and chronic obstructive airways disease, and they have been used to treat patients in status asthmaticus in the ICU.[2-4]

1. Available Inhalational Agents

1.1 Nitrous Oxide

Nitrous oxide is the oldest inhalational agent in current use. It has very low blood/gas and oil/gas partition coefficients, and therefore the onset of and recovery from sedation induced by this agent are rapid. It is also a potent analgesic and, premixed with oxygen in a 50 : 50 mixture (as 'Entonox'), it

is widely used to provide pain relief in many areas of clinical practice.

Nitrous oxide interferes with the metabolism of vitamin B12 and inhibits methionine synthase activity,[5] leading to bone marrow depression and polyneuropathy. These toxic effects are known to occur after relatively short exposures in critically ill patients.[6] Nitrous oxide can also induce acute expansion of air-filled spaces within the body. This could cause distension of the bowels, with resultant difficulty of ventilation, and life threatening expansion of an acute pneumothorax,[7] which is a recognised complication in mechanically ventilated patients. Thus, the routine use of nitrous oxide for analgesia and sedation in critically ill patients is no longer recommended.

1.2 Halothane

Halothane is a halogenated hydrocarbon and a potent inhalational anaesthetic. Although it has been used in the treatment of tetanus[8] and status asthmaticus, there are important drawbacks to its use for sedation in the ICU. Halothane causes a dose-dependant depression of myocardial contractility, leading to bradycardia and hypotension. It also sensitises the myocardium to the arrhythmogenic effects of endogenous and exogenous catecholamines and other drugs such as aminophylline. The potential for such drug interactions in critically ill patients is high. The other major disadvantage of halothane is its association with fulminant hepatic failure.[9]

1.3 Enflurane

Enflurane, a fluorinated methyl ethyl ether, is a commonly used agent in anaesthetic practice. Like halothane, however, it is not the inhalational agent of choice for sedation in the ICU. Seizure activity can be induced when enflurane is used in high concentrations in the presence of hypocapnia. The metabolism of enflurane generates a modest amount of inorganic fluoride, which was implicated in causing nephrotoxicity associated with methoxyflurane if levels of the ion reached 50 μmol/L.[10] Prolonged enflurane anaesthesia has led to elevated fluoride levels and evidence of impaired urine concentrating ability.[11,12] Patients at particular risk of fluoride ion nephropathy are those: (i) with pre-existing renal impairment; (ii) receiving enzyme-inducing drugs; (iii) who are severely obese; or (iv) who are receiving other nephrotoxic drugs. Many critically ill patients belong to these patient groups.

1.4 Isoflurane

Isoflurane is a methyl ethyl ether with a lower blood/gas partition coefficient than halothane or enflurane. The onset of and recovery from sedation, and adjustment of depth of sedation, are therefore rapid. The pungency of isoflurane has not been reported as being a problem in this situation.

Unlike enflurane, seizure activity is not induced in patients anaesthetised with isoflurane and, unlike halothane, isoflurane is not associated with hepatotoxicity and does not predispose the myocardium to arrhythmias.[13,14] Isoflurane does cause a dose-dependant decrease in myocardial contractility, but cardiac output is maintained by a drop in systemic vascular resistance and an increase in heart rate. At ≤1.0 MAC (minimum alveolar concentration), isoflurane has minimal effects on cerebral blood flow (CBF) and autoregulation of CBF is retained.[15] Although it has been suggested that isoflurane may produce a 'coronary steal' phenomenon by redistributing blood flow in patients with fixed coronary stenotic lesions,[16] this is unlikely to occur at sedative doses.[17]

Like halothane and enflurane, isoflurane may prevent or reverse bronchospasm by a variety of mechanisms,[18] leading to potentially beneficial effects in mechanically ventilated patients. As only 0.2% of an absorbed dose of isoflurane undergoes biotransformation, inorganic fluoride ion nephrotoxicity is unlikely. The effects of isoflurane on the different body systems are summarised in table I. Given its properties, isoflurane is a suitable agent for sedating mechanically ventilated patients in the ICU.

1.5 Desflurane and Sevoflurane

Desflurane and sevoflurane are newer inhalational anaesthetics which were introduced into clinical

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practice in the 1990s. Both agents have very low blood/gas partition coefficients with a rapid onset of and recovery from anaesthesia. Compared with isoflurane, an even smaller absorbed dose of desflurane (0.02%) is metabolised and the risk of toxic metabolites is very remote. However, desflurane has a low boiling point (23.5°C) and specially heated vaporisers are required for its administration.

When used with a high fresh gas flow, the costs of both desflurane and sevoflurane are high, although using desflurane with a closed circuit ventilator with soda lime would certainly make it less costly. Also, low flow rates could be used with a closed circuit ventilator which would reduce the costs. This would, however, increase the complexity of the equipment required in the ICU, and there are concerns regarding the accumulation of trace gases with prolonged closed circuit ventilation.[20] In addition, the use of sevoflurane with a closed circuit ventilator is inadvisable as the drug is unstable in soda lime and the degradation product (fluoromethyl-2,2 difluoro-1-vinyl-ether) is potentially toxic to humans. About 3 to 5% of sevoflurane is biotransformed and levels in excess of 50 μmol/L of inorganic fluoride have been measured, although the effect of this on renal function in the ICU patient is unclear. Neither desflurane or sevoflurane have been studied for sedating critically ill patients requiring mechanical ventilation.

2. Clinical Experience with Isoflurane Sedation

2.1 Efficacy and Safety

Several studies have demonstrated the efficacy and safety of isoflurane sedation in mechanically ventilated patients who have a range of severity of illness in different ICUs.[21-24] In these studies, the effective dose of isoflurane for sedating ventilated patients was confined to a narrow range (0.1 to 0.8%). The isoflurane vaporiser was initially set to deliver a concentration of about 0.4% and then subsequently adjusted according to clinical signs to achieve a desired level of sedation. Isoflurane sedation was discontinued when the decision to start weaning was made. When patients became alert with an adequate gag or swallow reflex, they were allowed to breathe spontaneously on a T-piece. Patients were extubated when they met the unit criteria for extubation. The results from the above studies have shown that patients were maintained

Table I. Effects of isoflurane on different body systems

System	Effect	Potential advantage/disadvantage
Cardiovascular system	No predisposition to arrhythmias	No potentiation of this when used with inotropes
	Some reduction in contractility but counteracted by reduced systemic vascular resistance and compensatory tachycardia	Potential disadvantage in patients in extremis, and unable to increase heart rate. Not found to be a problem in clinical studies to date
	Coronary steal phenomenon	Potential disadvantage in patients with coronary artery disease, but not seen in clinical anaesthetic practice, and unlikely to occur at sedative doses
Respiratory system	Prevents/reverses bronchospasm	Beneficial in patients with reversible airway disease
	May reduce pulmonary vascular resistance	Potential benefit in patients with primary pulmonary hypertension[19]
CNS	Anaesthetic effect (low blood/gas solubility of isoflurane)	Rapid recovery and adjustment of depth of sedation
	Levels of 1.0 MAC or lower have minimal effect on CBF	Cerebral autoregulation is maintained
	Reduction of $CMRO_2$	Advantage in patients with head injury
	No induction of seizure activity	Suitable for use in patients with epilepsy
Hepatic system	Maintenance of splanchnic circulation	Not detrimental to hepatic or gut perfusion. Not associated with hepatic toxicity
Renal system	Minimal biotransformation to inorganic fluoride ion	Not associated with nephropathy

CBF = cerebral blood flow; **$CMRO_2$** = cerebral metabolic rate and oxygen consumption; **MAC** = minimum alveolar concentration.

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Table II. Recovery profile in patients after stopping isoflurane, midazolam or propofol sedation[21-23]

After stopping sedation	Isoflurane	Midazolam	Propofol
Time to extubation			
No. of patients	14	13	
Median (range) [mins]	60 (30-135)	195 (50-1080)*	
Time to writing home address			
No. of patients	22	24	
Median (range) [mins]	60 (20-4260)	1260 (120-4320)**	
Time to writing name			
No. of patients	7		5
Median (range) [mins]	10 (2-30)		15 (1-300)

* $p < 0.01$; ** $p < 0.001$.

at a desired level of sedation for most of the total time under sedation and that isoflurane was significantly superior to midazolam in this regard.

The main advantages of the use of volatile agents over intravenous agents is the speed with which the level of sedation can be adjusted and the lower inter-individual variability in the dose required. The use of vaporisers allows the delivered concentration to be adjusted very rapidly, comparable with changing an infusion rate for an intravenous agent. There is the additional advantage of the facility to monitor the end-tidal agent partial pressure which gives a real-time indirect measure of the brain tissue partial pressure (effector site).[25] This allows a desired level of sedation to be reached and maintained without any overshoot.

The steeper dose-response curve with volatile agents would indicate a more consistent time to the onset of sedation and less variability in the doses required. This is consistent with the results obtained in studies which compared isoflurane with intravenous agents.[21-23]

The low rate of metabolism and the absence of active metabolites would be expected to result in a more rapid and reliable offset of the sedative effect of isoflurane on discontinuation. Studies comparing isoflurane with midazolam[21,22] support this view and demonstrated faster weaning from mechanical ventilation and extubation (table II). In the study comparing isoflurane with propofol[23] there was a trend in favour of the isoflurane group in terms of faster weaning, although the difference was not statistically significant.

2.2 Disadvantages and Potential Problems

As with most intravenous sedative agents, there is an associated fall in systemic arterial blood pressure on commencement of isoflurane sedation. This is not sustained in patients who are not hypovolaemic and who respond adequately to fluids and/or inotropic support.[26]

Isoflurane is biotransformed to a very small extent to the inorganic fluoride ion. In the isoflurane studies which measured fluoride levels, the highest mean level achieved was 25.3 μmol/L after 8.7 MAC hours.[27] Despite the high inorganic fluoride ion levels seen in these critically ill patients, no clinical or biochemical evidence of deterioration in renal function has been observed, and no renal complications attributable to fluoride ion nephropathy following isoflurane sedation have ever been noted. In addition, significant doubt has been cast on the validity of the plasma fluoride level *per se* as the risk factor for nephrotoxicity. Recent work seems to suggest that it is the renal metabolism of methoxyflurane which caused the renal damage, and that neither peak systemic fluoride levels nor duration of fluoride increase can be applied non-selectively to all anaesthetic agents to predict nephrotoxicity.[28]

In the crossover study which compared isoflurane with propofol,[23] 3 patients reported hallucinations during and after the study period. Two of

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these patients developed a reversible peripheral neuropathy. All patients had also received propofol for 24 hours prior to isoflurane sedation. A retrospective study in paediatric patients[29] implicated an association between a reversible neurological dysfunction in these patients and isoflurane sedation. There were, however, serious flaws with this study, and a variety of other sedative agents were also used including fentanyl and midazolam, which have been reported to produce reversible neurological abnormalities. Nevertheless, the safety and efficacy of prolonged isoflurane sedation in children need to be formally assessed and monitored.

Owing to the rapid recovery from isoflurane sedation, temporary disconnection from the ventilator circuit (such as during tracheal suction and chest physiotherapy) may cause problems. This can be overcome by closed circuit suction systems, which do not require disconnection from the circuit, and the use of a short-acting analgesic such as alfentanil just prior to the anticipated noxious stimulus.

Isoflurane has no analgesic properties. For those ICU patients who would predictably require pain relief, it is essential to coadminister an analgesic such as an opioid. In view of the possibility of increased CBF in patients anaesthetised with isoflurane, it should not be used for sedation in patients with head injury until more research in this area has been done.

3. Equipment Required

In order to use volatile anaesthetic agents in the ICU, specific equipment is required to deliver the agents and scavenge the gases.[30] These are not present in the vast majority of units and so intravenous sedation is used almost exclusively. However, most of the equipment is available for use in the operating theatres, and can be adapted.

With the increasing use of nitric oxide,[31] experience of using gaseous agents in the ICU is being obtained. It is of note that equipment has been specifically developed, such as the Pulmivox (Messer UK Ltd) which allows a set concentration of nitric oxide to be delivered and monitored. Thus, if clinicians are convinced that a need exists, it can be anticipated that equipment would be developed to meet that need.

3.1 Equipment for Delivery

Plenum vaporisers are designed to add volatile agents in accurate concentrations to the gases delivered to the patient. However, intensive care ventilators have not been designed to be used with such gases. The only suitable ventilator was the Servo 900B (Siemens, Scandinavia) which is no longer manufactured. Theatre ventilators, on the other hand, are made with exactly this application in mind. There has recently been a convergence in the facilities offered by both types of ventilators. Theatre ventilators now offer pressure control, synchronised intermittent mandatory ventilation (SIMV), and the facility for positive end expiratory pressure (PEEP), such as the Kestrel ventilator (MIE, Exeter, UK). However, as yet, no such ventilator has the facility to provide patient-triggered pressure support, which is a commonly used mode for weaning patients from mechanical ventilation in the ICU.[32]

An alternative is to use a drawover vaporiser which can be used with most intensive care ventilators, and is placed in the patient breathing system, distal to the ventilator. In a laboratory study,[33] the Oxford Miniature Vaporiser (OMV) [Penlon, Oxford, UK] was shown to perform predictably and safely over a clinically useful range of inspired concentrations and airway pressures. Moreover, a modification of this vaporiser has been made for isoflurane (OMV 50), which has a large reservoir and an output range of 0 to 1.2% in 0.1% increments. The only disadvantage of this set-up is that it cannot be used with ventilators which have a recirculation system for the inspired gases (for example the flow-by system). This is because there would then be the potential for the volatile agents to contaminate the ventilator.

3.2 Equipment for Scavenging

Despite legitimate concerns regarding possible occupational hazards to medical and nursing personnel exposed to trace concentrations of volatile

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Table III. Comparative costs of sedative agents in the doses normally used in patients in intensive care units (based on a 70kg adult, with the drug costs obtained from the British National Formulary, March 1999[35]) [reproduced with permission from Kong[36]]

Agent	Dosage rate	Cost per hour (£, 1999 values)
Isoflurane	0.1-0.4% inspired	0.71-2.90
Midazolam	0.02-0.2 mg/kg/h	0.12-1.19
Morphine	0.5-5.0 mg/h	0.02-0.20
Propofol	1-3 mg/kg/h	1.36-4.07
Alfentanil	0.05-2.0 μg/kg/min	0.11-4.45

anaesthetic agents, an extensive review concluded that there was no clear evidence of adverse effects.[34] British and European legislation do, however, set minimum acceptable concentrations of volatile anaesthetic agents in the environment,[30] and there are many scavenging systems available to comply with these standards.

Piped scavenging systems should be used when available, although this is usually installed in the building of an ICU. There are portable powered scavenging units which pump the gases through a duct in the wall or window, such as the Purair 500 (MEC, Medical Gas Systems, Bedfordshire, UK; complies with BS 6834). Alternatively, there is the Cardiff Aldasorber (Shirley-Aldred, Worksop, UK) which is connected to the expiratory limb of the ventilator. It contains a canister of 1kg of activated charcoal, which is capable of adsorbing 200g of isoflurane and, at the concentrations used, would need refilling every 12 to 24 hours.

4. Costs

The use of inhalational agents is not inexpensive and, based on an average inspired dose of 0.1 to 0.4% isoflurane, the estimated costs are between £1 and 3 per hour (1999 values). These amounts are slightly more than the intravenous agents such as midazolam and morphine, but are directly comparable with propofol and alfentanil infusions which are commonly used for ICU sedation (table III).

5. Conclusions

There is no doubt that most patients who are ventilated can be sedated with an opioid infusion, supplemented, if necessary, with incremental doses of a benzodiazepine. In postoperative patients, adequate analgesia is of paramount importance. However, some patients are more difficult to sedate to a desired level with these conventional approaches and an alternative agent such as isoflurane can have a role.

Patients who develop multiple organ failure form an increasingly large proportion of patients treated in the ICU. All the intravenous sedative agents can be expected to accumulate in this group of patients. In particular, morphine must be used with extreme caution in patients with renal failure due to the accumulation of active morphine metabolites. From the pharmacokinetic point of view, an inhalational agent such as isoflurane would seem an ideal sedative for these patients. The easily controllable dose-related level of sedation and the rapid recovery from inhalational sedation are particularly useful in patients who require a period of postoperative intensive care and stabilisation before tracheal extubation, such as postoperative cardiac surgical patients.[37] In severe asthma, isoflurane may have a specific role due to its bronchodilatory effects. Inhalational anaesthetics are also useful in facilitating treatment procedures in ICU such as bronchoscopy, the insertion of chest drains and invasive monitoring procedures by providing sedation ranging from a light level to that approaching a general anaesthetic.

The definitive role of inhalational anaesthetics as sedatives in the ICU will depend on the enthusiasm of intensive care clinicians and the development of more convenient methods of administration.

References

1. Bion JF, Ledingham IM. Sedation in intensive care: a postal survey [letter]. Intensive Care Med 1987; 13 (3): 215-6
2. O'Rourke PP, Crone RK. Halothane in status asthmaticus. Crit Care Med 1982; 10: 341-3
3. Bierman MI, Brown M, Muren O, et al. Prolonged isoflurane anaesthesia in status asthmaticus. Crit Care Med 1986; 14: 832-3
4. Revell S, Greenhalgh D, Absalom SR, et al. Isoflurane in the treatment of asthma. Anaesthesia 1988; 43: 477-9

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5. Sharer NM, Nunn JF, Royston JP, et al. Effects of chronic exposure to nitrous oxide on methionine synthase activity. Br J Anaesth 1983; 55: 693-701
6. Amos RJ, Amess JAL, Hinds CJ, et al. Incidence and pathogenesis of acute megaloblastic bone-marrow change in patients receiving intensive care. Lancet 1982; 2: 835-9
7. Eger EI II, Saidman LJ. Hazards of nitrous oxide anesthesia in bowel obstruction and pneumothorax. Anesthesiology 1965; 26: 61-6
8. Prys-Roberts C, Corbett JL, Kerr JH, et al. Treatment of sympathetic overactivity in tetanus. Lancet 1969; I: 542-6
9. Wright R, Eade EO, Chisholm M, et al. Controlled prospective study of the effect on liver function of multiple exposures to halothane. Lancet 1975; I: 817-20
10. Mazze RI. Fluorinated anaesthetic nephrotoxicity: an update. Can Anaesth Soc J 1984; 31 Suppl.: s16-22
11. Mazze RI, Calverley RK, Smith NJ. Inorganic fluoride nephrotoxicity: prolonged enflurane and halothane anaesthesia in volunteers. Anesthesiology 1977; 46: 265-71
12. Oikkonen M. Isoflurane and enflurane in long anaesthesias for plastic microsurgery. Acta Anaesthesiol Scand 1984; 28: 412-8
13. Stoelting RK, Blitt CD, Cohen PJ, et al. Hepatic dysfunction after isoflurane anesthesia. Anesth Analg 1987; 66 (2): 147-53
14. Johnston RR, Eger II EI, Wilson C. A comparative interaction of epinephrine with enflurane, isoflurane and halothane in man. Anesth Analg 1976; 55 (5): 709-12
15. Eintrei C, Leszniewski W, Carlsson C. Local application of 133Xenon for measurement of regional cerebral blood flow (rCBF) during halothane, enflurane and isoflurane anesthesia in humans. Anesthesiology 1985; 63 (4): 391-4
16. Reiz S, Balfors E, Sorensen MB, et al. Isoflurane: a powerful coronary vasodilator in patients with coronary artery disease. Anesthesiology 1983; 59: 91-7
17. Reiz S. Myocardial ischaemia associated with general anaesthesia. Br J Anaesth 1988; 61: 68-84
18. Hirshman CA, Bergman NA. Factors influencing intrapulmonary airway calibre during anaesthesia. Br J Anaesth 1990; 65: 30-42
19. Cheng DCH, Edelist G. Isoflurane and primary pulmonary hypertension. Anaesthesia 1988; 43: 22-4
20. Morita S, Latta W, Hambro K, et al. Accumulation of methane, acetone, and nitrogen in the inspired gas during closed-circuit anesthesia. Anesth Analg 1985; 64: 343-7
21. Kong KL, Willatts SM, Prys-Roberts C. Isoflurane compared with midazolam for sedation in the intensive care unit. BMJ 1989; 298: 1277-80
22. Spencer EM, Willatts SM. Isoflurane for prolonged sedation in the intensive care unit; efficacy and safety. Intensive Care Med 1992; 18: 415-21
23. Millane TA, Bennett ED, Grounds RM. Isoflurane and propofol for long-term sedation in the intensive care unit. Anaesthesia 1992; 47: 768-74
24. Appleyard TN, Hewlett A, Konieczko K, et al. Isoflurane sedation – a multi-centre study of 55 patients. Clin Intensive Care 1994; 5: 212-6
25. Eger EI, Saidman LJ, Brandstater B. Minimum alveolar anaesthetic concentration: a standard of anesthetic potency. Anaesthesiology 1965; 26: 756-63
26. Kong KL. The use of isoflurane for sedation of ventilated patients in the intensive therapy unit – a comparative study with midazolam [MD thesis]. Bristol: University of Bristol, 1991
27. Spencer EM, Willatts SM, Prys-Roberts C. Plasma inorganic fluoride concentrations during and after prolonged (>24 h) isoflurane sedation: effect on renal function. Anesth Anag 1991; 73: 731-7
28. Kharasch ED, Hankins DC, Thummel KE. Human kidney methoxyflurane and sevoflurane metabolism. Intrarenal fluoride production as a possible mechanism of methoxyflurane nephrotoxicity. Anesthesiology 1995; 82 (3): 689-99
29. Kelsall AWR, Ross-Russell R, Herrick MJ. Reversible neurologic dysfunction following isoflurane sedation in pediatric intensive care. Crit Care Med 1994; 22: 1032-4
30. Health and Safety Executive. Control of Substances Hazardous to Health (COSHH) requirement for anaesthetic agents. In: Occupational exposure limits 1999. Sudbury: HSE Books, 1999. (COSHH Series EH 40/96)
31. Beloucif S, Payen D. A European survey of the use of inhaled nitric oxide in the ICU. Working Group on Inhaled NO in the ICU of the European Society of Intensive Care Medicine. Intensive Care Med 1998; 24 (8): 864-77
32. Esteban A, Alia I. Clinical management of weaning from mechanical ventilation. Intensive Care Med 1998; 24 (10): 999-1008
33. McIndoe AK, Stewart P, Wilson IH. Drawover vaporizers for sedation in intensive care. Intensive Care Med 1997; 23: 704-7
34. Spence AA. Environmental pollution by inhalational anaesthetics. Br J Anaesth 1987; 59: 96-103
35. British National Forumlary. London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 1999 Mar
36. Kong KL. Inhalational anesthetics in the intensive care unit. In: Cheng EY, editor. Critical care clinics – sedation of the critically ill patient. Vol. 11. No. 4. Philadelphia (PA): Saunders, 1995: 899
37. Beechey APG, Hull JM, McLellan I, et al. Sedation with isoflurane. Anaesthesia 1988; 43: 419-20

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