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Isoflurane for prolonged sedation in the intensive care unit; efficacy and safety*

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Abstract. *Objective:* To compare isoflurane with midazolam for prolonged sedation in ventilated patients. *Design:* Randomised controlled study. *Setting:* General intensive care unit in university teaching hospital. *Patients:* Sixty patients aged 17–80 years who required mechanical ventilation for more than 24 h. *Interventions:* Sedation with either 0.1–0.6% isoflurane in an air-oxygen mixture (30 patients) or a continuous infusion of midazolam 0.02–0.20 mg/kg/h (30 patients). Sedation was assessed initially and hourly thereafter on a six point scale. The trial sedative was stopped when the patient was ready for weaning from ventilatory support. *Measurements and results:* Measurements were made of haemodynamic, respiratory and biochemical variables regularly during the period of sedation and for a week after stopping the sedative agent. There was no difference in any of the physiological or biochemical variables recorded between the two groups. Patients sedated with isoflurane recovered more rapidly and were weaned from mechanical ventilation sooner than those sedated with midazolam. *Conclusions:* Isoflurane is a useful agent for prolonged sedation of ventilated patients and does not have any adverse effect on the cardiorespiratory system or on hepatic, renal or adrenal function.

Key words: Anaesthetics – Isoflurane – Intensive care – Sedation

Patients requiring artificial ventilation of the lungs in the intensive care unit usually need some form of sedation and analgesia. They are subjected to continuous stimuli, such as pain after surgery or trauma, discomfort from the presence of a tracheal tube and mechanical ventilation, and fear from life-threatening illness. In addition, intermittent stimuli occur during physiotherapy, tracheal suction, invasive procedures and general nursing care. Sedative drugs used in the intensive care unit should be quick acting so that sedation can be easily controlled and of short duration to allow rapid recovery for neurological assessment and early weaning from ventilatory support. Many different drugs currently used have disadvantages due to prolonged and variable elimination half-lives of the drug or its metabolites. Propofol has been shown to be a useful sedative agent [1] but it can cause cardiovascular depression [2, 3].

The physio-chemical properties of isoflurane suggest that it might approximate the ideal sedative agent [4]. Its blood-gas solubility coefficient of 1.4 (at 37 °C) facilitates the control of sedation, and ensures rapid recovery. Biodegradation is minimal so nephrotoxicity and hepatotoxicity are unlikely. The elimination of isoflurane is independent of normal renal and hepatic function as it is rapidly excreted unchanged by the lungs. A recent study has shown that isoflurane is a useful agent for sedating ventilated patients with a range of severity of illness [5]. Kong compared the effects of subanaesthetic concentrations of isoflurane with those of a continuous intravenous infusion of midazolam for a mean duration of 18 h. The quality of sedation and the speed of recovery were better with isoflurane than with midazolam. In the absence of hypovolaemia, 0.1–0.5% isoflurane did not cause significant haemodynamic instability.

The purpose of our study was to evaluate the efficacy and safety of isoflurane as a sedative in comparison with midazolam for a period of greater than 24 h in patients in a general intensive care unit.

Methods

The study was approved by the Bristol and Weston District Ethics Committee. Informed written consent was obtained from the next of kin before the patient was admitted to the study. After baseline investigations, 60 critically ill adult patients who were expected to require controlled ventilation and sedation for longer than 24 h were allocated randomly to receive either isoflurane or midazolam. Patients were excluded from

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the study if there was any evidence of intracranial pathology, contraindication to opioid or benzodiazepines, or gross obesity (>150% of ideal body weight).

The severity of illness in individual patients was assessed daily using the Apache II score [6]. Patients who required analgesia when they were moved from the operating theatre were given increments of intravenous morphine. During the period of sedation, patients' requirements for analgesia were assessed either by talking to the patient or by autonomic signs (tachycardia and lacrimation), and intravenous incremental doses of morphine (0.05 mg/kg) were given as required. Intravenous doses of morphine were also given just before anticipated noxious stimulation such as chest physiotherapy. The dose and time of all increments of morphine were recorded.

All patients were intubated and ventilated mechanically with a Servo 900B ventilator. The tidal volume delivered was 8–15 ml/kg body weight at a respiratory rate necessary to maintain the arterial CO_2 tension between 4–5 kPa. The inspired oxygen concentration was adjusted to maintain an arterial oxygen tension >10 kPa, and positive end-expiratory pressure was added as necessary.

Sedation

The degree of sedation was assessed initially and hourly thereafter on a scale modified from Ramsay [7]. Score 1 represents inadequate sedation, scores of 2, 3, and 4 are acceptable degrees of sedation, and scores of 5 and 6 indicate that patients are too deeply sedated. At the same times, an assessment of the response to the specific command, "Squeeze my hand", was made. The dose of sedative was adjusted to maintain the patient cooperative, orientated and tranquil or asleep but responding to a loud auditory stimulus for as much of the time as possible. Patients were not scored if they had received neuromuscular blocking drugs. The patient was sedated for as long as was clinically indicated, and the sedative drug was discontinued when the patient was fit for weaning.

Midazolam was prepared as a 0.1% solution and was given at a rate of 0.05–0.1 mg/kg/h; a bolus dose of up to 0.1 mg/kg was given initially if indicated. Subsequently the infusion rate was adjusted according to clinical signs. The rate of infusion of midazolam was recorded hourly and any changes made in the infusion rate of midazolam were noted.

Isoflurane was added continuously to the inspired air-oxygen mixture using a Siemens' isoflurane vaporizer 952 mounted distal to the oxygen/air blender on a Siemens-Elema Servo 900B ventilator. Initially the vaporizer setting was adjusted to deliver an inspired isoflurane concentration of 0.2%. Thereafter the vaporizer setting was adjusted to maintain an end-tidal isoflurane concentration of between 0.1–0.6% according to clinical signs. The inspiratory and end-tidal concentrations of isoflurane delivered were monitored using a Siemens' Servo Gas Monitor 120 and were recorded hourly. Any changes made in the concentration of isoflurane delivered were noted. The expired gas from the patient was scavenged via the expiratory port of the Servo Ventilator into Cardiff Aldasorbers.

At the end of the administration of the sedative agent, responsiveness was tested to determine how soon after the sedation was discontinued the patient could obey the simple command "Squeeze my hand" and write down their home address. The time to spontaneous ventilation, defined as the time when the patient was breathing in an assist or CPAP mode without any mandatory breaths delivered by the ventilator, was noted. The time to extubation and the time the patient returned to the ward were also recorded.

Physiological measurements

All patients had their arterial blood pressure continuously monitored by means of an indwelling cannula. The systolic and diastolic arterial pressures, central venous pressure, heart rate, airway pressure, minute ventilation and ventilatory rate were recorded hourly during sedation and every 6 h for the first 48 h after stopping the sedation. Arterial blood gases and pH were recorded every 6 h during and after sedation. Barometric pressure was measured and the alveolar-arterial oxygen tension gradient calculated every 6 h. The end-tidal CO_2 was monitored continuously with an Engstrom Eliza Duo CO_2 analyzer and recorded hourly during the period of endotracheal intubation.

The core and peripheral temperatures were measured before sedation and monitored continuously during the period of study with readings recorded hourly.

Biochemistry

Haemoglobin, packed cell volume, white cell and platelet counts, prothrombin time, thrombin clotting time and activated partial thromboplastin time were measured regularly. Plasma and urinary urea and electrolytes were measured and creatinine clearance calculated. The total intake of blood and other fluids and hourly urine output were recorded. Bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, albumin, globulin, gamma glutamyl transpeptidase and glutathione S-transferase were measured regularly [8]. Plasma cortisol and adrenocorticotrophic hormone (ACTH) concentrations were measured before sedation and every 12 h during sedation. A short intravenous "Synacthen test" was performed at the end of sedation and at 24 h and 48 h later. The "Synacthen test" was not carried out on patients who had received corticosteroids as part of their treatment. Plasma fluoride concentrations were measured regularly [9].

Plasma midazolam concentrations were measured before sedation, every 12 h during sedation, when sedation was discontinued and regularly for 48 h. The midazolam and 1-hydroxy-midazolam concentrations were analysed using high-performance liquid chromatography [10]. Within batch variation for midazolam was 10.1% and for 1-hydroxy-midazolam was 8.1%.

Blood for isoflurane concentrations was taken before sedation, hourly for the first 5 h, at 12 h and then every 12 h during sedation. After sedation was stopped samples were collected every 10 min for the first hour, hourly for 6 h and then at 12 and 24 h. In this study, isoflurane blood concentrations were determined by a one-stage extraction with n-heptane followed by gas-liquid chromatography using electron capture detection [11]. Within batch variation was 13%.

Statistical analysis

Statistical tests used were: analysis of variance, the paired and unpaired *t*-tests, the χ^2 test, the Pearson product moment correlation coefficient and the Spearman Rank Correlation. Most of the biochemical data were skewed and so a logarithmic (base e) transformation was performed before analysis.

Results

Patient details

Sixty patients were admitted to the trial – 30 in each group. All the patients were emergency admissions to the intensive care unit either post-operatively or as acute medical emergencies. Their details are shown in Table 1. There were no significant differences between the groups except that the isoflurane group was slightly younger. The

Table 1. Details of the patients studied in the two groups

	Isoflurane ($n = 30$)	Midazolam ($n = 30$)
Sex (M:F)	19:11	21:9
Surgical: medical	20:10	24:6
Median (range) age (yr)	62 (17–80)	68 (32–77)
Mean (SD) weight (kg)	68 (10)	72 (14)
Median (range) duration of sedation (h)	36 (10–127)	36 (4–104)
Mean (range) admission Apache II scores	12 (1–23)	12 (3–24)
Died during sedation	5	1
Died within one week after sedation	1	4

severity of illness of the patients in the two groups was stratified according to the Apache scores and there was no significant differences between the groups.

Several patients in both groups died either during or within a week after the cessation of the sedation. All the deaths were due to the patients' underlying diseases and were unrelated to the sedative agent.

Several patients needed further surgery and these patients continued in the study on their return to the intensive care unit. Their sedative agent was continued at the same rate during surgery, and anaesthesia was maintained with propofol and increments of morphine. Their sedation scores were started at a suitable time after surgery, when the anaesthesia was considered to have worn off.

One patient in the midazolam group was withdrawn from the study because of a period of circulatory arrest due to a major haemorrhage following a thoraco-abdominal aneurysm repair.

Sedation

The mean (range) concentration of isoflurane used for sedation was 0.27% (0.1–0.4%) and for midazolam was 3.1 (1.5–7.3) mg/h. The mean morphine required was 0.97 mg/h in the isoflurane group and 0.88 mg/h in the midazolam group.

Seven patients (5 in the isoflurane group I and 2 in the midazolam group M) needed neuromuscular blocking drugs for a variable length of time; 3 (2 in group I and 1 in group M) because they had severe respiratory failure and inadequate oxygenation, and 4 patients (3 in group I and 1 in group M) were triggering the ventilator and required short periods of paralysis to establish controlled ventilation.

The overall sedation scores are shown in Table 2. At no time during sedation was there a significant difference between the two groups. Patients were maintained at the ideal level of sedation (between scores 2–4) for 70.07% of time in the isoflurane group and for 67.4% of time in the midazolam group.

Two patients in the midazolam group and one in the isoflurane group were discovered to have suffered cerebrovascular accidents during their illnesses and they were withdrawn from the analysis of recovery. In the midazolam group, 1 patient had been withdrawn; 1 had died on sedation; and 2 required further sedation, 1 for surgery and the other suffered a cardiac arrest in the immediate post-sedation period and required reintubation. In the isoflurane group, 5 had died during sedation and 2 required further sedation.

Therefore 24 patients in the midazolam group and 22 patients in the isoflurane contributed to the analysis of recovery. Three patients were not extubated, 1 in each group because of gross cervical or mediastinal swelling, and 1 patient in the isoflurane group because of a fractured cervical spine.

The recovery results are displayed in Table 3. The time to respond to command, write address, spontaneous ventilation, and extubation were all significantly different between the two groups. There was no difference in the time to return to the ward.

Table 2. Mean (range) time spent at each sedation score for the two groups of patients expressed as a percent of the total time sedated

Sedation level	Isoflurane	Medazolam
1 Anxious and agitated	6.6 (0–25)	8.9 (0–54)
2 Co-operative, accepting ventilation	14.2 (0–67)	18.7 (0–100)
3 Asleep. Brisk response to loud voice	23.0 (0–70)	24.9 (0–62)
4 Asleep. Sluggish response to loud voice	32.8 (4–93)	23.8 (0–70)
5 No response to loud voice	13.3 (0–42)	10.0 (0–76)
6 No response to pain	10.1 (0–53)	13.7 (0–100)

Table 3. The recovery times of the two groups of patients after stopping the sedation; median (range). (**$p<0.001$ between groups)

	Isoflurane	Midazolam
Respond to command (min)	10 (5–180)**	90 (10–3780)**
Write address (h)	1 (0.2–71)**	21 (2–72)**
Spontaneous ventilation (h)	0.25 (0.1–1.0)**	3 (0.17–42)**
Extubation (h)	0.9 (0.2–70)**	15 (1.3–223)**
Return to ward (h)	48.5 (4–600)	50 (7–129)

There was no correlation between the end-tidal isoflurane concentration and the sedation score. Similar analysis was done in the midazolam group but there was no correlation between the infusion rate and the sedation score.

Blood isoflurane concentrations

There was great variation in blood isoflurane concentrations, which did not follow a normal distribution (Table 4). There was no correlation between the blood isoflurane concentration and the sedation score. There was no correlation between the end-tidal and the blood isoflurane concentration.

Plasma midazolam concentrations

There was considerable variability in plasma midazolam concentrations between patients (Table 4). There was no correlation between the sedation score and the plasma midazolam concentration. The half-life of midazolam was calculated for each patient and the mean (95% CLs) was 33.2 (22.8, 43.5) h.

There was a wide range of the plasma concentration of the major metabolite, 1-hydroxy-midazolam seen during and after sedation. There was no correlation between the plasma 1-hydroxy-midazolam concentration and the sedation score or the plasma midazolam concentration.

Physiological measurements

All the cardiorespiratory variables recorded were analysed hourly using an analysis of variance and there were no differences between the groups for any variable at any of the times recorded (Fig. 1). Vasoactive drugs such as dopamine, dobutamine, noradrenaline, glyceryl trinitrate, hydrallazine and labetalol were required in most patients in both groups to maintain haemodynamic measurements within normal limits. A χ^2 test was performed on the

Table 4. The blood concentration of isoflurane and the plasma concentration of midazolam during the period of sedation; median, range and the number (n) of patients in the analysis

Time during sedation (h)	Isoflurane (mcg/ml)			Midazolam (ng/ml)		
	Median	Range	n	Median	Range	n
0	3.6	0–39	29	506	62–5900	26
1	16.36	0.8–90	28	642	100–4600	24
2	13.55	0.7–65	28	940	150–2400	28
3	16.7	0.82–87	24	750	150–2180	22
4	10.8	0.9–113	27	960	62–3200	27
12	18.3	1.4–90	28	900	70–4000	27
18	11.4	1.4–52	14	1000	80–6800	15
24	17.1	1.6–85	25	1150	400–8000	25
30	22.6	1.5–46	5	1250	270–9000	13
36	22.0	1.8–46	15	1410	250–7550	19
48	7.8	1.4–34	6	1150	403–12500	7

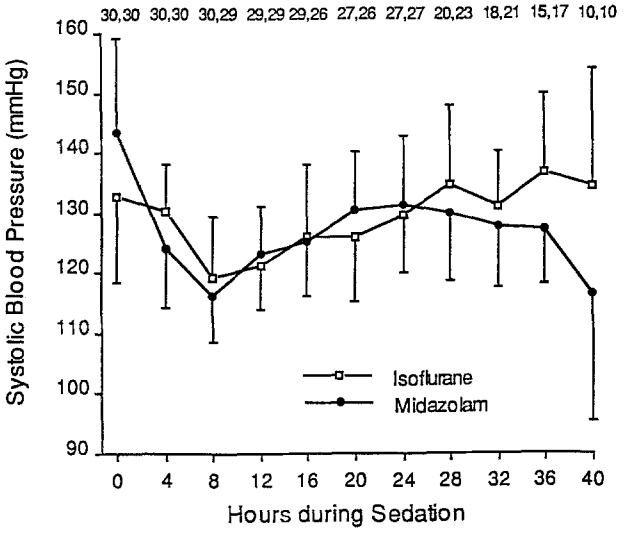

Fig. 1. Mean (95% CL) values of systolic blood pressure during sedation with isoflurane and midazolam. The number in the isoflurane and midazolam groups at each time is printed above

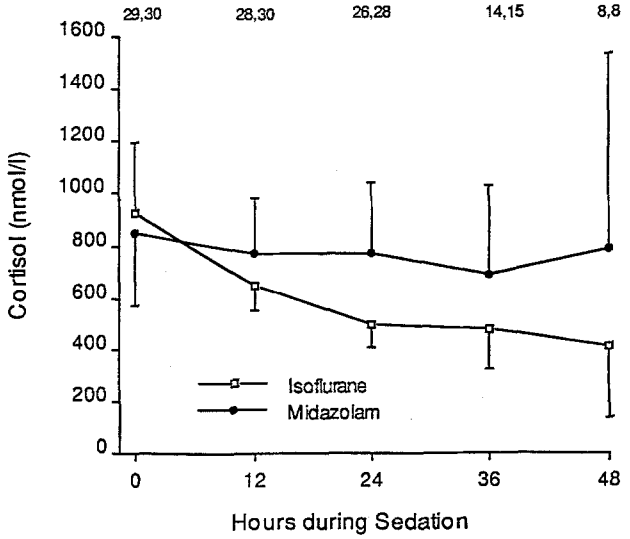

Fig. 2. Mean (95% CL) serum cortisol values (nmol/l) during sedation with isoflurane and midazolam. The number in the isoflurane and midazolam groups at each time is printed above

number of patients in each group on each day of the study who were receiving vasoactive drugs and there were no significant differences between the groups.

There were no differences in the rectal or axillary temperatures between the two groups.

Biochemical measurements

There were no differences in any of the haematological or coagulation tests between the groups during or after sedation. There were no significant differences between the groups in any of the hepatic or renal function tests [8, 9].

There were no differences in ACTH or cortisol concentrations between the two groups (Fig. 2). There were 3 patients in the isoflurane group and two patients in the midazolam group who were receiving steroids and the results from these patients were not included. The cortisol dropped significantly from baseline at 24 and 48 h in the isoflurane but not in the midazolam group (Figs. 3, 4).

The cortisol response to Synacthen was taken as the difference between the baseline and the higher of the 30 and 60 minute samples. It was defined as negative if the serum cortisol concentration rose by less than 250 nmol/l. There were 26 patients in the isoflurane group and 28 in the midazolam group in the analysis, as

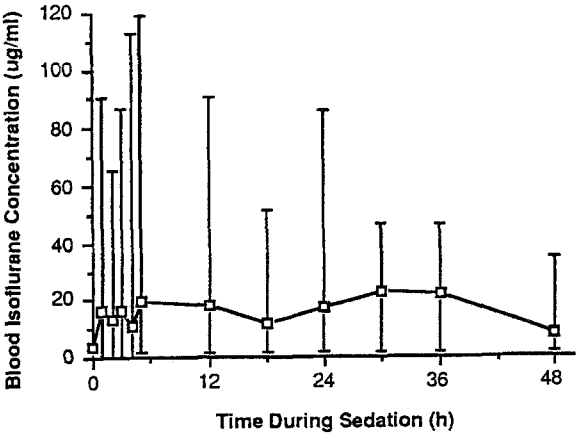

Fig. 3. Blood isoflurane concentrations during sedation for all patients in the isoflurane group, median and range

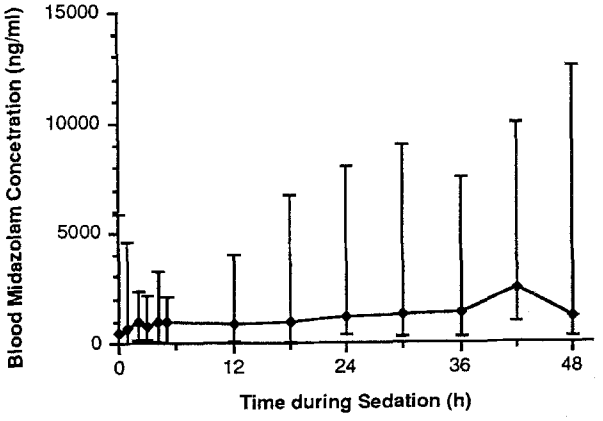

Fig. 4. Plasma midazolam concentrations during sedation for all patients in the midazolam group, median and range

the remainder had either died during sedation or were excluded because of receiving steroid therapy. There was no difference between the groups in the number of positive and negative responses to Synacthen. There was no significant correlation between the admission Apache II score and the baseline cortisol concentration for each patient.

Discussion

The sedation of critically ill patients in the intensive care unit needs constant reappraisal. It is important to avoid excessive sedation and its complications. Isoflurane provides satisfactory sedation in patients requiring mechanical ventilation for less than 24 h [5] but there are no studies of its use for a more prolonged period.

The results of this study illustrate that isoflurane can provide prolonged sedation in patients with a range of severity of illness, as determined by the Apache II scores. The level of sedation was easily and rapidly controlled by changing the inspired isoflurane concentration. The effective dose of isoflurane for sedating ventilated patients has a narrower range (0.13–0.4%) than the requirement for midazolam (0.02–0.11 mg/kg/h).

Kong used isoflurane for a mean period of 18 h [5]. Isoflurane provided satisfactory sedation for 86% of the time compared with 64% for those sedated with midazolam. Our results show no difference between the sedation produced by isoflurane and midazolam. This was expected as the constant attention to sedation scores by the investigator and the nursing staff allowed the rate of sedative agent to be regularly adjusted according to the hourly sedation score.

The dose of isoflurane could be varied between 0.1–0.6% according to clinical signs to achieve sedation at the desired level. In those patients who required a more prolonged period of sedation, there was no need to increase the inspiratory concentration of isoflurane to maintain a satisfactory level of sedation. There has only been one report of tolerance to isoflurane, in a young child [12]. Tolerance to isoflurane has not been observed in mice chronically exposed to low concentrations of isoflurane for up to 63 days [13].

Recovery was faster after discontinuing the isoflurane than after midazolam and patients responded, breathed spontaneously, and were extubated significantly sooner. This rapid recovery sometimes led to agitation and "panic" in the patient. As experience with the agent increased, this was adequately managed by explanation and reassurance.

There was no difference between the two groups in the time to return to the ward. Several factors, other than the respiratory system, determine when a patient is able to return to the ward such as cardiovascular stability, renal function, analgesia requirement and bed-availability.

When the patient was disconnected from the ventilator for physiotherapy rapid awakening could be helpful if the patient coughed spontaneously, but occasionally the patient became agitated and confused. Within the protocol of the project the only agent available for the treatment of this was morphine. A more suitable agent might be alfentanil given just prior to physiotherapy.

Midazolam is widely used in intensive care units and these results demonstrate that it provides satisfactory sedation although the recovery is variable and can be very prolonged. The serum concentrations of midazolam and 1-hydroxy-midazolam were variable during and after sedation both between patients and in individual patients. This agrees with previous work on the variable serum midazolam concentrations required in different patients to produce adequate sedation [14].

There was little correlation between the infusion rate, the serum midazolam concentration and the level of sedation. The elimination half-life of midazolam varied widely from 9–103 h which contrasts with Oldenhof's work in which 12 of his 17 patients had an elimination half-life of less than 10 h. As a result of the varying pharmacokinetics in patients with severe illness, midazolam is probably better given by repeated injections, according to the clinical level of sedation, rather than by continuous intravenous infusion.

There has been no previous work on blood isoflurane concentrations during sedation in the intensive care unit and little on blood isoflurane concentrations during anaesthesia. In this study there were no stable blood isoflurane concentrations achieved and there was considerable variation in the isoflurane concentrations between patients. This may be because the inspired concentration was adjusted according to the clinical sedation score, or it might reflect the wide variability in the pharmacokinetics of isoflurane in critically ill patients, who have different diseases, variable organ function or some degree of encephalopathy. There was a wide range of pulmonary dysfunction in our patients – some had respiratory failure with impaired gas exchange either because of a large shunt or increased deadspace ventilation. This would have resulted in a difference in inspired and alveolar and therefore arterial partial pressure of isoflurane.

No correlation was established between the level of sedation and the end-tidal or blood isoflurane concentration. It has been demonstrated that the end-tidal partial pressure of isoflurane may be used as a measure of anaesthetic depth [15]. However it is the partial pressure of the agent in the brain which is assumed to cause the loss of consciousness and the blood isoflurane concentration may not be a good reflection of this.

There have been some suggestions that isoflurane may have some analgesic properties [16] but we found no difference between the two groups in the amount of morphine required.

It is important when treating critically ill patients not to use drugs that compromise organ function. Haemodynamic stability is difficult to assess in these patients where vasoactive drugs are given frequently to maintain cardiovascular stability. This study shows that neither isoflurane nor midazolam has any deleterious effects on haemodynamic stability when given continuously in a low dose over a long period. There were no signs of myocardial ischaemia on the ECG attributable to the sedative agent. In this respect isoflurane is superior to pro-

pofol where there is a tendency for the patients to become hypotensive [2, 3].

Isoflurane decreases the bronchoconstriction produced by inhaling Ascaris antigen in allergic dogs [17] but has little or no effect on bronchial tone in normal human airways [18]. It has been used for its bronchodilatory properties in the ITU to treat patients with severe asthma and chronic obstructive pulmonary disease [19, 20]. In our study there was no difference between the two groups in airway pressure or any other parameter of respiratory function.

Mild renal dysfunction is difficult to assess in critically ill patients because of their changing haemodynamic status and numerous therapeutic interventions. There was no difference in renal function between the isoflurane group and the midazolam group. However, there were many abnormal results in both groups because of the underlying illness. There is no evidence that isoflurane has a direct adverse effect on the kidney.

Diagnosis of mild liver damage is difficult whether made on clinical, biochemical or histological criteria. The measurement of the hepatic isoenzymes of glutathione S-transferase (GST) is a sensitive and specific method for the detection of acute drug-induced hepatocellular damage [21, 22]. Our study suggests that prolonged administration of either isoflurane or midazolam has no detrimental effects on hepatocellular integrity [8].

There was no evidence in this study to suggest that prolonged isoflurane at these low concentrations could inhibit cortisol production. The levels of cortisol and ACTH and the response to Synacthen were similar in the two groups. All the baseline cortisol levels were high and it was interesting to see that the patients sedated with isoflurane showed a progressive reduction in plasma cortisol concentrations during the period of sedation compared to patients sedated with midazolam who showed no significant reduction in cortisol. It has previously been shown that isoflurane sedation reduces plasma catecholamine concentrations [23].

Although there is no clear evidence that there is an adverse effect on health produced by the working environment [24], scavenging is important in the ITU especially if the air conditioning is not ideal. Many ITUs (like ours) do not have piped scavenging and the most convenient means of scavenging the isoflurane is with Aldasorbers. These are small, convenient and cheap and, with low concentrations of isoflurane, do not require changing more than once in 24 h. The cost of isoflurane is considerable at about £80 (2 bottles) per day. This is similar to other agents currently used for sedation and compared with the overall cost of intensive therapy is negligible.

This study demonstrates that isoflurane is a suitable agent for long-term sedation of patients requiring mechanical ventilation. It provides a satisfactory level of sedation with rapid recovery. Compared to midazolam there is no cardiovascular depression and no deterioration of liver, renal or adrenal function.

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