Isoflurane compared with midazolam for sedation in the intensive care unit

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Abstract

Objective—To compare isoflurane with midazolam for sedation of ventilated patients.

Design—Randomised control study.

Setting—Intensive care unit in university teaching hospital.

Patients—Sixty patients aged 18-76 who required mechanical ventilation.

Interventions—Sedation with either 0·1-0·6% isoflurane in an air-oxygen mixture (30 patients) or a continuous intravenous infusion of midazolam 0·01-0·20 mg/kg/h (30 patients). Sedation was assessed initially and hourly thereafter on a six point scale. Incremental intravenous doses of morphine 0·05 mg/kg were given for analgesia as required. The trial sedative was stopped when the patient was judged ready for weaning from ventilatory support or at 24 hours (whichever was earlier).

End point—Achievement of a predetermined level of sedation for as much of the time as possible.

Main results—Isoflurane produced satisfactory sedation for a greater proportion of time (86%) than midazolam (64%), and patients sedated with isoflurane recovered more rapidly from sedation.

Conclusion—Isoflurane is a promising alternative technique for sedation of ventilated patients in the intensive care unit.

Introduction

Most patients requiring mechanical ventilation in the intensive care unit need sedation to allay anxiety, encourage sleep, facilitate controlled ventilation, minimise distress during uncomfortable procedures, and obtund the physiological responses to stress such as tachycardia and hypertension. All of the many different drugs and combinations of drugs currently used in the United Kingdom for this purpose have disadvantages and side effects, especially when given continuously to critically ill patients. The physicochemical properties of isoflurane (a fluorinated inhalational anaesthetic agent widely used in general anaesthesia) suggested to us that it might approximate closely to the ideal sedative agent. Its low solubility in blood facilitates control of anaesthetic concentrations and therefore the degree of sedation and ensures rapid recovery from both anaesthesia and sedation. The elimination of isoflurane is independent of normal renal and hepatic function, a highly desirable property of a sedative drug for use in the critically ill. Isoflurane is metabolised minimally (0·2%), and therefore nephrotoxicity and hepatotoxicity are unlikely.

In a pilot study of ventilated patients in the intensive care unit isoflurane produced a satisfactory level of sedation most of the time, with a rapid recovery from sedation.[1] We therefore conducted a controlled trial to compare the effects of isoflurane with midazolam for the sedation of ventilated patients with a range of severity of illness in the intensive care unit. We chose midazolam as the comparison drug because it is the sedative used routinely in our unit and widely used elsewhere.

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Patients and methods

Sixty patients aged 18-79 who were admitted to the intensive care unit and who needed mechanical ventilation for at least 12 hours were studied. The study design was approved by the Bristol and Weston district ethics committee. Informed consent for participation in the study was obtained either from the patient or the next of kin. When sedation was required before consent was obtained patients were given intravenous incremental doses of morphine (0·05 mg/kg). Baseline clinical and laboratory assessments were made before the start of the study. Patients were excluded if they were pregnant, had a head injury or were in coma, were already under an established scheme of sedation, had a history of allergic response to morphine or benzodiazepines, were grossly obese, or had uncontrolled haemorrhage.

The severity of illness in each patient was assessed using a modified APACHE II score.[2] All patients were ventilated on a Servo 900B ventilator (Siemens, United Kingdom) to maintain an arterial carbon dioxide tension of 4·0-5·5 kPa. The inspired oxygen concentration was adjusted to maintain an arterial oxygen tension >13 kPa and positive end expiratory pressure was added if necessary. None of the patients received neuromuscular blocking agents during the study period. Concurrent treatments such as blood transfusion, antibiotics, inotropic agents, and diuretics were given as required. Intravenous fluids were given as needed to maintain an adequate central venous pressure. Standard supportive care was provided to maintain patients' body temperature near normal.

SEDATION

On arrival in the intensive care unit patients were allocated randomly to receive either 0·1-0·6% isoflurane in an air-oxygen mixture or a continuous intravenous infusion of midazolam 0·01-0·20 mg/kg/h for sedation. Isoflurane was added to the air-oxygen mixture by a Siemens isoflurane vaporiser 952 (Siemens-Elema AB, Sweden). Gas was sampled from the catheter mount, and the inspiratory and end tidal concentrations of isoflurane were monitored with a Siemens gas monitor 120. The expired gas from the patient was scavenged by the expiratory port of the ventilator and passively discharged outside the unit. Midazolam was given as an 0·1% solution delivered by an infusion pump.

The degree of sedation was assessed initially and hourly thereafter on a scale modified from Ramsay and colleagues, in which a score of 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.[3] The dose of sedative (isoflurane or midazolam) was adjusted within the prescribed limits to maintain the patient as cooperative, oriented, and tranquil or as asleep but responding to a light glabellar tap or a loud auditory stimulus for as much of the time as possible.

The study was limited to 24 hours, and the trial sedative was stopped either when patients were judged ready for weaning from ventilatory support or at 24 hours (whichever was earlier). If sedation was required beyond 24 hours, an alternative scheme was used. Patients' requirements for analgesia were assessed individually either by direct communication with the patient or by observation of autonomic signs, and incremental intravenous doses of morphine (0·05 mg/kg) were given as required and were recorded.

WEANING FROM VENTILATION AND RESPONSIVENESS AFTER SEDATION

Patients were weaned from the ventilator when they were haemodynamically stable, had an arterial oxygen tension >10 kPa at an inspired oxygen concentration of 50%, and had a core body temperature of greater than 36°C. The trial sedative was stopped when the decision to start weaning was made, and patients were allowed to breathe spontaneously through a T piece. When patients were able to maintain a consistent, adequate pattern of ventilation (tidal volume >3 ml/kg, vital capacity >10 ml/kg, respiratory rate <30/min) without any appearance of distress they were extubated. The times from stopping sedation to tracheal extubation were recorded.

Responsiveness after sedation was determined by testing how soon after the trial sedative had been withdrawn the patient could obey the simple command to move the toes and write down his or her home address. Before these responses could be obtained from some patients it was necessary to reintroduce an alternative sedative agent because the patients were agitated or needed continued ventilation. The time interval between stopping isoflurane or midazolam sedation and starting the replacement sedative was measured.

TABLE I—*Details of patients given isoflurane and midazolam*

	Patients given isoflurane	Patients given midazolam
No of men/women	20/10	25/5
No of postoperative surgical patients/ others	27/3	24/6
Median (range) age (years)	67·5 (18·0-79·0)	67·5 (26·0-78·0)
Median (range) weight (kg)	65·0 (37·5-82·0)	70·0 (53·0-86·2)
Median (range) duration of sedation (h)	18·5 (7·0-24·0)	18·0 (10·0-24·0)
Median (range) APACHE II scores[2]	14 (4-28)	13 (0-27)

No significant differences between groups.

TABLE II—*Assessment of sedation and proportion of time at level of sedation for patients given isoflurane and midazolam*

	Clinical score[3]	Characteristics of sedated patient	Mean time under sedation (% of total): Patients given isoflurane	Mean time under sedation (% of total): Patients given midazolam	p Value
Inadequate sedation	1	Anxious and agitated or restless, or both	4	8	NS
Acceptable sedation	2	Cooperative, accepting ventilation, oriented and tranquil	30	10	0·0005
	3	Asleep. Brisk response to light glabellar tap or loud auditory stimulus	30	27	
	4	Asleep. Sluggish response to light glabellar tap or loud auditory stimulus	26	27	
Excessive sedation	5	No response to light glabellar tap or loud auditory stimulus, but responds to painful stimulus	8	17	0·0014
	6	No response to painful stimulus	2	11	

TABLE III—*Time after stopping sedation with isoflurane or midazolam to tracheal extubation, moving toes to command, and writing home address and resedation when necessary*

	Group given isoflurane	Group given midazolam
Stopping sedation to tracheal extubation:		
No of patients	14	13
Median (range) (min)	60 (30-135)	195 (50-1080)
Approximate 95% confidence interval for difference in median	45 to 205	
p Value	0·0016	
Stopping sedation to writing home address:		
No of patients	16	12
Median (range) (min)	58 (20-270)	275 (75-1440)
Approximate 95% confidence interval for difference in median	105 to 390	
p Value	0·0001	
Stopping sedation to moving toes to command:		
No of patients	29	27
Median (range) (min)	0 (0-10)	0 (0-300)
Approximate 95% confidence interval for difference in median	−0·1 to 10·1	
p Value	0·0167	
Stopping trial sedative to need for resedation:		
No of patients	12	14
Median (range) (min)	15 (5-230)	108 (5-490)
Approximate 95% confidence interval for difference in median	45 to 120	
p Value	0·0014	

OTHER 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, and heart rate were recorded before and at hourly intervals after the trial sedative was started.

STATISTICAL ANALYSIS

Nominal data were analysed by the χ^2 test. For other data that could reasonably be assumed to be normally distributed the unpaired t test was used to compare means between groups; otherwise the Mann-Whitney U test was used. Where multiple comparisons were made repeated measures analysis of variance was used.

Results

Thirty patients were included in each group. There were no significant differences between the two groups with regard to sex, age, weight, duration of sedation, and APACHE II scores (table I). Most of the patients were postoperative surgical patients who required ventilatory support. One patient in the group given isoflurane died during the trial period after seven hours of sedation and one patient in the group given midazolam died after 10 hours of sedation; both these deaths were due to fulminant septicaemia.

SEDATION

The average concentration of isoflurane used for sedation was 0·21% (range 0·1-0·4%). The mean infusion rate of midazolam was 3·1 mg/h (range 1·0-9·8 mg/h). The median total doses of morphine given in the two groups of patients were similar: 11·8 mg (range 0-77) in the isoflurane group and 13·3 mg (range 0-41) in the midazolam group.

Table II shows the mean proportion of time spent at any level of sedation. Patients who received isoflurane were satisfactorily sedated (at sedation levels 2, 3, and 4) for a mean of 86% (range 46-100%) of the trial period and those who received midazolam for a mean of 64% (range 8-100%) of the time. This difference was significant (p=0·0005).

WEANING FROM VENTILATION AND RESPONSIVENESS AFTER SEDATION

Fourteen patients who received isoflurane and 13 who received midazolam met the criteria for weaning during the trial period and were successfully weaned and extubated. The median times from stopping sedation to tracheal extubation and to patients writing

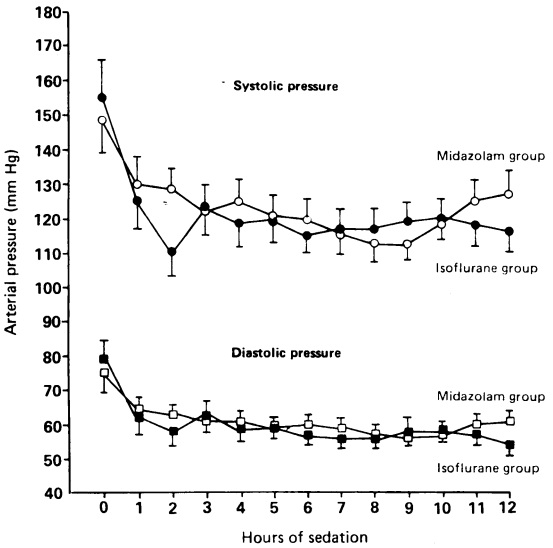

FIG. 1—*Changes in arterial pressure for first 12 hours after patients were sedated. Values are means (SE) of systolic pressure for patients given isoflurane (●) or midazolam (○) and diastolic pressure for patients given isoflurane (■) or midazolam (□)*

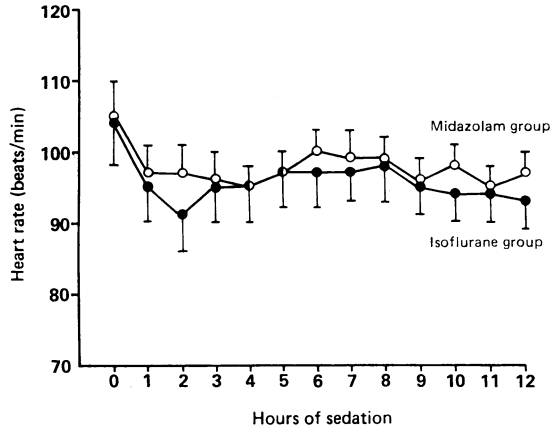

FIG 2—*Changes in heart rate for first 12 hours after patients were given isoflurane (●) or midazolam (○). Values are means (SE)*

their home address were significantly shorter for patients sedated with isoflurane compared with those sedated with midazolam (p=0·0016 and 0·0001, respectively). The median sedation scores when the trial sedative was stopped were 2 in the group given isoflurane and 4 in the group given midazolam. Of those patients who responded, all those sedated with isoflurane moved their toes to command within 10 minutes of sedation being stopped, whereas only 19 of those sedated with midazolam were able to do so. Twelve patients in the group given isoflurane and 14 in the group given midazolam had to be resedated after the trial sedative had been stopped. On average, the group given isoflurane had to be resedated much earlier than the group given midazolam. Table III summarises these findings.

OTHER MEASUREMENTS

There was no significant difference between the two groups in systolic and diastolic arterial pressures, heart rate, and central venous pressure at any of the times of testing. Figures 1 and 2 show changes in systolic and diastolic arterial pressures and heart rate for the first 12 hours of the study.

Discussion

An important concern in treating critically ill patients is to avoid excessive sedation and its complications. Deep sedation is undesirable, and the ideal level of sedation to aim for is that at which the patient is comfortable and from which he or she would rouse spontaneously from sleep or could be roused if required.[4] In line with current opinion we chose sedation scores of 2, 3, and 4 as acceptable levels of sedation[3] and aimed to maintain our patients at these levels of sedation for as much of the time as possible.

In a recent postal survey of intensive care units in the United Kingdom 60% reported using opioids and benzodiazepines in combination for sedation.[4] Morphine provides effective analgesia and sedation in a large proportion of patients receiving intensive care, but in large doses it may reduce immunocompetence and may be associated with an increased risk of infection.[5] Although its elimination half life is one or two hours in normal subjects, this is appreciably increased in patients with impaired liver function or reduced blood flow to the liver.[6] Severe and prolonged depression of ventilation and delayed recovery may occur in patients with impaired renal function owing to the accumulation of active morphine-6-glucuronide.[7] Phenoperidine produces severe depression of ventilation, which facilitates controlled mechanical ventilation, although recent reports of the effects of phenoperidine on intracranial pressure are disconcerting.[8,9] The newer opioid alfentanil has been shown to be useful for sedation in ventilated patients in the intensive care unit,[10,11] but its prolonged elimination half life in some patients has resulted in prolonged depression of ventilation in critically ill patients.[12,13]

Diazepam is widely used for sedation in the intensive care unit, even though it has a long duration of action with active metabolites and produces a wide inter-individual variability in response. Midazolam showed promise in early pharmacokinetic studies, but in critically ill patients its half life is appreciably increased and highly unpredictable.[14,15] An abnormally prolonged elimination half life (8-22 hours) seen in some patients has been attributed to the existence of a subpopulation who are slow to metabolise the drug.[16] The hydroxymetabolites of midazolam have sedative properties, although their contribution to the drug's overall clinical effects and the relative potency and precise duration of these effects have not been established.

A specific benzodiazepine receptor antagonist, flumazenil, is now available in the United Kingdom. Although it may have a specific role in treating drug overdose, its effectiveness in reversing midazolam sedation in the critically ill has not been proved, and it may be associated with dangerous complications.[17,18] Based on the sparse clinical data available, its routine use to reverse midazolam sedation in the critically ill cannot be recommended.

Propofol is the latest hypnotic under investigation for long term sedation in the intensive care unit. It has been shown to provide a controllable level of sedation and usually a rapid recovery.[19,20] A recent large multicentre study comparing midazolam with propofol (A R Aitkenhead and colleagues, unpublished data) confirms the ease of control of sedation with propofol and the patient's rapid recovery on stopping the infusion, but there was no difference between the two groups in the quality of sedation achieved.

The use of an inhalational anaesthetic for sedation is not a new concept. Nitrous oxide was used to sedate paralysed patients with severe tetanus who required long term mechanical ventilation, and halothane was used to suppress cardiovascular disturbances in tetanus.[21] Nitrous oxide was, however, found to interfere with the metabolism of vitamin B-12, causing bone marrow depression and other toxic effects.

The efficacy and safety of isoflurane as a general anaesthetic has been evaluated extensively. It has many of the properties of an ideal sedative agent for use in the

intensive care unit. Our results confirm that it provides satisfactory sedation in patients requiring mechanical ventilation with a range of severity of illness as determined by their APACHE II scores. The degree of sedation with isoflurane was easily and rapidly controlled by changing the inspired isoflurane concentration delivered to the patient. The effective dose of isoflurane for sedating ventilated patients in the intensive care unit was confined to a narrow range (0·1-0·4% concentration), whereas the requirement for midazolam showed considerable variability between patients (0·014-0·140 mg/kg/h). Patients sedated with isoflurane were often tranquil and cooperative, whereas those sedated with midazolam were often confused and disruptive, requiring increasingly higher infusion rates that resulted in oversedation. Provided that patients were not hypovolaemic, isoflurane or midazolam sedation did not have deleterious effects on haemodynamic stability.

In conclusion, isoflurane in subanaesthetic concentrations (0·1-0·6%) provides a useful alternative technique for sedation of ventilated patients in the intensive care unit. It has many advantages over conventional intravenous sedative agents. The quality of sedation and speed of recovery from sedation are significantly better with isoflurane than midazolam. Further studies are required to assess the side effects of prolonged isoflurane sedation.

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Local hyperthermia benefits natural and experimental common colds

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Abstract

***Objective*—To determine whether inhaling fully humidified air at 43°C gave more benefit to cold sufferers than inhaling air at 30°C.**

***Design*—Randomised double blind trial.**

***Setting*—General practice and the common cold research unit.**

***Subjects*—87 Unselected patients with typical acute nasal and upper respiratory symptoms (general practice study), and 84 volunteers aged 18-50 without a history of chronic or allergic diseases.**

***Interventions*—Subjects breathed from apparatus delivering 40 litres of room air heated to 43°C or 30°C and fully humidified (relative humidity 100%) per minute.**

***End point*—Reduction in severity of disease.**

***Measurements and main results*—Patients recorded their symptoms (general practice study) and observers recorded symptoms and signs, weight of nasal secretions, isolation of virus, and antibody responses in volunteers. Patients treated for 20 minutes at 43°C had in the succeeding days roughly half the score for symptoms of those treated at 30°C. Volunteers treated for 30 minutes on three occasions when they were starting a cold showed a 43% reduction in symptoms. Treatment of volunteers for 20 minutes at the onset of the cold and for 10 minutes on succeeding days showed no difference between 43°C and 30°C.**

***Conclusions*—Nasal hyperthermia can improve the course of a common cold and also give immediate relief of symptoms.**

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Introduction

Inhaling warm, damp air is widely accepted to relieve the symptoms of colds and other acute respiratory infections, and, indeed, inhaling humidified air is part of the management of lower respiratory disease in some paediatric centres. Greater benefit, however, may be obtained by administering hot humidified air so that the temperature of the nasal mucosa is raised. Equipment to do this has undergone preliminary trials (A Beacham, J Levenstein, unpublished), which suggested that inhalations that raised the temperature of the nasal mucosa to 43°C for 20 minutes led to a rapid resolution of common colds.

Lwoff suggested that raising the mucosal temperature to 43°C for three periods of 30 minutes at intervals of two hours would block the replication of rhinoviruses and so abort common colds.[1] An apparatus to do this (the Rhinotherm) was developed in Israel, and it was claimed that 80% of subjects who used the apparatus in the early stages of a cold were better the next day.[2] The control groups in this trial were not apparently balanced with the experimental group, and the control apparatus would have been readily distinguished from the active apparatus as it