

A prospective randomised pilot study of sedation regimens in a general ICU population: a reality-based medicine study

Simon R Finfer, Anne M O'Connor and Malcolm M Fisher

Background: For logistical reasons sedation studies are often carried out in elective surgical patients and the results extrapolated to the general intensive care unit (ICU) population. We question the validity of this approach. We compared the two sedation regimens used in our general ICU in a trial structured to mimic clinical practice as closely as possible.

Results: Forty patients were randomised to intermittent diazepam or continuous midazolam and sedation monitored with hourly sedation scores; 31 patients completed the study. Scores indicating undersedation were more common with diazepam ($P < 0.01$); overall adequate sedation midazolam 64.7%, diazepam 35.7% ($P = 0.21$). No patient exhibited inappropriately prolonged sedation. Cost was: midazolam AUS \$ 1.98/h; diazepam AUS \$ 0.06/h.

Conclusion: Both regimens produced rapid onset of acceptable sedation but undersedation appeared more common with the cheaper diazepam regimen. At least 140 patients should be studied to provide evidence applicable to the general ICU population. Used alone, a sedation score may be an inappropriate outcome measure for a sedation trial.

Addresses: Intensive Therapy Unit, Royal North Shore Hospital of Sydney, St Leonards NSW, Australia

Correspondence: Dr SR Finfer, MB BS, MRCP, FRCA, FFICANZCA, Senior Staff Specialist, Intensive Therapy Unit, Royal North Shore Hospital of Sydney, St Leonards NSW 2065, Australia. Tel: 02 9926 8656; fax: 02 9439 8418, e-mail: sfinfer@med.usyd.edu.au

Keywords: critical care, midazolam, diazepam, sedatives, nonbarbiturate, therapeutic use, comparative study

Received: 12 June 1998

Revisions requested: 28 February 1999

Revisions received: 26 May 1999

Accepted: 6 June 1999

Published: 24 June 1999

Crit Care 1999, 3:79–83

The original version of this paper is the electronic version which can be seen on the Internet (<http://ccforum.com>). The electronic version may contain additional information to that appearing in the paper version.

© Current Science Ltd ISSN 1364-8535

Introduction

To provide the highest quality patient care, an intensive care unit (ICU) must constantly review treatment in search of 'best practice' for that unit. The medical literature is the prime source of evidence and randomised controlled trials (RCTs) are considered the gold standard for the evaluation of competing treatments. Nevertheless, RCTs have been criticised as strict inclusion and exclusion criteria may exclude the very patients who clinicians are obliged to treat [1]. The conduct of trials in intensive care is further complicated by the varying case-mix between different units so that the results of even perfectly conducted studies may not be relevant to a unit with a different case-mix. As a result, it becomes necessary to develop protocols and systems for examining practice in one's own unit.

ICU sedation regimens provide a good example of the difficulty of extrapolating evidence from the literature to one's own practice. For logistical reasons most sedation studies in intensive care are carried out on patients undergoing short-term sedation following elective surgical pro-

cedures. This patient population is not representative of the population of our general ICU, making such results inapplicable to our patients.

Two sedative regimens have evolved in our unit and the published literature does not enable us to compare their relative merits in our patients. We therefore set out to compare the two regimens and, in order that our study should produce 'medicine-based evidence' [2], we chose to conduct a study that mimicked our unit's clinical practice as closely as possible.

Sedatives are amongst the most commonly prescribed drugs in ICUs and contribute significantly to ICU costs [3–5]. Many agents are used and none can claim to be ideal [5,6]. In our unit, we use intermittent intravenous diazepam and continuous intravenous midazolam. Potential advantages of midazolam are its water solubility, its short distribution and elimination half lives (20 min and 90 min, respectively) [7], and its lack of long-acting active metabolites. In contrast diazepam has an elimination half life of 44 h [8] and its major active metabolite, desmethyl-

diazepam, a half life of 93 h [9]. These data are derived from single dose administration to normal subjects and much of midazolam's pharmacokinetic advantage is lost when administered by infusion to critically ill patients [3,8,10]. In ICU patients, its elimination half life may be greatly prolonged [8] and clinically important accumulation may occur [11]. By using intermittent diazepam there is a clinical disincentive to overdosage as administration of each dose is a deliberate action by the bedside nurse. Continuous infusions of sedatives are more convenient but risk oversedation if the infusion rate is not regularly reduced to test the lower limit of acceptable sedation. In terms of cost, diazepam has a clear advantage being one-tenth the price and having twice the potency. Because of cost and the prolonged elimination half life of midazolam in the critically ill, our standard sedative regimen has been intermittent intravenous diazepam, but midazolam by continuous intravenous infusion may also be used at the discretion of the duty ICU specialist. We set out to compare these two regimens in our patient population in a pilot study in 40 patients to evaluate the regimens, to allow power calculations for future studies and to evaluate study design.

Materials and methods

The study was approved by the Royal North Shore Hospital and Community Health Services Human Research Ethics Committee. Forty consecutive adult patients admitted to the ICU for whom benzodiazepine sedation was to be prescribed were entered in the study. On admission, the patients were allocated to one of two regimens by means of randomly ordered cards invisibly sealed in gummed opaque envelopes. The regimens were either intermittent diazepam 1–5 mg by intravenous injection, or continuous intravenous midazolam 0.05 mg/kg as a loading dose, followed by an infusion at 0.05 mg/kg/h. Depth of the sedation was monitored by the nursing sister caring for the patient using a local modification of the Ramsay Sedation Scale [12] (Table 1). The target sedation range was a score in categories 1–4; category 0 was classified as undersedation and categories 5 and 6 as oversedation. The dose per bolus and frequency of administration of diazepam, and the rate of midazolam infusion were adjusted by the bedside nurse with the aim of achieving and maintaining the level of sedation within the target range of 1–4. Patients receiving the midazolam infusion could receive additional bolus doses of midazolam as required to maintain the target level of sedation. All patients in the study received intravenous morphine as a continuous infusion as indicated for the management of pain. Outcome measures for the study were: time to target range, percentage of time within target range, percentage of time over- or undersedated; number of patients adequately sedated (defined as at least 80% of total time in target range); number with inappropriately prolonged sedation; cost of sedation. Statistical analysis

Table 1

Modified Ramsay Sedation Score

0	Agitated
1	Awake, but tranquil and cooperative
2	Asleep, opens eyes to surroundings
3	Asleep, opens eyes to name
4	Asleep, opens eyes to physical stimulus*
5	Asleep, moves and reacts to physical stimulus* only
6	Unconscious or unrousable

*Stimulus, hand clap next to ear or moderate tap on forehead.

was performed by Chi square with Yates correction and the Mann-Whitney U test.

Patients were withdrawn from the study when they reached one of the following points.

- (1) Treatment failures: patients in whom it proved impossible to maintain sedation within the target range with the regimen to which they had been randomised.
- (2) Change of target range: patients in whom a change in clinical condition made maintenance of sedation in the target range inappropriate. This included patients for whom sedation was no longer indicated as mechanical ventilation was to be weaned, and patients in whom deteriorating respiratory function necessitated a deeper level of sedation to ensure adequate ventilation. In those patients being weaned from mechanical ventilation, administration of sedation for both groups was discontinued according to standard unit weaning practice but could be recommenced should patient agitation required it. Any sedation administered during the weaning period was included in the record of total sedation administered and sedation scoring was continued until weaning from mechanical ventilation was successful.
- (3) Death.

Exclusion criteria are given in Table 2.

In addition to recording of hourly sedation scores, the amount of sedation and morphine administered during the study period was recorded. Cost of drug use was calculated on the basis of the amount of drug administered to the patient or discarded. The standard infusion regimen for midazolam was to dilute 50 mg midazolam in the patient's maintenance intravenous fluid to make a total volume of 100 ml. This was costed as 50 mg midazolam used regardless of the volume administered to the patient.

Inappropriately prolonged sedation

Patients were classified as exhibiting inappropriately prolonged sedation if they had a continued requirement for

Table 2

Study exclusion criteria
Allergy to benzodiazepines or morphine
At risk of epilepsy
Intracranial hypertension
Admission diagnosis of drug overdose

endotracheal intubation or were unable to obey commands once sedation was discontinued. If inappropriately prolonged sedation was suspected the patient was given a slow intravenous injection of 0.5 mg flumazenil in 0.1 mg aliquots to determine if persisting benzodiazepine sedation was the cause of depressed conscious level.

Results

Twenty patients were randomised to each group and a total of 31 patients completed the study (17 in the midazolam group and 14 in the diazepam group). Reasons for failure to complete the study are given in Table 3. There was no significant difference between the two groups in the sex distribution, age, admission Acute Physiology And Chronic Health Evaluation (APACHE) II score, mortality, incidence of renal or hepatic impairment, or dose of morphine per hour given during the study period (Table 4). The results for the sedation endpoints are given in Table 5. The only significant difference was an increase in the percentage of hours undersedated in the group treated with diazepam. Overall, 11 out of 17 patients treated with the midazolam regimen (64.7%) were adequately sedated in comparison with five out of 14 (35.7%) treated with the diazepam regimen (odds ratio 3.33, 95% confidence interval 0.75–14.5, $P=0.21$) no patient in either group exhibited inappropriately prolonged sedation attributable to benzodiazepine. One patient known to have chronic liver impairment and admitted to the ICU with sepsis exhibited prolonged sedation despite receiving only 2.5 mg diazepam. However, there was no improvement in this patient's conscious level with flumazenil suggesting the prolonged sedation was not due to benzodiazepine.

The number of hours of sedation, mean dose of drug administered, and mean cost per patient and per hour of sedation are given in Table 6.

Based on this study's results, we determined that the following changes to our study protocol should be made to conduct a larger study comparing an intermittent with continuous sedation regimen.

Approximately 70 patients would need to be entered into each limb of an unpaired case-control study with 1:1 ran-

Table 3

Reasons for randomised patients not completing study	Midazolam	Diazepam
Exclusion reason		
Treatment failure*	1	1
No sedative given	1	4
Data incomplete	1	1

*Treatment failure defined as patient given other sedative during first hour of study as not adequately sedated by regimen to which they had been randomised.

Table 4

Patient demographics, analgesia, and incidence of renal and hepatic impairment	Midazolam	Diazepam
Number (% male)	17 (76.5%)	14 (64.3%)
Mean age (SD)	44.1 (17.7)	56.6 (16.8)
Median APACHE II (range)	17 (5–35)	15 (3–33)
Mortality (%)	1/17 (5.9%)	1/14 (7.1%)
Incidence of renal impairment	1/17 (5.9%)	2/14 (14.2%)
Incidence of hepatic impairment	0/17 (0%)	2/14 (14.2%)
Morphine (mg/h), median (range)	2.8 (0–6.6)	1.6 (0–4.5)

APACHE, Acute Physiology And Chronic Health Evaluation.

Table 5

Sedation results	Midazolam	Diazepam	<i>P</i>
Hours to target	2 (0–39)	2 (0–22)	NS*
Hours with target score (%)	85.0 (0–100)	59.2 (0–100)	NS*
Hours undersedated (%)	0 (0–21)	21.1 (0–43)	$P=0.01$
Hours oversedated (%)	14.8 (0–100)	2.8 (0–97)	NS*

Values are shown as median (range). * $P > 0.05$.

Table 6

Cost data for two sedation regimens	Midazolam	Diazepam
Drug cost (AUS \$/mg)	0.32	0.032
Mean hours of sedation per patient	46.5	39.4
Mean dose per patient	286 mg	62 mg
Average cost per patient	AUS \$92.24	AUS \$2.07
Average cost per hour of sedation	AUS \$1.98	AUS \$0.06

domisation to demonstrate a significant difference in quality of sedation.

The Ramsay sedation score should be further modified so that patients who exhibited a short period of agitation requiring either a single bolus of the continuous agent or a single additional bolus of the intermittent agent were not classified as undersedated.

Measures other than a sedation score should be used to determine the quality of sedation in the ICU. They should include a record of the need for physical restraints to prevent patients removing endotracheal tubes or intravascular lines. A record of the number of times endotracheal tubes or intravascular lines were accidentally removed by patients, along with the occurrence of potentially harmful physiological abnormalities such as hypertension, tachycardia, cardiac arrhythmias or intracranial hypertension which were attributable to inadequate sedation should be made. In the same regard, hypotension attributable to the sedation regimen should be recorded. Finally, and possibly most importantly, surviving patients should be interviewed following discharge from the ICU to determine their recollection of their time in ICU and whether or not they found their stay in ICU painful or mentally disturbing.

Discussion

Many drugs have been used to sedate critically ill patients including intravenous anaesthetic agents [3,12–14], inhalational anaesthetic agents [15–17], opiates [18,19], and barbiturates [20]. No drug can claim to be the ideal ICU sedative, and benzodiazepines remain the most commonly used [5,6]. In 1991, lorazepam, diazepam and midazolam were used almost equally in the USA [5]. Most units gave drugs intermittently although 36% used midazolam by infusion. In 1987, midazolam and diazepam were used approximately equally in the UK, but 65% of units preferred to give sedatives by continuous infusion [6]. Sedation practice in Australian ICUs is not well documented.

In this randomised, controlled, pilot study, we have examined the two sedation regimens currently used in our ICU. This study is not a comparison between two drugs, but rather between two sedation regimens. Although intermittent dosing was the preferred method in the USA [5], most published studies have compared drugs being given by continuous infusion. A computerized literature search from 1963 to date revealed only one study comparing intermittent and continuous regimens [21]. Intermittent dosing imposes additional nursing work but makes accumulation less likely, and inappropriately prolonged sedation due to intermittent diazepam was not seen in this study. Administration by continuous infusion is more convenient, may provided a more uniform level of sedation, but risks greater drug use and accumulation if sedation

level is not closely monitored. Our study supports these theoretical differences. Some of the results are inconclusive due to the small sample size and the heterogeneity of a general ICU population. Despite the similarity of the patients, and the duration of sedation in the two groups, more midazolam was administered and cost AUS\$45.00 more per day. This cost may be justified if it results in better patient outcomes, savings in staff costs [22], or shorter ICU stays [3]. There was no difference in mortality between the groups, and this would not be expected in a study of this size. There was higher rate of undersedation apparent in the diazepam group, but this may be an artefact as the scoring system used was not designed to monitor intermittent dosing regimens, and patients had to exhibit agitation to receive a bolus dose of diazepam.

Our recommendations for future sedation studies include the use of measures other than the sedation score to evaluate the adequacy of sedation. Studies conducted in our unit suggest that patients surviving ICU are disturbed by having no memory of that period of their life [23]. Thus, what appears to medical and nursing staff to be an ideal sedative agent, in particular more recently available short-acting anaesthetic agents which provide titratable sedation, but by nature of their very short duration of action allow patients to be heavily sedated without the risk of significant accumulation, may encourage staff to over-sedate patients. Despite the patients being 'well-sedated', they may later be disturbed by having no memory whatsoever of their time in ICU. This is an area of ICU practice that requires considerable further study.

References

1. Anonymous: **Is this the end of research as we know it?** *BMJ* 1997, **315**:388.
2. Knottnerus JA, Dinant GJ: **Medicine based evidence, a prerequisite for evidence based medicine: future research methods must find ways of accommodating clinical reality, not ignoring it.** *BMJ* 1997, **315**:1109–1110.
3. Barrientos-Vega R, Sanchez-Soria M, Morales-Garcia C, Robas-Gomez A, Cuena-Boy R, Ayensa-Rincon A: **Prolonged sedation of critically ill patients with midazolam or propofol: impact on weaning and costs.** *Crit Care Med* 1997, **25**:33–40.
4. Cernaianu AC, DelRossi AJ, Flum DR, *et al*: **Lorazepam and midazolam in the intensive care unit: a randomized, prospective, multi-center study of hemodynamics, oxygen transport, efficacy, and cost.** *Crit Care Med* 1996, **24**:222–228.
5. Hansen-Flaschen JH, Brazinsky S, Basile C, Lanken PN: **Use of sedating drugs and neuromuscular blocking agents in patients requiring mechanical ventilation for respiratory failure. A national survey.** *JAMA* 1991, **266**:2870–2875.
6. Bion JF and Ledingham I M: **Sedation in intensive care: a postal survey.** *Intensive Care Med* 1987, **13**:215–216.
7. Shelly MP, Richards G, Dhillon S, *et al*: **A comparative pharmacokinetic study of intravenous and intramuscular midazolam in patients with epilepsy.** *Epilepsy Res* 1991, **10**:183–190.
8. Shelly MP, Mendel L, Park GR: **Failure of critically ill patients to metabolise midazolam.** *Anaesthesia* 1987, **42**:619–626.
9. Greenblatt DJ, Divoll MK, Soong MH, Boxenbaum HG, Harmatz JS, Shader RI: **Desmethyldiazepam pharmacokinetics: studies following intravenous and oral desmethyldiazepam, oral clorazepate, and intravenous diazepam.** *J Clin Pharmacol* 1988, **28**:853–859.
10. Dirksen MS, Vree TB, Driessen JJ: **Clinical pharmacokinetics of long-term infusion of midazolam in critically ill patients – preliminary results.** *Anaesth Intensive Care* 1987, **15**:440–444.

11. Shelly MP, Sultan MA, Bodenham A, Park GR: **Midazolam infusions in critically ill patients.** *Eur J Anaesthesiol* 1991, **8**:21–27.
12. Ramsay MA, Savege TM, Simpson BR, Goodwin R: **Controlled sedation with alphaxalone-alphadolone.** *BMJ* 1974, **2**:656–659.
13. Ronan KP, Gallagher TJ, George B, Hamby B: **Comparison of propofol and midazolam for sedation in intensive care unit patients.** *Crit Care Med* 1995, **23**:286–293.
14. Millane TA, Bennett ED, Grounds RM: **Isoflurane and propofol for long-term sedation in the intensive care unit. A crossover study.** *Anaesthesia* 1992, **47**:768–774.
15. Willatts SM, Spencer EM: **Sedation for ventilation in the critically ill. A role for isoflurane?** *Anaesthesia* 1994, **49**:422–428.
16. Spencer EM, Willatts SM: **Isoflurane for prolonged sedation in the intensive care unit; efficacy and safety.** *Intensive Care Med* 1992, **18**:415–421.
17. Kong KL, Willatts SM, Prys Roberts C: **Isoflurane compared with midazolam for sedation in the intensive care unit.** *BMJ* 1989, **298**:1277–1280.
18. Sear JW, Fisher A, Summerfield RJ: **Is alfentanil by infusion useful for sedation on the ITU?** *Eur J Anaesthesiol Suppl* 1987, **1**:55–61.
19. Bion JF, Logan BK, Newman PM, *et al*: **Sedation in intensive care: morphine and renal function.** *Intensive Care Med* 1986, **12**:359–365.
20. Durbin CG Jr: **Sedation in the critically ill patient.** *New Horiz* 1994, **2**:64–74.
21. Cernaianu AC, DelRossi AJ, Flum DR, *et al*: **Lorazepam and midazolam in the intensive care unit: a randomized, prospective, multi-center study of hemodynamics, oxygen transport, efficacy, and cost.** *Crit Care Med* 1996, **24**:222–228.
22. Sherry KM, McNamara J, Brown JS, Drummond M: **An economic evaluation of propofol/fentanyl compared with midazolam/fentanyl on recovery in the ICU following cardiac surgery.** *Anaesthesia* 1996, **51**:312–317.
23. McKinley S, Nagy S, Bramwell M, Hudson J, Stein-Parby J: **Living after intensive care.** *Am J Crit Care* 1997, **6**:242.