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Use of Flumazenil to Provide Adequate Recovery Time Post-Midazolom Infusion in a General Intensive Care Unit

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ABSTRACT

Sedation permits patients to tolerate the various treatment modalities to which they are subjected. However it may sometimes cause prolonged sedation in critically ill patients. Flumazenil, a benzodiazepine antagonist, reverses midazolam-induced sedation and amnesia. We prospectively designed a double-blind randomized study to evaluate the effects of flumazenil on thirty (30) Iranian General Intensive Care Unit (ICU) patients. They were requiring mechanical ventilation for more than 12 hours and they were sedated by midazolam infusions. Sedation levels were measured hourly during the infusion, at the end of the infusion, and at 5, 15, 30, 60, and 120 min after cessation of the midazolam infusion. Reversal of sedation was observed in all patients who received flumazenil, and re-sedation occurred in seven of these patients. Reversal was not seen in any of the patients who received placebo.

Key words: Benzodiazepine, Flumazenil, Midazolam, Intensive Care Unit, Sedation, Amnesia.

INTRODUCTION

Mechanical ventilation is required in approximately 60% of the critically ill intensive care patients. Adequate sedation is an essential part of the management of all ICU patients. Even when the surgical wound has healed and incisional pain has subsided, anxiety, fear, and pain from multiple sources (dressing changes, endotracheal suction, invasive procedures, indwelling catheters, and tubes) are still part of the stressful routine of the ICU. Appropriate sedation may result in a more cooperative patient, assure amnesia and facilitate sleep, which is essential for physical and mental recovery. While many different commercially available drugs may be safely used, the benzodiazepines are often preferred for their reliable amnestic action, cardiovascular stability, and minor ventilatory depression. (1) In patients requiring very large doses of sedative because of excessive agitation and confusion, a continuous infusion of a sedative hypnotic may be very effective. Drugs available for continuous infusion should have a short duration of action, fast recovery, minimal hemodynamic effect, and should exhibit a flexibility in their pharmacodynamic action. The water-soluble benzodiazepine midazolam which has recently been approved by FDA for sedation of ventilated ICU patients(2) with a half-life of approximately 1.5 to 3 hours in normal subjects, shall be suitable for providing I.V. sedation in the ICU patients. However, it may sometimes cause prolonged sedation in critically ill patients. (2, 16, 18). Flumazenil, a specific benzodiazepines antagonist, reverses the sedation of benzodiazepines, including midazolam. Its use in ICU patients should contribute to the safe use of midazolam for I.V. sedation (2,3,,17). In this double-blind, randomized study, flumazenil's efficacy and safety were tested on recovery, post-midazolam sedation.

MATERIAL AND METHODS

Our study was double blind with 15 patients in

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each group. Patients were excluded from this study if they had a history of allergy to benzodiazepines, were comatose, had a systolic BP of < 90 mm Hg, or were otherwise considered unsuitable by the attending clinician. All patients were endotracheally intubated and were receiving mechanical ventilation. Written consent form was required from the patients' family member. On entry into the trial, a bolus dose of midazolam of 0.1 mg/kg was administered intravenously over 2 min, followed by a continuous infusion at the the rate of 0.65 mg/kg/hr for the next 15 min. The aim of this regimen was to reach a steady-state concentration faster. Thereafter, the infusion rate was maintained at 0.13 mg/kg/hr. The sedation level was assessed hourly by the attendant using a sedation scale with five levels (Table 1) similar to the one previously described (9). A level between two and four reflected the desired sedation level. The rate of infusion of midazolam was adjusted to achieve this level. The depth of sedation was increased, if required, by giving an additional IV bolus of midazolam equal to 50% of the initial bolus, and thereafter increasing the infusion rate by 25%. The level of sedation was decreased by decreasing the rate of infusion by 25%. The infusion was ceased when clinically indicated. At the time of cessation of the midazolam, the test drug either flumazenil, up to 1 mg, or placebo (normal saline) was administered according to a previously blinded, randomized regimen. The drug ampoules contained 20 ml of the test drug or 20 ml of placebo. Aliquot portions were administered every 2 min until either the patient's sedation level increased by two levels or until all the drug had been given. The initial two portions were 3 ml (0.15 mg) and subsequent portions were 2 ml (0.1 mg). Sedation-level scoring was continued for 4 hrs in order to detect re-sedation (10). The Mann-Whitney U test was used to compare both groups. The wilcoxon signed-rank test was used to compare the sedation levels before and after the administration of flumazenil. A P value <0.05 was set as the level of significance.

RESULTS

Thirty male patients were entered into the study (Tables 2,3). Sedation was achieved in all patients with sedation level scores 3.5±0.6 (SD) and 3.8 +/- 0.4 in both groups. All 15 patients who had received the test drug had been satisfactorily reversed, while none of those patients who received the placebo fulfilled the criteria for reversal. Initial reversal of sedation was achieved 0.15 mg in all patients. Re-sedation occurred in five patients within 60 min, affecting six patients within 30 min. An additional dose of flumazenil was given to four patients. Seven patients were temporarily agitated and restless after reversal.

DISCUSSION

A constant level of clinical sedation can theoretically be attained by continuous intravenous infusion. Because of its short elimination half-life, midazolam is well-suited to use by continuos infusion in critical care medicine (3). Loading doses are generally administered at the start of infusions to accelerate the attainment of steady-state. As a general principle, steady-state plasma levels within a given individual will increase in direct proportion to the final infusion rate. However, at any infusion rate , steady-state levels will change inversely with metabolic clearance which is variable among individuals.

Table 1. Sedation Level Scale

Best Verbal Response:	Adequate = 1 Confused = 2 Inappropriate = 3 Incomprehensible = 4 None = 5
Orientation In Time and Space:	Excellent Orientation =1 Only Orientation In Time = 2 Only Orientation In Space = 3 Total Disorientation = 4 No Response = 5
Eye Opening:	Obeying Commands =1 Spontaneous = 2 To Speech = 3 To Pain = 4 None = 5

Table 2. Patient's Diagnosis

Diagnosis	No. of Patients
Respiratory Failure	15
Sepsis	5
Cardiogenic Shock	3
Vascular Surgery	2
Head Trauma	1
Others	4
Total	30

Unfortunately, midazolam clearance for a given patient cannot be accurately determined without a study of midazolam pharmacokinetics in that particular patient (11,12).

In the phase of recovery from intravenous sedation, recovery from midazolam-induced sedation should be relatively rapid, however from previous reports (4, 5, 6) we know that there may be delayed awakening after the use of infusions in ICU patients. This prolonged sedation may be caused by the failure of critically ill patients to metabolize midazolam to its less active metabolite hydroxy-midazolam, poor hepatic perfusion, increased redistribution, or a genetic defect (6, 11, 12). The benzodiazepine receptor "antagonist" flumazenil can be administered in unusual clinical situations in which CNS effects of benzodiazepines need to be reversed on an urgent basis (14,15,16). This finding is of potential benefit to those patients who have prolonged sedation after the use of midazolam. It would also aid neurologic assessment of some sedated ICU patients (7,10).

In this study, midazolam provided satisfactory sedation in all patients. The mean dose of midazolam was 6.5 mg/hr (infusion rate), which is similar to the findings of previously published series (6,18). Flumazenil had a visible effect in reversing the sedation in a similar manner to that previously described in normal patients (10,14). However, re-sedation, which is well described with the used of flumazenil (16,18) was seen in nearly 60% of our patients. Flumazenil has a high clearance and short half-life in humans (0.7 to 1.3 hrs) less than of midazolam (13), which explains the recurrence of sedation. An infusion of flumazenil or additional boluses would be sufficient to treat re-sedation (10, 14). No significant adverse effects, due to midazolam or flumazenil, were noted during the study. The prolonged effect of midazolam in some patients, its poor metabolism and wide inter-patient pharmacokinetic variability in the critically ill, and the fact that some patients are poor metabolizers of the drug (2, 5, 6, 12,13) make desirable the availability of an agent, such as flumazenil, which reverses the sedation as required. Future studies in midazolam pharmacokinetic behavior in our critically ill patients may further support these findings.

Table 3. Characteristics of Patients (n=30)

	Flumazenil Group	Placebo Group	P Value
Mean Age (Yr)	40±10.8	48±10.8	0.3
Length Of Sedation	15.2±2.55	17±3.8	0.18
Mean Dose of Misazolam (Mg/hr)	6.8±2.55	6.0±1.83	0.8
Mean Dose of Midazilam (Mg/Kg/hr)	0.1	0.08	
Mean Sedation Level	3.5±0.6	3.8±0.4	0.22

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