The Use of Diazepam, Midazolam and Propofol for Sedation in the Surgical Intensive-Care Unit

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Thirty critically ill patients (acute physiological and chronic health evaluation II score <20) in the surgical ICU were randomly allocated to 3 groups respectively to receive diazepam, midazolam or propofol sedation to facilitate mechanical ventilation over a 24-hour period. Analgesia was provided by intravenous morphine. To maintain adequate sedation, the mean total dose of diazepam given in intermittent boluses was 56.4±0.3 mg/24hr. The mean continuous infusion rates of midazolam and propofol were 0.08±0.01 mg/kg/hr and 1.4±0.5 mg/kg/hr respectively. In terms of reversibility of sedation, midazolam and propofol outscored diazepam. Recovery tended to be prolonged in patients with liver disease in all three groups, especially in the diazepam group. Systolic and diastolic blood pressures fell 30 minutes after drug administration in all groups ($p<0.05$). Patients sedated with midazolam showed significant increase in oxygenation ($p<0.05$). We conclude that either midazolam or propofol infusion can provide effective and safe sedation for ventilated patients in ICU.

Key words: ***benzodiazepines: diazepam, midazolam, anesthetics, intravenous: propofol, intensive care unit, sedation, mechanical ventilation***

Introduction

Many patients in the surgical Intensive Care Unit (ICU) suffer from pain or anxiety resulting from operative procedures, mechanical ventilation, physical therapy or nursing procedures. The perception of pain and anxiety can cause psychic disturbances which are hazardous to the critically ill patients[1]. The addition of sedative drugs offers the benefits of well-controlled ventilation, reduced metabolic rate and a decrease in the stress response[2].

An ideal sedative agent should have minimal effects on the respiratory or cardiovascular system and maintain an appropriate duration of action with high therapeutic index. It should be metabolized by pathways not dependent on normal renal, hepatic or pulmonary function and have minimal drug interaction[3].

Benzodiazepines which represent the class of sedatives[4] most frequently used have the special advantage of being able to reverse their effects by a specific antagonist, flumazenil[5]. Sedation with diazepam is frequently used but adverse effects occur such as venous thrombosis and prolonged sedation. The long elimination half-life (20-50 hours)[6] makes diazepam more difficult to titrate and dangerous for continuous infusion, especially

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in elderly patients. Midazolam, a new water-soluble imidazo-benzodiazepine, is rapid onset and has a short elimination half-life. Its metabolites are inactive. All these attributes make the drug suitable for continuous infusion[7,8].

Propofol (2,6-di-isopropyl phenol) is characterized by a short elimination half-life and rapid recovery. Initial studies on its use for limited periods in the ICUs are very encouraging[9,10].

The present study was designed to compare continuous infusion of propofol and midazolam with conventional intermittent administration of diazepam for sedation in critically ill patients undergoing mechanical ventilation.

Material and Method

Patients in the surgical ICU who fulfilled the following indications for sedation were included in the study. The indications were (1) inability to coordinate with ventilator, or intermittent peak airway pressure > 60 cmH_2O; (2) evidence of tachypnea with a respiratory rate > 30/min; (3) or intention for hyperventilation therapy to keep $PaCO_2$ < 30 mmHg. Exclusion criteria included a history of allergy, head injury and the need for neuromuscular blockade or other sedative drugs. The severity of illness for each patient was assessed using the APACHE II scoring system[11]. Patients with APACHE II scores of 20 or more were also excluded because extremely ill patients might have different cardiovascular responses to drugs and the severity of illness could also affect the level of consciousness. The study patients were randomly divided to receive either diazepam, midazolam or propofol for up to 24 hours. Morphine was also given at an initial rate of 2 mg/hr, which could be adjusted upwards if pain was a major associated factor. Assessment of the degree of sedation was based on the scale modified by Ramsay and colleagues[12]:

Level 1. Patient awake, anxious and agitated or restless, or both.

Level 2. Patient awake, cooperative, oriented, and tranquil.

Level 3. Patient awake, responds to commands only.

Level 4. Patient asleep, brisk response to light glabellar tap or loud auditory stimulus.

Level 5. Patient asleep, sluggish response to light glabellar tap or loud auditory stimulus.

Level 6. Patient asleep, no response to light glabellar tap or loud auditory stimulus.

A desired sedation was considered in level 2, 3, 4 or 5.

The protocol was approved by the hospital committee for investigation and patient's informed consent was obtained before the study.

In the diazepam group[13,14], all the 10 patients received an initial bolus dose of 0.15 mg/kg and a maintenance dose of 2.0 mg every two hours with intermittent supplemental boluses of 2 mg to achieve the goal of Ramsay sedation score[15,16] within level 2-5. The midazolam group consisted of 10 patients who were given an initial bolus dose of 0.1 mg/kg and a maintenance dose of 0.01-0.2 mg/kg/hr. The propofol group comprised of 10 patients who received an initial bolus dose of 1 mg/kg and maintenance infusion at 1-3 mg/kg/hr. The infusion rates of midazolam or propofol were adjusted to maintain patients at the desired level of sedation for as much of the time as possible.

The administration of sedative drug was stopped after a period of 24 hours to allow assessment of post-sedation recovery. Recovery from sedation was assessed every 5 minutes beginning from cessation of midazolam or propofol infusion and from 1 hours (half time of two-hours interval) after the last bolus of diazepam until the patient could obey a simple but specific command (e.g. move your toes twice).

The sedation score was recorded hourly to assess the depth of sedation. The pulse rate, systolic

and diastolic blood pressures, cardiac output and pulmonary capillary wedge pressure were recorded as a baseline, at 30 minutes and then hourly after the beginning of treatment. The dynamic compliance of the lung was calculated using the equation:

Cdyn = Vt / (Ppk-PEEP)

Vt: tidal volume, Ppk: peak inspiratory pressure, PEEP: positive end expiratory pressure[18]. The dynamic compliance of the lung and the arterial blood gas were recorded at the baseline and every 4 hours after sedation.

Statistical comparisons among the three groups were made using the one-way repeated ANOVA test (Scheffe's comparison) or the Kruslkal-Wallis Signed-Rank test (multiple comparison); statistical comparisons within the same group was made using the paired-t test or Wilcoxon test. The results were considered significant with $p<0.05$ and all were expressed as mean ± sem.

Results

Of the 30 patients who required mechanical ventilation because of various respiratory problems, twenty four patients had undergone major thoracic or abdominal surgery, three patients had sustained trauma and the others patients suffered from adult respiratory distress syndrome. The distribution of the three different types of patients was similar proportion among the three groups.

The mean proportions of time over the 24-hour period during which the patients were adequately sedated, as assessed hourly using the Ramsay score amounted to 61% in the diazepam group; 80% in the midazolam group; and 85% in the propofol group. The sedative quality of midazolam or propofol was superior than that of diazepam, which could have been the result of the intermittent dosing schedule for diazepam.

All three groups were similar with respect to age, weight and APACHE II score. The respective mean initial dose and the mean maintenance dose of the three agents is shown in Table 1.

The baseline hematological and biochemistric data were of no significant differences among the three groups (Tab 2).

The recovery times were 299±74 min, 58±7 min and 13±3 min respectively for the diazepam group, midazolam group and propofol group (Fig 1). In all three groups, the recovery time seemed not to be influenced by impairment of kidney func-

Table 1. Physical characteristics, initial dose and maintenance dose

	diazepam	midazolam	propofol	
n	10	10	10	
Age (year)	67.1±3.1	66.8±3.2	64.4±4.0	p>0.05
Bw (kg)	62.9±1.6	58.2±2.4	59.6±2.6	p>0.05
F/M	2/8	1/9	2/8	
APACHE II Score	16.4±1.0	14.8±1.3	14.8±1.5	p>0.05
Initial Dose				
(mg/kg)	0.20±0.03	0.08±0.01	1.2±0.1	
Maintenance Dose				
(mg)	56.4±0.3	113.6±2.8	1982±23	
(mg/kg)	0.86±0.03	1.86±0.03	33.6±0.4	
(mg/kg/hr)	0.036±0.021	0.08±0.01	1.4±0.5	

Data displayed as mean ± SEM

Table 2. Baseline hematologic data, biochemistric data

	diazepam	midazolam	propofol
n	10	10	10
Hb (g/dl)	10.5±0.6	9.9±0.8	10.4±0.7
WBC (K/ul)	14.7±1.7	15.2±1.4	16.3±3.0
Platelate (K/ul)	106.0±27.1	147.3±36.1	193.0±64.3
Na (mmole/l)	135.0±1.5	136±1.4	136.8±1.6
K (mmole/l)	3.5±0.1	3.8±0.2	3.5±0.3
BUN (mg/dl)	28.6±9.5	35.7±11.2	41.4±9.9
Cr (mg/dl)	1.9±0.4	2.1±0.4	2.1±0.5
Alb (g/dl	2.5±0.2	2.6±0.1	2.7±0.2
Total Bil (mg/dl)	2.9±1.3	4.0±2.4	3.2±1.2

Data displayed as mean ± sem, all $p > 0.05$

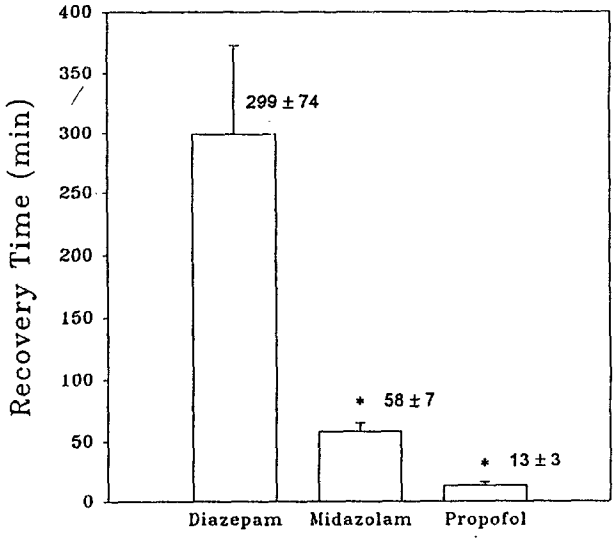

Fig 1. The post-sedative recovery times of three grous. Data displayed as mean (sem). *Significant difference from diazepam group, $p \leq 0.05$.

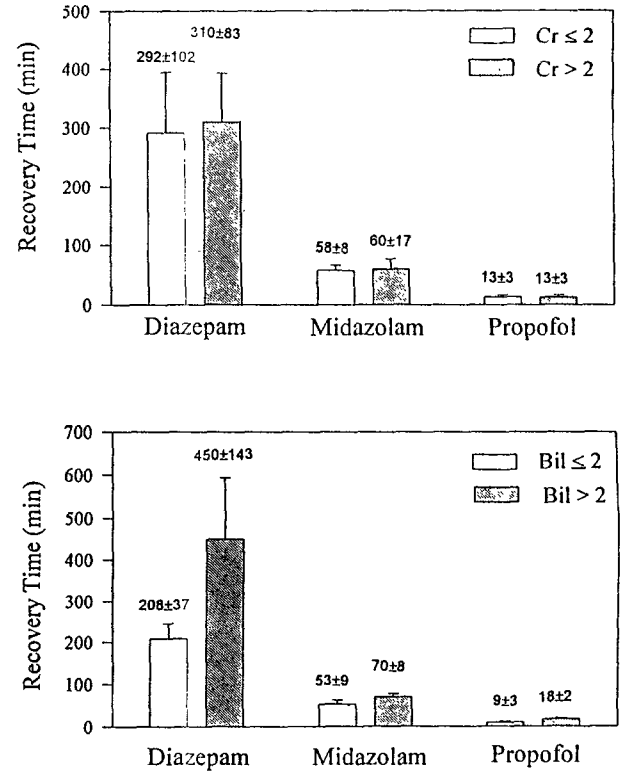

Fig 2. (above) The difference of recovery times between in the patients with normal kidney function (creatinine ≤ 2) and patients with kidney dysfunction (creatinine > 2)
(below) The difference of recovery times between in the patients with normal liver function (total bilirubin ≤ 2) and patients with liver dysfunction (total bilirubin > 2)
Data displayed as mean (sem).

tion (serum creatinine > 2 mg/dl), but tended to be prolonged in patients with liver dysfunction (total bilirubin > 2 mg/dl), especially in the diazepam group (Fig 2). However, in view of the small number of subjects associated with impaired metabolic systems in our investigation, a concrete and solid conclusion could not be drawn.

The cardiac output and pulmonary capillary wedge pressures showed no significant differences

between the baseline and 30 minutes later within the same group. Those patients sedated with midazolam or propofol showed a decrease in pulse rate at 30 minutes ($p<0.05$). In all three groups, the systolic and diastolic pressures fell 30 minutes after administration of the drugs ($p<0.05$) but the falls were within 20% of baseline and did not sustained (Fig 3).

Oxygenation was improved in patients receiving midazolam after 24 hours sedation ($p<0.05$). The dynamic compliance of the lung following treatment showed a tendency to improve in all groups when compared with the baseline but a significant difference was only seen in the propofol group (Fig 4).

Discussion

The pharmacokinetic properties of diazepam, which had a long elimination half-life and a low clearance rate, were not suitable for continuous infusion. In Reves report[18], the half-life after cessation of 30 minutes infusion of diazepam was 150 minutes. It was hazardous for elder patients in our ICU to give diazepam by continuous infusion. The short-interval intermittent bolus of diazepam giving in the study was dependent on clinical sedation level, which could lessen the accumulation effect. This regimen, however, was not easy to keep patients in level 2 (patient awake: cooperative, tranquil state), even in level 3 (patient awake: responds to commands only). The bolus diazepam sedated patients in deeper levels and severe post-sedation obtundation was noted. The recovery time from 1 hours after the last bolus of diazepam was relatively long. In many intensive care unit, physicians were accustomed to using diazepam to sedate patients who were mechanically ventilated prior to 1981[19,20]. Instances of prolonged coma proved to be closely related to sedation with diazepam in repeated doses[21]. In addition, the metabolism of di-

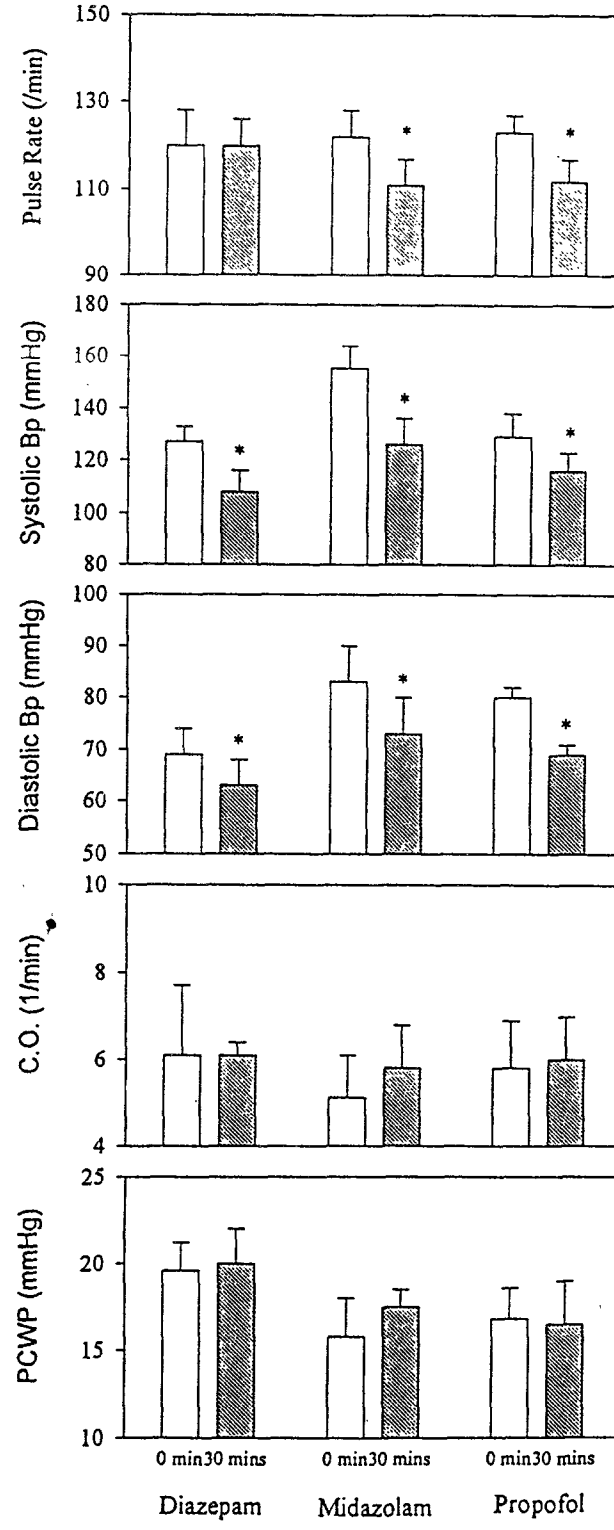

Fig 3. The changes of cardiovascular parameters between 0 min and at 30 mins in three groups. Data displayed as mean (sem). *: Significant difference from 0 min within the group, $p\leq0.05$.

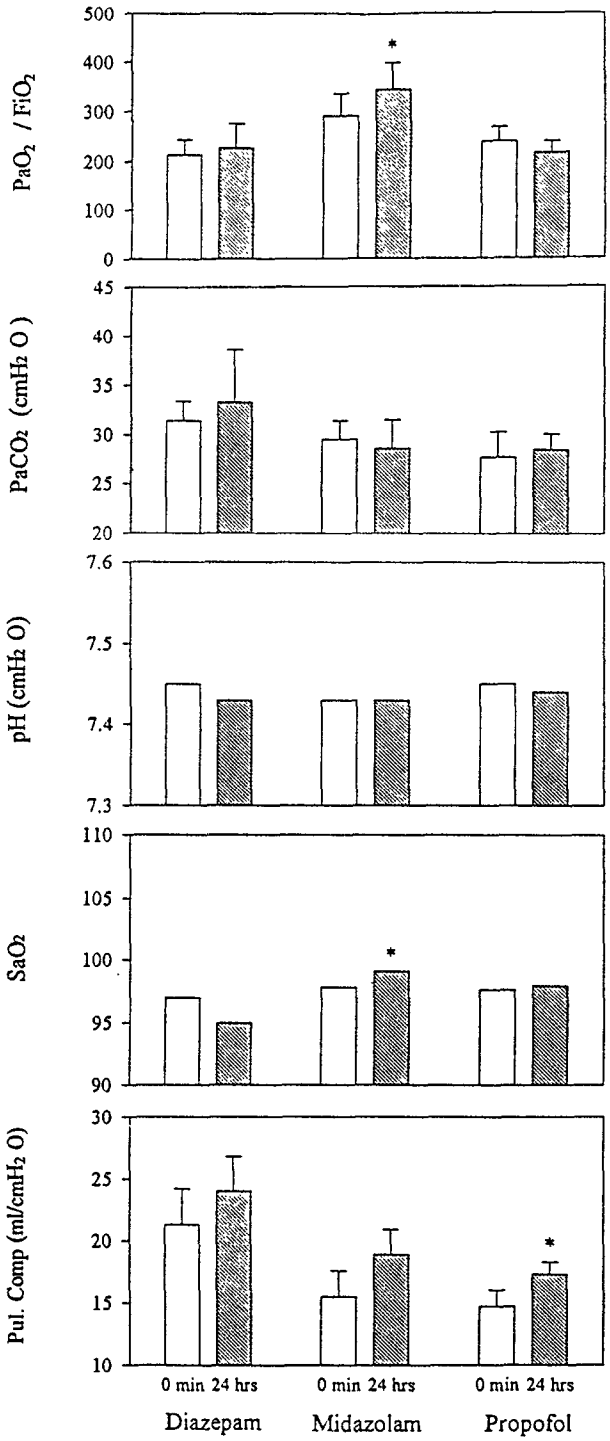

Fig 4. The changes of pulmonary parameters throuph 24hr sedation Data displayed as mean (sem). *Significant difference from baseline within the group, p≤0.05.

azepam and its active metabolites are altered in ICU patients fowith liver disease, making the sedative effect difficult to predict. We found that the mean recovery time following diazepam in patients with impaired liver function was 450±143 min vs. 208±37 min in patients with normal liver function. We recently reported two patients who had seizures following the use of flumazenil to reverse the sedative effect of diazepam[22]. Both of them were suspect to have sepsis with liver dysfunction. The seizures most likely resulted from a septic encephalopathy that was masked by diazepam. The use of diazepam for sedation in those patients whose metabolic systems are impaired or whose neurologic systems are under an ongoing change may not be suitable. In this study, the slow reversibility of diazepam after repeated administration makes it hard to assess a patient's neurologic status.

Midazolam has several advantages over diazepam: it is devoid of venous irritation upon injection; its potency is twice that of diazepam; its onset is more rapid with a half-life of only 2-3 hours; its metabolites are inactive[23] and has a rapid recovery[24]. Between individuals, however midazolam showed a wide variability in recovery (range from 30 min to 90 min). The sedative effects also tended to prolong in patients with liver disease (Mean recovery time in patients with impaired liver function was 70±8 min vs. 53±9 min in patients with normal liver function). Our study found that midazloam did not produce prolonged sedation in patients with renal impairment and this is consistent with the results reported by Vinik[25].

In the propofol group, the recovery time was most reliable. Five patients with associated liver dysfunction had a moderately prolonged recovery time (Mean recovery time in patients with impaired liver function was 18±2 min vs. 9±3 min in patients with normal liver function). The rapid recovery of propofol, even in the liver-impaired patients, was important for the daily assessment of neurologic status[26].

The objective assessment of sedative quality showed little difference between the midazolam group and propofol group[27]. Nevertheless, the nurs-

ing staff and the investigator seemed to have a preference for propofol because it was easier to titrate the dose, though the reflection might not be free of observer bias.

Our results showed that the cardiovascular effects of the three agents were quite uniform (Fig 3). The arterial blood pressure decreased slightly in all patients, but the cardiac output or left ventricular filling pressure was not affected. The findings indicate that the changes in arterial pressure were attributable to a decrease in peripheral vascular resistance[28,29]. Tissue perfusion was not compromised as cardiac output was well maintained and metabolic acidosis did not develop[16,27]. A moderate decrease in heart rate and arterial pressure suggested that the sedative effects of diazepam, midazolam or propofol effectively suppressed the sympathetic discharge to noxious stimuli[30].

One indication for sedation was to facilitate mechanical ventilation. After adequate sedation was achieved, the dynamic lung compliance improved in all three groups. The improvement was of statistical significance only in the propofol group (Fig. 4). We speculate that those patients had a poorer baseline in comparison to the diazepam or midazolam group. In the midazolam group, the improvement in oxygenation was possibly due to better ventilation/perfusion matching with an increased cardiac output (Fig. 3).

In summary, both midazolam and propofol infusion offered a superior quality in sedation and their rapid degradation made them suitable for long-term infusion use, when compared to bolus diazepam. The advantage of midazolam over propofol was that its sedative effects and respiratory depression could be promptly reversed by flumazenil, a benzodiazepine antagonist. The advantage of propofol was that it was easy to titrate the dose. Both midazolam and propofol appeared to be safe and effective sedatives in the ICU. In view of their cardiovascular effects, they should be used with caution in patients with poor cardiac reserve.

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外科加護病房中比較Diazepam, Midazolam和Propofol之鎮靜效果

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選擇三十位住進外科加護病房，疾病嚴重程度相同(APACHE II分數小於20)，且使用呼吸器的病患做為研究。將他們隨意分為三組，分別於24小時內使用Diazepam, Midazolam和Propofol做為鎮靜劑，並使用Morphine止痛。Diazepam組24小時平均使用56.4±0.3 mg, Midazolam組和Propofol組分別以0.08±0.01 mg/kg/hr和1.4±0.5 mg/kg/hr連續灌流以達到滿意之鎮靜程度。結果顯示Midazolam和Propofol比diazepam有較佳之鎮靜滿意度和意識快速恢復的特性，而Diazepam組意識恢復慢，尤其用在肝功能異常之病人。在維持不變的心輸出量下，血壓三組皆有明顯下降。Midazolam組並能明顯改善血氧濃度。總體而言，Midazolam或Propofol之連續灌流可視為加護病房中既安全又有效的鎮靜方式。

關鍵詞：Diazepam, Midazolam, Propofol，加護中心，鎮靜，機械式換氣

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