with either a prolonged or normal QT interval, the occurrence with a normal QT interval being more unusual. PVT that occurs in the setting of a prolonged QT interval is more commonly referred to as TdP. Although this distinction is controversial, it does have implications in management. Those PVTs with prolonged QT intervals should not be treated with class I antidysrhythmic agents, but rather with discontinuation of these drugs. Prolonged episodes may be treated with electrical conversion plus subsequent isoproterenol infusion or overdrive atrial pacing. On the other hand, those cases with a normal QT interval respond well to treatment with a class I dysrhythmic agent.

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Midazolam Infusion for Sedation in the Intensive Care Unit: Effect on Adrenal Function

J. M. Shapiro, M.D.,* L. M. Westphal, B.A.,† P. F. White, Ph.D., M.D.,‡
R. N. Sladen, M.B., M.R.C.P. (U.K.), F.R.C.P.(C.),§ M. H. Rosenthal, M.D.¶

Benzodiazepines, opioids, and butyrophenones are frequently used in the intensive-care setting to treat agitation that, if uncontrolled, might prove hazardous to the critically ill patient. Problems related to agitation include cardiorespiratory instability, injuries to patients and hospital personnel, inability to cooperate with nursing care, failure to maintain optimal positioning in bed, and disruption of life-sustaining tubes and catheters. Thus, the ability to provide safe, controllable, and reversible sedation can be important in the care of critically ill patients.

The multitude of drugs used to control agitation attests to the lack of an ideal drug or combination of drugs.[1] The most popular benzodiazepines, diazepam and lorazepam, have a slow onset and long duration of action, which may make titration difficult in the agitated patient. Morphine sulfate, the prototype opiate analgesic, can produce dose-related respiratory depression, hemodynamic instability, and inhibition of gastrointestinal motility. Haloperidol, an antipsychotic tranquilizer with sedative and antiemetic properties, can produce dysphoria and hypotension. The sedative–hypnotic etomidate can provide effective sedation in both mechanically ventilated[2] and spontaneously breathing patients.[3] However, critically ill patients receiving prolonged sedation with etomidate

* Fellow, Critical Care Medicine.
† Medical Student Research Assistant.
‡ Assistant Professor of Anesthesia; Chief, Outpatient Anesthesia Service.
§ Associate Professor of Anesthesia; Associate Medical Director, Intensive Care.
¶ Associate Professor of Anesthesia, Medicine, and Surgery; Medical Director, Intensive Care Unit.

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Address reprint requests to Dr. White: Department of Anesthesia, Room S-268C, Stanford School of Medicine, 300 Pasteur Drive, Stanford, California 94305.

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TABLE 1. Demographic Data Regarding Patients Receiving a Midazolam Infusion for Control of Excessive Agitation

Case No.	Age (yr)	Weight (kg)	Brief History	Days in ICU		Degree of Agitation
				Before Infusion	Total Stay	
1	60	87	Unstable angina, cardiac arrest emergency coronary artery bypass surgery, intraaortic balloon pump	6	19	Thrashing, uncooperative, pulling endotracheal tube
2	73	67	Ventricular tachycardia, cardiac arrest, aspiration pneumonia, pneumothorax, anoxic encephalopathy, sepsis	13	33	Thrashing, uncooperative
3	29	67	Acquired immune deficiency syndrome, acute renal failure, pneumocystis pneumonia, ARDS*, sepsis	20	32	Irritable, uncooperative, pulled out nasogastric tube
4	22	66	Status asthmaticus, bilateral pneumothoraces	6	11	Thrashing, uncooperative, pulled out two chest tubes
5	77	60	Abdominal aortic aneurysm repair, postoperative exploratory laparotomy	5	17	Thrashing, uncooperative, pulling out tubes
6	33	64	Mixed connective tissue disease, ARDS*	10	23	Thrashing, uncooperative

* Adult respiratory distress syndrome.

may have an increased mortality rate when compared with patients receiving benzodiazepines and opiates.[4] Furthermore, etomidate inhibits adrenal steroidogenesis in a manner analogous to the imidazole-containing antifungal agent ketoconazole.[5] An impaired adrenal response to stress and infection might account for the reported increased mortality associated with the use of etomidate in the intensive care unit (ICU).

Midazolam is a new, water-soluble imidazobenzodiazepine with a rapid onset of action and short elimination half-life compared with diazepam or lorazepam.[6] We evaluated the use of midazolam by continuous infusion for prolonged sedation of critically ill adult patients. Like etomidate, midazolam is an imidazole-containing compound; thus, adrenocorticotropic hormone (ACTH) stimulation tests were performed to assess adrenocortical function during midazolam administration.

METHODS

Six adult patients in the ICU were studied according to a protocol approved by our Committee for the Protection of Human Subjects in Research. Informed consent was obtained from each patient's family or guardian. Patient demographic data are summarized in table 1. Five of the patients had received prolonged mechanical ventilatory support. All six required four-extremity restraints to control agitation despite a sedative regimen consisting of benzodiazepines, opiates, and butyrophenones (table 2).

Using pharmacokinetic data from the anesthesia literature,[6] it is possible to calculate a loading dose ("priming infusion") and an initial maintenance infusion rate. If the serum level of midazolam required to produce sedation ranged from 50–250 ng/ml,[7,8] the loading dose (equal to the serum drug concentration multiplied by the volume of distribution) would range from 0.05–0.6 mg/kg. Assuming a clearance rate equal to approximately 50% of hepatic blood flow, the maintenance infusion rate (equal to the serum drug concentration multiplied by the clearance rate) might be expected to vary between 0.3 and 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

Prior to beginning the midazolam infusion, an ACTH stimulation test was performed using synthetic ACTH (Cortrosyn®) 250 μg iv.[9] Plasma cortisol levels were de-

TABLE 2. Intravenous Drugs Used to Control Agitation during the 48-h Interval prior to Initiating Midazolam Infusion

Case No.	Drug Name				
	Morphine (mg)	Diazepam (mg)	Lorazepam (mg)	Haloperidol (mg)	Miscellaneous
1	109	70.5		21	fentanyl 9.23 mg
2	33	12.5	10	8	
3	14		25		codeine 30 mg
4	35	106	16	8	hydromorphone 176 mg and ketamine 180 mg
5	123	84.5			fentanyl 8.97 mg
6			8		fentanyl 20.12 mg and sufentanil 175 μg

TABLE 3. Effect of Midazolam Infusion on Plasma Cortisol Levels (μg/dl) Following Adrenocorticotropic Hormone (ACTH) Stimulation

Patient No.	Prior to Infusion		During Midazolam*	
	Basal	60 min Poststimulation	Basal	60 min Poststimulation
1	14	38	12	38
2	29	46	26	46
3	†	†	8	37
4	†	†	†	†
5	15	42	16	44
6	8	15	6	25

* After receiving infusion for 24 h.
† Data not available (plasma sample lost by clinical laboratory).

termined by specific radioimmunoassay[10] before and 60 min after administration of the ACTH. Normal cortisol values are 5–25 μg/dl, and a normal cortisol response to ACTH stimulation is an increase of at least 7 μg/dl.[9] The ACTH stimulation test was repeated after midazolam had been infused for 24 h.

All patients were monitored with arterial catheters and standard electrocardiography. After measurement of baseline arterial blood pressure and heart rate, midazolam was administered as a loading infusion (25 $\mu g \cdot kg^{-1} \cdot min^{-1}$) to control agitation, followed by an initial maintenance infusion of 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The maintenance infusion was continued for 48 h and adjusted according to the following criteria: 1) if the patient became agitated, a midazolam bolus (0.05 mg/kg) was administered, and the maintenance infusion was increased by 50–100% of the existing rate; or 2) if excessive sedation was noted (*e.g.*, unresponsiveness to verbal stimuli), the infusion rate was decreased by 50–100%. After completing the 48-h study period, the midazolam infusion was discontinued, and therapy was resumed with a combination of sedative and opiate drugs (*e.g.*, diazepam, morphine).

Total doses of sedative, analgesic, and tranquilizing agents were determined for the 48-h period prior to the midazolam infusion in each patient (table 2). On starting the midazolam infusion, these drugs were discontinued except for small doses of opiate analgesics (*e.g.*, morphine 1–2 mg iv, every 2–4 h), which were administered as necessary for pain control.

TABLE 4. Administration of Intravenous Midazolam during the 48-h Study Period

Case No.	Loading Dose		Infusion rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	Total Dose (mg)
	(mg)	(mg/kg)		
1	14	0.16	0.3–1.4	280
2	10	0.15	0.4–2.5	252
3	20	0.30	0.1–0.4	58
4	20.5	0.34	0.2–9.0	646
5	8	0.18	0.5–7.2	563
6	32	0.50	2.5–20.3	1586

RESULTS

Midazolam infusion effectively controlled severe agitation in all patients studied without suppressing adrenal responsiveness to ACTH stimulation (table 3). The dose of midazolam administered as a loading infusion was variable and ranged from 0.15 to 0.5 mg/kg (table 4). The maintenance infusion rate also showed marked individual variation, ranging from 0.1 to 20.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Titration of the maintenance infusion provided easily controllable and effective sedation during the 48-h study period. This permitted discontinuation of physical restraints, muscle relaxants, and other sedative medications except for small doses of opiates (maximum dose of morphine sulfate 2 mg/h). As a result of its clinical effectiveness, house staff and nursing staff requested that the midazolam infusion be restarted in four of the six patients after completion of the study.

Although the patients received large total doses of midazolam, excessive sedation responded promptly to decreases in the infusion rate, and all patients were responsive to verbal commands within 1 to 2 h after terminating the infusion. This included two elderly patients (no. 2 and no. 5) who received 252 mg and 563 mg, respectively, during the 48-h study period. There was no evidence of increasing sedation in a patient (no. 3) with acute renal failure (serum creatinine 7 mg/dl) who received a total dose of 346 mg over 9 days. When he was receiving large doses of sedative and analgesic drugs prior to the study, patient no. 4 was dysphoric, uncooperative, and unable to recognize his family members. The midazolam infusion was increased at night and decreased during the day in order to restore a normal sleep–wake cycle. After termination of the infusion, the patient became alert and oriented within 2 h and required no additional sedative medication during the remainder of his stay in the ICU.

No episodes of cardiovascular or respiratory depression attributable to midazolam occurred during the study period. Even in patients who became hypotensive following small doses of morphine sulfate or lorazepam, hemodynamic instability was not observed during the midazolam infusion. Three of the patients required inotropic agents for blood pressure support prior to initiating therapy with midazolam. Neither the loading nor the maintenance infusion of midazolam produced hypotension requiring an increase in the dose of the inotropic agent or discontinuation of the midazolam infusion. The infusion of midazolam did not alter the cardiac output in the three patients with pulmonary artery catheters. Five of the patients were endotracheally intubated and were receiving synchronous intermittent mandatory ventilation (SIMV),

while one patient (patient no. 4) received supplemental oxygen *via* face mask. All patients maintained spontaneous ventilatory rates of at least 10 breaths/min, and Pa_{CO_2} values were in the normal range. Four of the six patients recovered from their illnesses and were ultimately discharged from the ICU (table 1). Patients no. 3 and no. 6 both died of respiratory failure on the 32nd and 23rd ICU days, respectively.

Discussion

In a survey of modes of sedation in 34 ICUs, Merriman described a variety of drugs and techniques.[1] There is no consensus regarding the optimal approach to managing the agitated, ventilator-dependent patient. With the introduction of shorter-acting sedative and analgesic drugs, the use of iv infusions is becoming increasingly popular in the ICU.[2,3,11] Continuous infusion of etomidate produces effective sedation in healthy postoperative patients[2,3] and critically ill patients.[4,5] A 20-h infusion of etomidate in an ICU patient, however, suppressed adrenal steroidogenesis for 4 days.[5] *In vitro* studies have demonstrated inhibition of 11-β-hydroxylase and cholesterol side-chain cleavage enzymes by the imidazole-containing sedative.[5] Like etomidate, midazolam contains an imidazole ring structure. Animal studies have revealed that midazolam, 0.2 mg/kg, suppressed the elevation of plasma cortisol in response to a hypotensive stimulus at 2 and 10 min, but not at 20 min.[12] In our study, adrenal steroidogenesis was not suppressed by a 24-h midazolam infusion.

Midazolam is approximately twice as potent as diazepam, and its chemical properties confer clinical advantages when compared with other available benzodiazepines. In contrast to diazepam, midazolam is water-soluble and associated with a lower incidence of venous complications.[6] The imidazole ring undergoes rapid hydroxylation, resulting in a short elimination half-life (1–4 h)[13–15] compared with diazepam (21–37 h)[16] or lorazepam (12–14 h).[17] In addition, midazolam is more lipophilic and has a more rapid onset of action than diazepam or lorazepam.[18] This study demonstrated the safe and effective use of a midazolam infusion for prolonged sedation in a small but diverse group of critically ill patients. However, because of the small number of subjects involved in this investigation, one must be cautious in extrapolating these results to a larger population of patients requiring iv sedation.

Since completing this study, we have used midazolam infusions in the treatment of several additional patients without any significant problems. Recently, a 67-yr-old woman with adult respiratory distress syndrome required midazolam (25–100 mg/h) to control severe agitation refractory to a combination of diazepam, morphine, and haloperidol. This patient received a total dose in excess of 2,000 mg over a 36-h period without clinical or laboratory evidence of toxicity related to the midazolam. In the study patient with renal failure (no. 3), midazolam did not produce prolonged sedation. This is consistent with a recent study showing that midazolam's elimination half-life is not significantly altered in patients with renal failure.[19]

Infusions of iv anesthetics are frequently administered on an empirical basis. However, if the desired blood level of the drug is known, pharmacokinetic variables can be used to predict the dosage requirement. Because most pharmacokinetic studies are performed on healthy subjects, these data are less useful when managing critically ill patients. In the ICU environment, patients often receive a variety of centrally active drugs (table 2). The development of pharmacodynamic tolerance to the sedative effects of these drugs would be expected to increase the blood (and hence brain) concentration of drug required to produce a given effect. Central tolerance to midazolam's sedative effects might account for the high maintenance infusion rate required by some of our patients (table 4).

Opiate analgesic infusions are a rational alternative to the use of sedatives and tranquilizers for control of agitation in ventilator-dependent patients. However, problems associated with their use include respiratory depression, inhibition of gastrointestinal motility, chest wall rigidity, development of tolerance, and the withdrawal syndrome. Tolerance to fentanyl has been reported to develop within hours after its administration,[20] thereby increasing the opiate dosage requirement and expense. Shafer *et al.*[11] described a patient receiving a fentanyl infusion over a 9-day period who was awake and responsive with serum fentanyl levels of 60 ng/ml, two to three times the level normally achieved during high-dose fentanyl anesthesia for cardiac surgery. In three of the six patients in the present study, agitation was *inadequately* controlled with a fentanyl infusion prior to initiating the midazolam infusion.

Midazolam decreases tidal volume in healthy volunteers.[21] Equipotent doses of diazepam (0.3 mg/kg) and midazolam (0.15 mg/kg) produce a comparable degree of respiratory depression.[22] Although the effects of midazolam on respiratory function were not quantitated, adverse efects attributable to respiratory depression were not observed during the midazolam infusion. Because benzodiazepines are frequently given in combination with opiate analgesics, further studies are necessary to determine the combined effects of these drugs on ventilation when infusion techniques are used.

In summary, a continuous infusion of midazolam provided safe and readily reversible control of extreme agitation in six critically ill patients. The residual effects of the centrally active sedative tranquilizing drugs (*e.g.*, diazepam, lorazepam, haloperidol) may have contributed

to the improved clinical state observed during the midazolam infusion. However, it was only after adding midazolam that adequate sedation was obtained. In addition, effective sedation was achieved using a midazolam infusion without inhibiting adrenal steroidogenesis or producing cardiorespiratory instability. We conclude that a midazolam infusion may be a useful drug in the management of agitated patients in the ICU setting.

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Changes in T-wave Morphology Following Anesthesia and Surgery: A Common Recovery-room Phenomenon

MICHAEL J. BRESLOW, M.D.,* CLAIR F. MILLER, M.D.,* STEPHEN D. PARKER, M.D.,* A. TERRY WALMAN, M.D.,* MARK C. ROGERS, M.D.†

Preoperative and postoperative electrocardiograms (ECGs) are commonly obtained in patients at risk for perioperative ischemic events. In our institution, this practice identified a large number of patients with new postoperative T-wave abnormalities in whom there were no other signs or symptoms of myocardial ischemia. Concern that these acute changes represented myocardial ischemia often prompted intensive care unit admission, cardiology consultation and, occasionally, treatment with drugs. These patients, however, uniformly had an uneventful course without cardiovascular complications. This suggested to us that postoperative repolarization abnormalities may not be due to myocardial ischemia and that a less aggressive management approach might be warranted.

* Assistant Professor.
† Professor and Chairman.

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Address reprint requests to Dr. Breslow: Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins Hospital, Baltimore, Maryland 21205.

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