Treatment of Refractory Generalized Status Epilepticus with Continuous Infusion of Midazolam

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Objective: **To determine the efficacy and safety of midazolam given as a continuous infusion in the treatment of refractory generalized status epilepticus (RGSE).**

Method: **Prospective, open study. Eleven patients with RGSE, who received intravenous doses of 0.3 mg/kg of diazepam (three times at 5 min intervals), 20 mg/kg of phenytoin, and 20 mg/kg of phenobarbital that failed to bring the episode under control were administered a bolus of midazolam (200 mg/kg iv) followed by a continuous infusion at 1 mg/kg/min. The dose was increased every 15 min until the episode of seizure was brought under control. Time to control seizures, infusion rate, and side-effects were monitored.**

Results: **The mean age of the patients was 22.8 yrs (range 16 yrs to 73 yrs; 5 females and 6 males). In ten of the patients, seizures were completely controlled in a mean time of 2.1 hrs (range 0.4 hrs to 4.5 hrs), with an infusion rate of 8.4 mg/kg/min (range 3 to 12). In one patient seizures did not stop. None of the patients had clinically important changes in blood pressure, heart rate, oxygen saturation or respiratory status attributable to the use of midazolam. The mean time to full consciousness for patients after stopping the infusion was 1.6 hrs (range 2 to 8.5).**

Conclusion: **Midazolam is an effective and safe drug to control RGSE and may represent a substantial improvement over current therapeutic approaches such as pentobarbital anesthesia.**

Key words: *Midazolam, anticonvulsants, status epilepticus, neurologic emergencies.*

Status epilepticus is one of the most common and perhaps one of the most poorly understood neurologic emergencies encountered in critical care (1). The term is applied to situations in which seizures occur so frequently that complete recovery between fits does not take place, or that were continuous for at last 30 minutes (2).

Prolonged seizure activity itself produces irreversible cerebral damage, independent of accompanying hypoxia and acidosis. Cell death is thought to occur as a result of the excessive metabolic demands and nutrient depletion of continuously firing neurons (3). The correct management of patients with seizures focuses largely on the underlying pathology and the speed at which seizures can be controlled (3,4). Generalized status epilepticus is refractory to standard anticonvulsant therapy in approximately 10 to 15% of patients (5). The significant morbidity and mortality of refractory generalized status epilepticus (RGSE) is due to the nature of the underlying illness and sustained seizure activity as well as the toxicity of current treatment modalities (6-8). Midazolam has been shown to have a wide margin of safety and a broad therapeutic index (9,10). There are a few studies in which midazolam are used successfully to treat seizures in adults and children (11-14) and status epilepticus (10,15,16). In this study we planned to investigate efficacy of midazolam in RGSE in adults.

Material and Method

Eleven patients with the diagnosis of RGSE were admitted to the intensive care unit of our institution from May 1995 through July 1999. RGSE was diagnosed (determined by clinical observation or EEG) in patients who continued to have seizures after receiving intravenous doses of 0.3 mg/kg of diazepam (three times at 5 min intervals), 20 mg/kg of phenytoin, and 20 mg/kg of phenobarbital. Midazolam was then given intravenously at a concentration 200 mg/kg as a bolus followed immediately by a constant infusion (XL Plum infusion pump, Abbott, Chicago, USA) started at 1 mg/kg/min and increased every 15 min until there was no clinical findings of seizures. Once the event was under control, we maintained the continuous infusion for a 12-hrs period free of relapsing episodes. Once that goal was achieved, the infusion rate was gradually decreased (1mg/kg/min every 15 min) until tapering was completed. The treatment of these patients was based on a protocol (Table I) using midazolam for RGSE that was put into place in March 1992 (15).

Variables such as age, weight, sex, history of seizures, underlying disease(s) and the time required for the clinical manifestation of seizure activity to be brought under control were carefully recorded for each patient. The onset of breakthrough seizures after control had been achieved. Heart rate, noninvasive determination of blood pressure respiratory rate, pulse oxygen saturation (ABL 50, Radiometer, Copenhagen, Denmark) and the quality and quantity of nasopharyngeal secretions were also recorded on admission and hourly thereafter. All patients had oxygen supply via an intranasal cannula (Argyle, Sherwood Medical, USA) to prevent hypoxia and patients were closely monitored (the standard care in our unit).

All patients were monitored for the development of adverse effects of midazolam, diazepam, phenytoin and phenobarbital therapies, such as hypotension, hypoxia, and respiratory depression. In order to determine the underlying etiology rapidly, history, physical examination, standard laboratory evaluations including determination of

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Table I. Protocol of intravenous midazolam for refractory generalized status epilepticus at the University of California, San Francisco

1. Proceed with midazolam protocol only after the patient has received full loading doses of lorazepam, phenytoin, and phenobarbital. Monitor vital signs closely and treat hyperthermia. Initiate therapy for the underlying etiology of status as soon as possible.
2. If the patient is still seizing, intubate (if not yet done) using a short-acting paralytic agent, ventilate and transfer to the intensive care unit.
3. If the patient remains comatose, begin EEG monitoring. If the EEG suggests ongoing seizures or if the patient has overt convulsions, proceed with midazolam infusion. Place an arterial line and consider central venous monitoring as indicated.
4. Administer midazolam loading dose of 200 μg/kg as a slow intravenous bolus, followed by 0.75 to 10 μg/kg/min continuous intravenous infusion. Higher doses may be necessary, especially with prolonged infusions, due to possible tachyphylaxis. Adjust the maintenance dose to stop electrographic seizures based on EEG monitoring. EEG should be recorded continuously for the first 1 to 2 hours during and after the initiation of midazolam loading and infusion and then monitored either continuously or for 30- to 60- minute intervals every 2 hours during the maintenance phase. The primary end point for therapy is suppression of electrographic seizures.
5. Continue maintenance doses of phenytoin and phenobarbital, and follow levels to determine optimal doses.
6. Use intravenous fluids and low- dose dopamine (up to 10 μg/kg/min) to treat hypotension. If necessary, low-dose dobutamine may be added. Decrease the dosage of midazolam if any signs of cardiovascular compromise arises.
7. Discontinue the midazolam infusion at 12 hours while monitoring the EEG and observe for further clinical or electrographic seizure activity. If seizures recur, reinstate the infusion and repeat this step at 12-to 24- hour intervals or longer if the patient's seizures remain refractory.

Table II. Description of midazolam treatment of RGSE in eleven patients.

Patient	Age	Sex	Weight (kg)	RGSE etiology	Midazolam effect latency (min)	Maximum infusion rate (μg/kg/min)	Duration of infusion (hrs)	Outcome
1	16	Male	46	Idiopathic epilepsy	90	12	13.5	Full recovery
2	18	Male	74	Idiopathic epilepsy	45	8	12.75	Full recovery
3	73	Female	80	Viral encephalitis	60	8	13	Death
4	19	Female	57	Symptomatic epilepsy	40	6	12.6	Full recovery
5	22	Male	67	Idiopathic epilepsy	70	6	13.1	Full recovery
6	27	Female	55	Metabolic disorders	120	7	14	Full recovery
7	60	Female	79	Renal failure	25	4	12.41	Death
8	73	Male	65	Meningitis	45	3	12.75	Mild
9	24	Male	57	Cardiac arrest	120	10	14	Mild
10	20	Female	69	Symptomatic epilepsy	30	3,5	12.5	Full recovery
11	16	Female	48	Unknown	No effect	21	1.2	Death

electrolytes, glucose, blood urea nitrogen, liver function, a complete blood count, alcohol level, toxicology screen, cerebrospinal fluid, blood gases, serum anticonvulsant levels, EEG and brain imaging studies were performed and 12 hours following the initial evaluation, serum sodium, potassium, chloride, total calcium, serum glucose and magnesium concentrations were measured in all patients again.

Results

Of 11 patients admitted to our intensive care unit with status epilepticus, 5 were male and 6 female. Mean age was 29.8 yrs (range 16 to 73 yrs) and the mean weight was 63.3 kg (range 46 to 80 kg). Five patients had a history of epilepsy and were receiving anticonvulsant ambulatory therapy. At the moment of admission, the serum concentrations of drugs taken were not known. The other six patients presented the emergency room with their first convulsive episode. An overview of the hospital course and details of the seizure management are described for each patient (Table II).

The ictal episode presented in patients were both generalized tonic-clonic (n=9); and focal, but secondary generalized seizures (n=2). The mean time between admission to the emergency room and the establishment of the midazolam infusion was 1.2 hrs (range 0.27 to 3.5). All patients were well oxygenated as demonstrated by pulse oximetry, and excessive saliva was removed by frequent naso-oropharyngeal suctioning.

Complete arrest of seizures was achieved with

midazolam therapy in ten patients. The mean time between the start of midazolam infusion and the total cessation of seizures was 2.1 hrs (range 0.4 to 2 hrs). The mean infusion rate of midazolam necessary to control the fits was 8.04 mg/kg/min (range 3 to 12). In one patient convulsion did not stop in spite of the constant infusion dose of 21 mg/kg/min of midazolam. Because high dose of midazolam failed to stop status epilepticus within 1hr, high dose pentobarbital was started immediately.

None of the patients experienced clinically important changes in blood pressure, heart rate, oxygen saturation or respiratory status while receiving midazolam as an intravenous infusion. Two (18%) of 11 patients had a slight increase in pharyngeal secretions but frequent suctioning solved the problem in all cases. On admission and at 12 hrs of intravenous midazolam, serum electrolytes and glucose concentrations were determined to be within normal limits in all patients

Discussion

There is no consensus about the optimal management of patients with RGSE. Among the treatments proposed are paraldehyde, lidocaine, inhalation anesthetics and high-dose barbiturates (17,18). Perhaps the most well-studied therapy is pentobarbital coma (6-8,15). Although pentobarbital coma is extremely effective in terminating RGSE, it often causes hemodynamic instability due to myocardial depression and vasodilatation. Due to its high lipid solubility after intravenous administration, and its redistribution to muscle, fat, and eventually all body tissues, pentobarbital metabolizes slowly (12% to16% per hour). Thus, days are required to have a patient completely awake and cooperative. Patients treated with pentobarbital coma frequently require prolonged intubation, invasive hemodynamic monitoring and the use of pressor agents (8,15).

Paraldehyde is difficult to handle because the drug deteriorates to acetaldehyde and acetic acid when exposed to light or air and has to be administered in a glass syringe. It has several side-effects, such as pulmonary hemorrhage, pulmonary edema, renal and liver toxicity and severe phlebitis when used intravenously (19). Isoflurane, an inhalational general anesthetic agent, is effective in controlling refractory seizures. However, it also produces respiratory depression and muscle relaxation yet little change in hemodynamic status. When isoflurane is used, most patients will need endotracheal intubation and mechanical ventilation (20). The significant morbidity associated with this therapeutic approach has prompted investigators to search for an alternative regimen that is equally effective and less toxic (15).

Midazolam, a 1.4 benzodiazepine agent of the group of 1.2 annulated benzodiazepines, is a water-soluble compound with rapid central nervous system penetration and a short elimination half-life of 1.5 to 3.5 hours (21). It is commonly used as an amnestic and anxiolytic agent and for operative induction and sedation of critically ill patients. The finding of anticonvulsant efficacy in animal studies was followed by anecdotal reports of the success of IV and intramuscular midazolam in terminating seizures and status epilepticus in humans (10,14-16,22,23).

Our results are comparable with those results published in previous studies (15,16,24,25). Compared with other drugs used to treat status epilepticus, midazolam offers various advantages. It acts more rapidly and is safer and more effective (26). Comparing the efficacy and safety of intramuscular and intravenous midazolam with those properties of diazepam during the acute phase of seizure disorder, midazolam appeared to be more effective for the control of seizures than a comparable dose of diazepam (27). In our series, midazolam was 91% efficacious in taking seizures under control. Our patients did not have electroencephalographic monitoring and all observations were mostly clinical. Treiman and co-workers (28) showed that there are several types of electroencephalographic patterns during the course of generalized convulsive status epilepticus and it is possible that some of them continue to be present even when the clinical icteric manifestation has ceased. Nevertheless, it is difficult in clinical practice to connect all patients with continuous electroencephalographic monitoring equipment. Also, the decision to increase the dose of drugs based on electrical seizure activity is not clear.

Midazolam given as an IV bolus followed by continuous infusion appears to be a relatively safe and effective alternative for the management of patients with RGSE. It offers the advantage of more rapid clearance than other benzodiazepines and pentobarbital. This allows for earlier clinical assessment of patient and a reduction in the associated complications and cost of prolonged stays in the intensive care unit. Furthermore, the study by Rivera et. al (10) suggests that initiating midazolam immediately to patients with RGSE for whom first-line benzodiazepine and phenytoin therapy has failed may obviate the need for mechanical ventilation in selected patients, thus further reducing related complications.

Ghilain and co-workers (15) found a 15% occurrence rate of slight hypotension and a 10% frequency of bradycardia when 0.2 mg/kg of midazolam was given intramuscularly to patients with seizures. Kumar and Bleck (16) reported the successful treatment of seven patients with RGSE using IV midazolam given as a bolus followed by continuous infusion. Adverse effects were minimal and only one patient developed mild hypotension. None of our patients experienced episodes of hypotension or changes in heart rate while midazolam was infused. Respiratory depression was not detected in any of our patients.

Walton and Treiman (29) showed that status epilepticus becomes more difficult to control as a function of its duration. In one of our patients (case 11), seizure did not stop in spite of the administration of high-dose midazolam (a bolus of midazolam 200 mg/kg followed by a continuous infusion at 21 mg/kg/min). The most important factor affecting the course of the therapy was probably the delay in admission to emergency room from the beginning of

status epilepticus (13 hrs).

These results suggest that midazolam is an effective and safe therapeutic approach for the management of patients with RGSE and may represent a substantial improvement over current therapeutic approaches such as pentobarbital anesthesia. We recommend now that given the safety of the drug, the interval to increase the dose be reduced to 3 min and that the time to control the episode be reduced.

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