Continuous midazolam infusion as treatment of status epilepticus

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Abstract

In a tertiary referral centre, midazolam infusion was tried as treatment for 20 children with status epilepticus over a period of two years. The mean age of the children was 4.07 years. Twelve children with refractory status epilepticus had received intravenous or per rectal diazepam and intravenous phenytoin/phenobarbitone or both before midazolam was given (0.15 mg/kg bolus followed by 1–5 µg/kg/min infusion). Eight children required only midazolam to control the established status epilepticus. The seizures were controlled in 19 children. The mean time required for complete cessation of seizures was 0.9 hours. The mean infusion rate required was 2.0 µg/kg/min. All children had regained full consciousness by a mean of 5.1 hours after discontinuation of midazolam treatment. No metabolic derangement or compromise of vital functions was noted in any of the children. Midazolam infusion is thus an effective and safe therapeutic approach for the management of childhood status epilepticus.

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Status epilepticus is a medical emergency that requires prompt intervention. The term is applied to situations in which seizures occur so frequently that complete recovery between fits does not take place.[1] A more substantive definition is continuous seizures lasting for 30 minutes or longer or recurrent seizures occurring with impairment of consciousness between seizure activity.[2] Status epilepticus is more common in childhood, and the reported death rate varies between 3 and 20%.[3] Prolonged seizure activity itself produces irreversible cerebral damage, independent of accompanying hypoxia, acidosis, and consequent biochemical derangements. The excessive metabolic demands of continuously firing neurones leading to depletion of essential nutrients is currently thought to be the most important factor leading to cell death during continuous seizures.[4] Although the majority of children who suffer continuous seizures respond to intravenously administered diazepam and phenytoin sodium, some require other modalities of treatment including general anaesthesia, which could lead to serious adverse effects.

Midazolam is a recently developed water soluble benzodiazepine, commonly used as a preanaesthetic agent with remarkable anticonvulsant action.[5] It has been shown to have a wide margin of safety and a broad therapeutic index. Furthermore, it diffuses rapidly across the capillary wall into the central nervous system and can be mixed with saline or glucose solutions to allow its administration as a continuous infusion.[6]

Subjects and methods

Twenty children suffering from status epilepticus admitted to the paediatric ward from November 1993 to November 1995 were included in this study. Eleven were already taking various antiepileptic drugs.

Status epilepticus was diagnosed according to the criteria of Engel, namely continuous seizures for 30 minutes or longer or several seizures occurring with impairment of consciousness between seizure activity.[2] Refractory status epilepticus was the diagnosis if the seizures continued, despite at least two doses of diazepam intravenously or rectally in succession followed by phenytoin sodium/phenobarbitone or both 20 mg/kg given over 30 minutes as an infusion, or failure to respond to the latter alone or in combination. The duration of status before midazolam therapy was approximate, based on the history obtained from the patient's attendants and the referring physician's notes. Electroencephalography (EEG) was not used for the diagnosis. It was, however, performed after the seizures had been controlled to monitor the electrical suppression of seizure discharge. Continuous EEG monitoring was not available. However, it was used to diagnose non-convulsive status epilepticus at onset. All children underwent computed tomography scanning of the brain and other relevant investigations.

All 20 children received intravenous midazolam at 0.15 mg/kg as a bolus followed by a constant infusion starting at 1 µg/kg/min up to 5 µg/kg/min increasing by 1 µg/kg/min every 15 minutes until complete control of seizures was achieved. The optimum rate of infusion at which seizure control was achieved was maintained for a period of 24 hours. Subsequently the midazolam infusion rate was gradually decreased (by 1 µg/kg/min every two hours) until tapering was completed.

Variables such as age, weight, sex, history of seizures, underlying diseases, and the time required for control of seizures were carefully recorded for each patient. Vital parameters

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Table 1 Type, duration, and control of status epilepticus

					Status			Midazolam			
No	*Age*	*Sex*	*Diagnosis*	*Previous antiepileptic drugs*	*Type*	*Duration (minutes)*	*Antiepileptic drugs received to control*	*Rate (μg/kg/min)*	*Cessation of seizures (minutes)*	*Side effects*	*Outcome*
1	2 months	M	Acute purulent meningitis	Nil	GTC	40	DZP PR, IV, PHT IV	1	15	Nil	No recurrence
2	10 years	M	Idiopathic epilepsy	SVA, VGB, LTG, PHT, ETH	GTC	45	DZP PR, IV	1	30	Nil	No recurrence
3	10 years	F	Idiopathic epilepsy	—	GTC	30	PHT IV	1	15	Nil	No recurrence
4	4 years	F	Neurological degeneration	SVA	Partial motor/MYO	300	DZP PR	2.5	50	Nil	Several
5	1 year	M	Postencephalitic sequalae	PHT, PHB	GTC	180	DZP IV (3)	2.5	60	Nil	No recurrence
6	2 months	M	Cerebrovascular accident	SVA, PHT	GTC	120	DZP IV	1.5	25	Nil	No recurrence
7	6 months	M	Acute purulent meningitis	—	GTC	45	DZP IV, PHT IV	1.5	25	Nil	No recurrence
8	8 months	M	Acute purulent meningitis	—	Partial motor	60	DZP IV, PHB IV	1	25	Nil	No recurrence
9	5 years	M	Chronic encephalitis	SVA, CLZ	GTC, MYO	1440	DZP PR, IV, PHT IV	5	220	Nil	Lost to follow up
10*	3 years	M	Idiopathic epilepsy	CBZ	MYO, T	90	DZP IV	2	40	Nil	No recurrence
11	3 years	M	Idiopathic epilepsy	—	MYO, astatic	30	DZP PR	1	10	Nil	Recurred twice
12	13 years	M	Cerebrovascular accident	—	GTC	40	DZP IV	2	60	Nil	No recurrence
13*	4 years	M	Idiopathic epilepsy	CBZ, SVA, CLZ	MYO, T	120	DZP PR (2)	2	25	Nil	No recurrence
14	9 years	F	Idiopathic epilepsy	SVA, CBZ	Complex partial	65	PHT IV	2	30	Nil	No recurrence
15	3 years	F	Acute meningoencephalitis	—	Complex partial	60	PHT IV	2.5	50	Nil	No recurrence
16	6 months	M	Cerebral dysgenesis	PHB, PHT, SVA	GTC	720	DZP PR, PHT IV	5	240	Nil	Recurred twice
17	3 years	M	Idiopathic epilepsy	SVA, PHT	GTC, MYO	120	PHT IV	2	60	Nil	No recurrence
18	7 years	M	Idiopathic epilepsy	SVA, PHT	GTC	45	PHT IV	2	60	Nil	No recurrence
19	2 years	F	Acute meningoencephalitis	—	GTC	30	PHT IV, PHB IV	1	15	Spo_2 90%	No recurrence
20	2.5 years	M	Acute meningoencephalitis	—	GTC, dystonic	60	PHT IV, PHB IV	1.5	25	Spo_2 90%	No recurrence

GTC = generalised tonic-clonic; T = tonic; MYO = myoclonic; IV = intravenous; PR = per rectum; DZP = diazepam; PHT = phenytoin sodium; PHB = phenobarbitone; SVA = sodium valproate; CBZ = carbamazepine; VGB = vigabatrin; LTG = lamotrigine; ETH = ethosuximide; Spo_2 = oxygen saturation; * Lennox-Gastaut syndrome status.

including respiratory rate, heart rate, and blood pressure were documented. The oxygen saturation of each child was monitored continuously by pulse oximetry.

The children were also monitored for the development of adverse effects of benzodiazepines including hypotension, hypoxia, and respiratory depression. In order to exclude electrolyte and metabolic disturbances as a cause of the seizures, blood samples were taken on admission and at 24 hours to measure circulating sodium, potassium, calcium, glucose, and magnesium concentrations.

Results

Of the 20 children with status epilepticus admitted to our high dependency care unit, 15 were boys (table 1). The mean age was 4.07 years (range 2 months to 13 years). Eleven children had a history of seizures and were already taking antiepileptic drugs, which included various combinations of sodium valproate (n = 9), carbamazepine (n = 3), phenobarbitone (n = 2), phenytoin sodium (n = 6), clonazepam (n = 2), ethosuximide (n = 1), vigabatrin (n = 1), and lamotrigine (n = 1). Eight children had idiopathic epilepsy, three acute purulent meningitis, three acute meningoencephalitis, and the remainder had various vascular or degenerative lesions of the brain.

The type of status presented in the children as follows: generalised tonic-clonic (n = 13), partial seizure status (partial motor (n = 2), complex partial (n = 2)), myoclonic astatic (n = 1), and Lennox-Gastaut status (myoclonic + tonic; n = 2). Myoclonic seizures were seen as a combination of myoclonus with generalised tonic-clonic status in three others. Twelve patients had refractory status epilepticus (table 2). Their seizures continued for more than 30 minutes after administration of diazepam, followed by phenytoin sodium/phenobarbitone or both intravenously. Eight children being followed up in the outpatient department who were on various antiepileptic drugs were given midazolam infusion alone.

Table 2 Drugs given before midazolam in refractory status epilepticus

Drug	*No of cases*
Diazepam	12
IV	9
PR	7
Combined	3
Phenytoin	11 (2 with phenobarbitone)
Phenobarbitone	3 (2 with phenytoin)

IV = intravenous; PR = per rectum.

Table 3 Control of status epilepticus with midazolam infusion

	No of patients	Dose (μg/kg/min)		Time (minutes)	
		Range	Mean	Range	Mean
Refractory status epilepticus	12 (1)	1–5	2.12	15–240	64.6
Established status epilepticus	8	1–2.5	1.79	10–60	34.3
	20 (1)	1–5	2.0	10–240	54

Numbers in parentheses indicate numbers of patients in which seizures were not controlled.

Table 4 Dose of midazolam required to control status epilepticus and length of time required

Midazolam (μg/kg/min)	No of patients	Time (minutes)	
		Range	Mean
1	6	10-30	18.3
1-2	9	25-60	43.7
2- < 5	3	50-60	53.3
5	2 (1)	240	240.0

One seizure was not controlled (shown in parentheses).

Complete arrest of seizures was achieved with midazolam infusion in all but one of the 20 children (table 3). The non-responder had Batten's disease. The mean time taken to control status in refractory status epilepticus was 64.6 minutes (range 15–240 minutes) and in established status epilepticus, 34.3 minutes (range 10–60 minutes). However, the mean time between the start of midazolam infusion and total cessation of seizures in all patients was 0.90 hours (54 minutes). The mean infusion rate of midazolam required to control the seizures completely was 2 μg/kg/min (range 1–5 μg/kg/min). Fifteen of the patients were controlled with 2 μg/kg/min or less (table 4). In two of the children there was a transient fall in oxygen saturation (to 90%), as demonstrated by pulse oximetry. However, there was no associated hypotension or change in heart rate. No active intervention was needed except oxygen by mask (2 litres/minute for two hours).

Both these children had received intravenous phenobarbitone (20 mg/kg) from the peripheral hospital three hours before transfer. All the vital parameters of the other 18 children remained well within normal limits. No child required endotracheal intubation or mechanical ventilation. The electrolyte and glucose levels were within normal limits in all the children at the time of admission and 24 hours later. All children regained consciousness at a mean time of 5.1 hours after discontinuation of the midazolam infusion.

Discussion

If normally adequate doses of diazepam, phenytoin, and phenobarbitone fail to terminate seizures in status epilepticus, the condition is then considered to be refractory.[7] In a review article, Shorvon divided status epilepticus into early, established, and refractory.[8] Refractory is the description if the seizures continue for 60–90 minutes after the initiation of therapy.

Midazolam, a 1,4-benzodiazepine agent of the group of 1,2-annelated benzodiazepines, is a water soluble compound which penetrates the central nervous system rapidly and has a short elimination half life of 1.5–3.5 hours.[9] It is commonly used as an amnestic and anxiolytic agent and for operative induction and sedation of critically ill patients.[10] The finding of anticonvulsant efficacy in animal studies[11] was followed by anecdotal reports of the success of intravenous midazolam in terminating seizures and status epilepticus in humans.[6 12]

In our study, midazolam infusion controlled seizures in all cases of established status epilepticus and 11of 12 cases of refractory status epilepticus, giving an overall 95% success rate, which is almost equal to the results of Rivera *et al*.[13] One patient with refractory status epilepticus was confirmed to have Batten's disease, a progressive neurodegenerative disorder, and failed to respond. The mean rate of infusion of midazolam required to control seizures was 2.12 μg/kg/min in refractory status epilepticus and 1.79 μg/kg/min in established status epilepticus (table 3). These results are comparable with those reported for adult patients.[12 14] The maximum midazolam dose given to achieve control was 5 μg/kg/min, which is much lower than the 18 μg/kg/min used in an earlier study.[13] The mean time required to control the seizure was 34.3 minutes (10–60 minutes) in established status epilepticus and 64.6 minutes (15–240 minutes) in refractory status epilepticus, which is very similar to the 0.78 hours (range 15 minutes to 4.5 hours) found by Rivera *et al*.[13] All types of status epilepticus were treated with midazolam. The majority of our cases (75%) were convulsive, with five cases (numbers 10, 11, 13, 14 and 15, see table 1) that were non-convulsive. About 25% of cases of status epilepticus are non-convulsive,[15 16] and aggressive management has been recommended to terminate clinical and EEG detected seizure activities.[16 17] The mean infusion rate of midazolam required to control seizures was 1.9 μg/kg/min and the duration was 31 minutes.

It is not clear how midazolam works, when diazepam and phenytoin/phenobarbitone have failed to control seizures.[18] The more rapid rate of arrival at the receptors concerned with termination of seizures may be the critical factor.[18] It acts more rapidly, is safer and more effective.[19] Several other antiepileptic mechanisms of midazolam do not distinguish it from diazepam or lorazepam.[20]

During the acute phase of seizure disorder, midazolam was more effective and safer for the control of seizures than comparable doses of diazepam.[21] Because of the effective control of status epilepticus with midazolam, eight patients who had status epilepticus as the result of drug default were given midazolam alone to control the condition in addition to the defaulted oral antiepileptic drug (given via a nasogastric tube).

Drugs such as pentobarbitone, paraldehyde, and isoflurane have been used to treat status epilepticus with variable degrees of success. Pentobarbitone, which is commonly used in the treatment of the condition, is a general anaesthetic and its use is frequently accompanied by myocardial depression and hypo-

tension.[1] As it is a respiratory depressant, its use at high dose for the control of seizures often has to be accompanied by endotracheal intubation and mechanical ventilation. Paraldehyde, which is no longer recommended,[22] has serious side effects such as pulmonary haemorrhage, pulmonary oedema, and renal and liver toxicity. Isoflurane, an inhalational general anaesthetic agent, although effective in controlling refractory seizures, produces considerable respiratory depression and muscle relaxation, often warranting endotracheal intubation and mechanical ventilation.[23]

Ghilain and coworkers found a 15% rate of occurrence of mild hypotension and a 10% frequency of bradycardia when 0.2 mg/kg midazolam was given intramuscularly to adult patients with seizures.[24] Two children in our series developed transient mild hypoxia. As the oxygen saturation fell to 90%, the children needed oxygen by mask for two hours. Without any further intervention the oxygen saturation returned to normal. The vital parameters of the remaining 18 children were well within normal limits. No child had to be intubated or mechanically ventilated, and there were no electrolyte abnormalities.

Conclusion

The results of our study using midazolam at 1–5 μg/kg/min as a constant intravenous infusion after a bolus dose of 0.15 mg/kg, substantiate the suggestion that midazolam infusion is an effective and safe therapeutic approach for the management of childhood status epilepticus including the refractory condition. It can be used alone in status epilepticus resulting from drug default. In addition, the dose of midazolam can be conveniently titrated to the requirement of each child. Adverse effects such as respiratory depression are not seen when the drug is given alone or with phenytoin. Midazolam also has the pharmacokinetic advantage over other commonly used drugs in having a shorter duration of action. We suggest that midazolam should be the drug of choice for treatment of childhood status epilepticus.

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