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Efficacy of continuous midazolam infusion and mortality in childhood refractory generalized convulsive status epilepticus

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KEYWORDS
Refractory status epilepticus;
Midazolam;
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Summary

Purpose: Continuous midazolam infusion is commonly used for the management of status epilepticus (SE). The purpose of this study was to assess the efficacy of midazolam and mortality in childhood refractory generalized convulsive SE.
Methods: We included 27 children with refractory generalized convulsive SE. Midazolam was given 0.2 mg/kg as bolus, followed by 1–5 μg/kg/min as continuous infusion. Clinical data and response to treatment were recorded for each patient.
Results: Acute symptomatic SE accounted for 52%, and central nervous system (CNS) infections were the most frequently associated etiologic condition (44%). Complete control of seizures was achieved with midazolam infusion in the 26 (96%) children within 65 min; at a mean midazolam infusion rate of 3.1 μg/kg/min. Adverse effects such as hypotension, bradycardia or respiratory depression did not occur during midazolam infusion. In one (4%) patient with acute meningoencephalitis, SE could not be controlled. Five (19%) patients died; four had acute symptomatic aetiology and one had progressive encephalopathy.
Conclusion: Midazolam is effective and safe in the control of refractory generalized convulsive SE. The response to treatment and mortality were related to the underlying aetiology.

Introduction

Status epilepticus (SE) is a serious, life-threatening emergency that requires prompt intervention in children. Prolonged and uncontrolled refractory status epilepticus induces severe neurological sequel, or death.[1,2] There is no consensus as to the optimal therapy for refractory SE. Currently, barbiturate coma, midazolam and propofol are being used in treatment of refractory SE.[3,4] Midazolam has a remarkable anticonvulsant activity. Several clinical reports have described the successful use of

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midazolam to terminate SE. It is usually used after conventional anticonvulsant therapy for status epilepticus, such as diazepam, phenytoin or phenobarbital.[5–10]

The mortality of refractory SE in children varies from 16 to 44%.[11–14] A recent study reported that the mortality of SE was very low in children given midazolam. On the contrary, Singhi et al.[12] reported the midazolam was associated with higher mortality in refractory SE compared with diazepam. This discrepancy may be resulting from the differences of underlying cause because mortality has been reported to be associated with the aetiology of SE. A meta-analysis of refractory SE in childhood reported that the mortality was less frequent in midazolam-treated patients stratifying for aetiology.[11] Thus, the objectives of this study were to investigate the efficacy of midazolam infusion and mortality in childhood refractory generalized convulsive SE.

Patients and methods

The children suffering from refractory generalized convulsive SE admitted to "Dr. Behcet Uz Children's Hospital, Division of Paediatric Emergency, Izmir" from 1997 to 2000 were included in this study. Refractory SE was defined as the persistence of seizure activity for longer than 60 min, despite receiving 0.3 mg/kg diazepam (at least three doses), 20 mg/kg phenytoin and 20 mg/kg Phenobarbital.[1,2] All the criteria for refractory SE were met by all patients. All patients were transferred to the paediatric intensive care unit as soon as they had been stabilized. Midazolam was given 0.2 mg/kg as bolus, followed by a continuous infusion starting at 1 μg/kg/min up to 5 μg/kg/min increasing by 1 μg/kg/min every 15 min until complete control of seizures was achieved.[8] Subsequently, the midazolam infusion rate was gradually decreased until tapering was completed when patient had remained seizure free for a period of 24 h. Electroencephalography (EEG) was not used for the diagnosis of SE in all patients. But, it was performed after the seizures had been controlled to monitor the suppression of seizure discharge.

The maintenance doses of phenytoin and phenobarbital was continued, and their serum levels were followed. Twenty-four hours after admission, serum electrolytes and glucose levels were measured again. Aetiological therapy was started in addition to the treatment of SE. Vital parameters including heart rate, blood pressure, respiratory rate and oxygen saturation were monitored in all patients. Clinical data including age, sex, seizure history, underlying aetiology, and prognosis in the first 30 days were carefully recorded for each patient. Status epilepticus was classified according to aetiology into five groups by using previously published scales and ILAE recommendations as follows: (a) idiopathic; (b) acute symptomatic: seizures occurring concurrent with an acute neurological insult or systemic disorder; (c) remote symptomatic: seizures occurring without acute provocation in a child with a history of neurological insult related to an increased risk of seizures; (d) progressive encephalopathy: seizures occurring in a child with a progressive neurological disease; (e) febrile SE: seizures occurring with fever, but without any other acute provocation or history of neurologic insult.[15,16]

Results

Twenty-seven patients suffering from refractory status epilepticus were identified (16 boys and 11 girls). Their mean age was 5.1 ± 3.5 years (range 8 months to 14 years). All the patients had generalized convulsive refractory SE. Ten patients had a history of seizure and were receiving ambulatory antiepileptic drug; serum levels of received drugs were not known at admission. The remaining 17 patients presented at the hospital with their first convulsive episode. Acute central nervous system (CNS) infections were the most common aetiology: 12 (44%) had meningitis or encephalitis, one (4%) had drug overdose, one (4%) had acute subarachnoid haemorrhage, two (7%) had neurodegenerative disease, four (15%) had a history of hypoxic ischemic encephalopathy and epilepsy, one (4%) had brain tumour. The underlying aetiology was not identified in six (22%) patients. The classification of SE according to aetiology was as following acute symptomatic (41%), remote symptomatic (19%), progressive encephalopathy (7%), febrile (11%) and idiopathic (22%). Initially, three previously healthy children who had fever were classified as febrile SE and then, encephalitis was diagnosed by a cerebrospinal fluid examination revealing cell pleocytosis and elevated protein in all; therefore, they were placed in acute symptomatic group.

Complete control of seizures was achieved with continuous midazolam infusion in 26 of 27 patients (96%). The mean duration of SE was 91.3 min (range 45–280 min). The mean time between the start of midazolam infusion and complete control of seizures was 65 min and the mean infusion rate was 3.1 μg/kg/min. None of patients experienced hypotension, bradycardia or respiratory depression during midazolam infusion. Twenty–four hours after