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Intravenous midazolam in convulsive status epilepticus in children with pharmacoresistant epilepsy

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ABSTRACT

Although the efficacy of midazolam in refractory status epilepticus and as a first-line agent in children with established status epilepticus has been reported, differences in starting doses, continuation method, timing of efficacy assessment, and discontinuation pose limitations in deriving a specific protocol for midazolam use. An audit of clinical experience with a protocol of midazolam as first-line agent for impending status epilepticus (defined as a continuous, generalized, convulsive seizure lasting >5 minutes) in 76 episodes of unprovoked convulsive status epilepticus in children 1–15 years old with treatment-refractory epilepsy demonstrated that: (1) repeated bolus midazolam 0.1 mg/kg (every 5 minutes, maximum 5) controlled 91% of events; (2) three bolus doses controlled 89% of the episodes, with minimal chance of response beyond that; (3) treating impending status resulted in lower doses (mean 0.17 mg/kg) than reported and infrequent utilization of additional anticonvulsants (9%); and (4) adverse events were infrequent (respiratory depression 13%, assisted ventilation 3%).

1. Introduction

Convulsive status epilepticus is defined as a single tonic–clonic seizure lasting more than 30 minutes, or a series of seizures between which full consciousness is not regained [1]. The proposition to define status epilepticus as a continuous, generalized, convulsive seizure lasting >5 minutes or two or more seizures during which the patient does not return to baseline consciousness is still under discussion; many prefer to talk of early or impending status in this situation, whereas others refer to seizures lasting more than 5 minutes. Most, however, recognize the need to treat earlier rather than later [2]. The rationale is that most tonic–clonic seizures last less than 2 minutes and treatment of prolonged seizures in the early stages is more likely to succeed than treatment in the later stages. As a result, treatment is recommended to commence as soon as it is apparent that the seizure is persisting longer than 5 minutes [3–6].

The treatment of status epilepticus in children remains a challenge for researchers because clinical studies are difficult to carry out [7]. There is a lack of randomized controlled trials on anticonvulsants used for this condition in childhood; current protocols are based mostly on adult data. Practices vary widely in different countries depending on availability of medications, licensing, and the physicians' experience [2]. One benzodiazepine widely used in some countries, yet understudied in pediatrics, is intravenous midazolam. Most of the published work refers to refractory status epilepticus [8–12]; treatment is initiated with a bolus dose and is subsequently sustained by continuous infusion of midazolam titrated to seizure control. Although there is general agreement on its efficacy in refractory status epilepticus [13], there is considerable difference in the published doses, the requirement for ventilatory support, and the morbidity and mortality associated with it [14]. A recent retrospective multicenter study in established status epilepticus in 358 inpatients (mean age 48.6 ± 46.5 months), supported the efficacy and safety of midazolam as a first-line agent in children with epilepsy and in those with acute symptomatic status epilepticus [15]. Despite the large number of patients in this study, several factors that differed among participating centers, such as midazolam dosage, method for increasing the dosage, duration of treatment, timing of efficacy assessment, and method for midazolam discontinuation, pose limitations in deriving a specific protocol and may be responsible for the relatively low efficacy rate reported in this study (64.5%), compared with most of the previous reports. Several studies have reported midazolam efficacy rates ranging between 67.7 and 100% [7,16–18] for status epilepticus and even higher (86–100%) for refractory status epilepticus [19–22]. In these studies, midazolam was given either as a bolus followed by continuous infusion or as a continuous infusion from the onset of treatment.

Based on our favorable experience in terms of efficacy and safety with midazolam with acute symptomatic or remote symptomatic status epilepticus in patients hospitalized in the depart-

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ment of neurology or in the ICU, we have been using a protocol with midazolam as first-line agent for the treatment of convulsive status epilepticus. This protocol has provided a treatment algorithm for the house officers with respect to bolus dosage, additional drugs, and initiation of midazolam continuous infusion. We have adopted early treatment of status epilepticus, that is, after an unprovoked continuous tonic–clonic seizure at least 5 minutes long.

The purpose of this article is to describe our experience in terms of efficacy and safety of intravenous midazolam as first-line agent for the treatment of impending generalized convulsive status epilepticus in patients with known epilepsy.

2. Methods

This is an audit of clinical experience with midazolam as first-line agent for status epilepticus at the prodromal stage. The patients were children with symptomatic and cryptogenic epilepsy already receiving antiepileptic drugs. Only hospitalized patients were included so that the time of seizure onset could be ascertained; they were admitted because of refractory seizures or difficult-to-control epilepsy. They were undergoing EEG monitoring or medication change. They were receiving two to four anticonvulsants at the time of status epilepticus. Inclusion criteria were: (1) a well-established diagnosis of epilepsy, symptomatic or cryptogenic; and (2) continuous, generalized, convulsive seizure lasting >5 minutes, or two or more seizures during which the patient did not return to baseline consciousness, witnessed by a physician or nurse. Patients who had received benzodiazepines rectally or anticonvulsants intravenously for 12 hours prior to the status episode were excluded from this audit.

The protocol called for the following steps: intravenous bolus midazolam was given at a dose of 0.1 mg/kg, followed by repeated doses of 0.1 mg/kg, 5 minutes after the previous injection was completed, for a maximum of five injections, as needed for seizure cessation, as long as cardiorespiratory monitoring permitted. In case of respiratory depression, the protocol was to be aborted and alternative therapy to be initiated (Fig. 1). If the patient did not respond to five successive midazolam injections, the alternatives, in order of preference, were: (1) intravenous phenytoin at 18 mg/kg; (2) intravenous phenobarbital at a loading dose of 20 mg/kg; (3) intravenous valproate at a dose of 15 mg/kg, followed by continuous intravenous infusion at 1 mg/kg/hour for the next 6 hours; (4) continuous intravenous midazolam infusion at 0.1–0.4 mg/kg/hour for about 12 hours (in case this dose needed to be exceeded, the patient had to be moved to the ICU); (5) clonazepam 0.2 mg/kg/24 hours as a continuous intravenous drip. The choice of medication depended largely on the child's condition and the anticonvulsants the patient was already receiving. In case of status recurrence within 1 hour, the protocol was to continue from the previous step; if longer, it was to be re-initiated.

For the purpose of this article, total midazolam dose required for status epilepticus cessation, additional medications, number of patients transferred to ICU, side effects, and recurrences within the ensuing 24 hours were recorded.

3. Results

Seventy-six episodes of convulsive status epilepticus were treated with this protocol over a 3-year period. There were 42 patients with symptomatic (55%) and 34 with cryptogenic (45%) epilepsy, with a mean age of 8.4 ± 4.5 years (range: 1–15 years).

Seizure cessation with midazolam was achieved in 69 of 76 episodes (91%), whereas 7 status events (9%) required additional anticonvulsants. All 7 received phenytoin 18 mg/kg; in 4 the status was successfully terminated after phenytoin loading. In 3, who continued having seizures after phenytoin, phenobarbital loading 20 mg/kg (1 patient) and clonazepam continuous intravenous drip 0.2 mg/kg/24 hours (2 patients) were required for seizure cessation. Midazolam dose (mean ± SD) for status termination was 0.17 ± 0.09 mg/kg. Forty episodes (53%) were controlled with 0.1 mg/kg, 20 (26%) with 0.2 mg/kg, 8 (11%) with 0.3 mg/kg, and 1 (1%) with 0.5 mg/kg (Table 1). There was a 53% response rate (40/76) with the first midazolam dose, a 55% response rate (20/36) with the second bolus, and a 50% (8/16) with the third. None responded to the fourth bolus and only one to the fifth dose. In 6 patients the midazolam protocol was aborted (2 at 0.1 mg/kg, 2 at 0.2 mg/kg, and 2 at 0.3 mg/kg) because of respiratory depression; alternative treatment was given. Seven children (9.21%) were admitted to the ICU, all for respiratory depression (Table 2); in 3, seizures were controlled with midazolam 0.1, 0.3, and 0.5 mg/kg, respectively, then respiratory depression ensued; in 3, the protocol was aborted because of respiratory depression; in 1, respiratory depression occurred after midazolam 0.5 mg/kg was completed and seizures remained refractory. Of the 8 children who received the fourth and fifth bolus doses, only one responded; 2 (25%) experienced respiratory depression and were admitted to the ICU. Two of the patients admitted to the ICU required assisted ventilation. No cardiovascular or other toxicity was reported. No recurrences were recorded within the ensuing 24 hours. These convulsive status events resulted in prompt changes in anticonvulsant treatment to prevent further recurrences.

4. Discussion

This simple protocol of intravenous midazolam in repeated bolus administration of 0.1 mg/kg for a maximum of five doses proved successful in aborting the majority of impending status events in patients with treatment-refractory or difficult-to-control epilepsy who were receiving multiple anticonvulsants. The great majority of events (89%) were terminated with the first three doses of the drug; there was very little chance for response after the third bolus dose. This is important information for those who use this drug as first-line agent as we do, particularly because of the eight patients who proceeded to the fourth and fifth bolus doses, only one responded and two experienced respiratory depression and were admitted to the ICU. Therefore, one conclusion we derived from this audit was that the response rate after the third bolus is very small while the chance of respiratory depression is increased.

There is an obvious advantage in controlling patients with difficult-to-control epilepsy with a relatively short-acting agent, without interfering with the existing anticonvulsants, thus avoiding drug interactions. This is almost never the case with the existing management algorithms in which intravenous lorazepam or diazepam administration is usually followed by intravenous phenytoin or, alternatively, by phenobarbital or valproate. The value of these algorithms is well known [7], and it could be argued that they are still preferable because midazolam in the scheme described here does not terminate all status events and appears unhelpful after the third bolus dose. Nevertheless, this study demonstrated the value of a short-acting agent like midazolam in bolus doses rather than continuous infusions in patients receiving multiple anticonvulsants.

Midazolam was originally introduced in 1986; it is more potent than diazepam as a sedative, as a muscle relaxant, and in terms of its influence on electroencephalographic measures. It is fast acting and has a shorter duration of action than diazepam and lorazepam; as a result it causes a briefer sedation, but also provides shorter protection against seizure recurrence. The elimination half-life ranges between 1 and 4 hours, which is shorter than that of diazepam and lorazepam, resulting in shorter duration of side effects compared with both of these benzodiazepines [23]. It is important

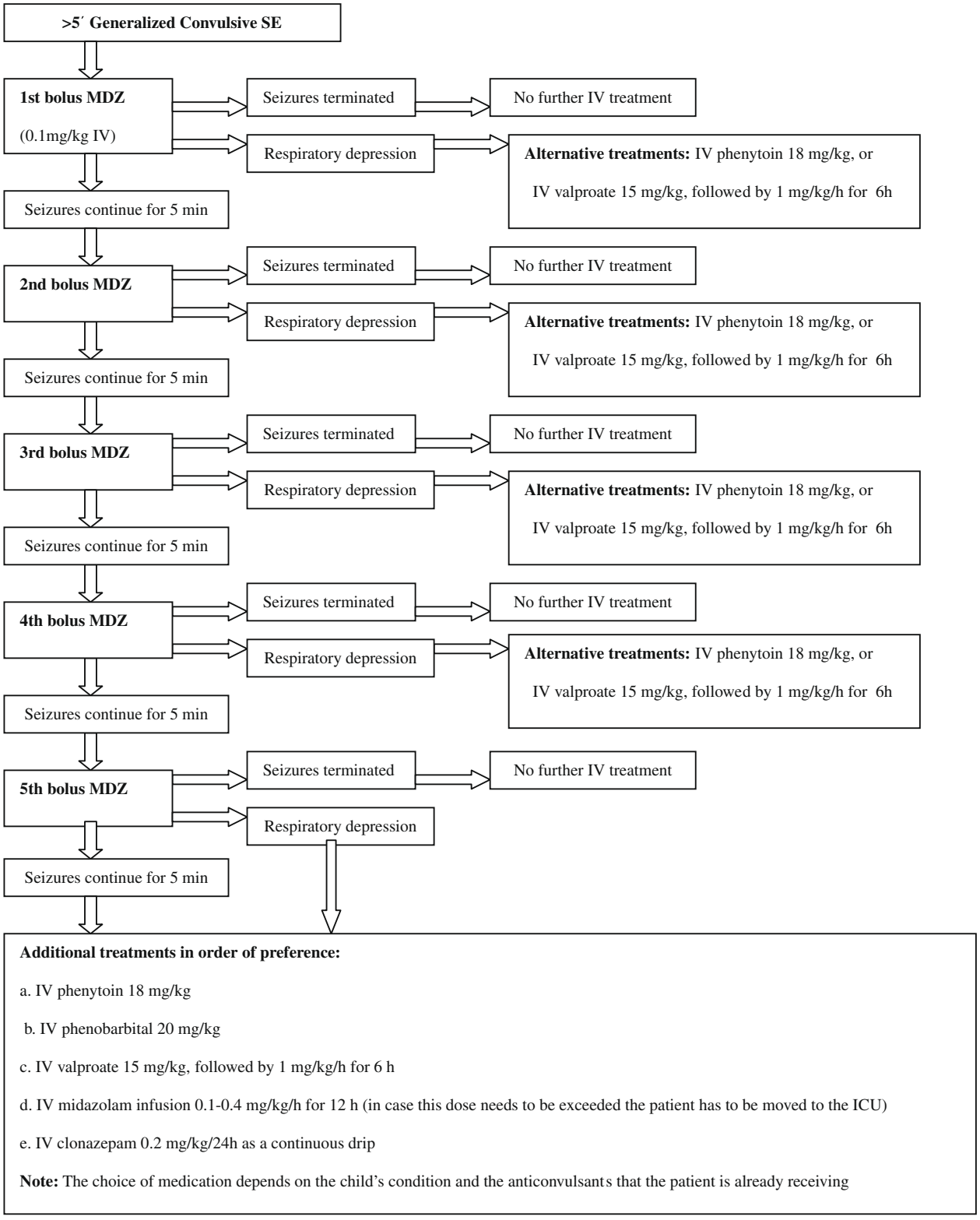

Fig. 1. Treatment algorithm for status epilepticus with midazolam as first-line agent. MDZ, midazolam.

to emphasize that with prolonged use, there may be tolerance, tachyphylaxis, and significant prolongation of half-life, from a few hours to days [24]. In this study, even though midazolam doses were rather low, no recurrences were noted within the ensuing 24 hours. Given the short-acting quality of the drug, we can postulate that this was not the result of midazolam. If the lack of recurrences had anything to do with the treatment, it is rather attributed to the prompt medication changes that were possible because these children had been hospitalized and historical and laboratory data were readily available for further decisions.

The midazolam doses for status epilepticus in children are not established. Most articles report administration of midazolam

Table 1
Midazolam dose and efficacy.

Midazolam dose (mg/kg)	Number treated (% responders)
0.1	40/76 (53%)
0.2	20/76 (26.3%)
0.3	8/76 (10.5%)
0.4	0/76 (0%)
0.5	1/76 (1.3%)
Total	69 (90.7%)

Table 2
Dose of midazolam and adverse events.

Dose (mg/kg)	Protocol aborted for respiratory depression		ICU admission for respiratory depression		Total with respiratory depression/number with dose (%)
	N	% of total	*N*	% of total	
0.1	2	2.6%	1	1.18%	3/42 (7.1%)
0.2	2	2.6%	3	3.9%	3/22 (13.6%)
0.3	2	2.6%	1	1.18%	2/10 (20%)
0.4					
0.5			2	2.6%	2/8 (25%)
Total	6	7.8%	7	9.2%	10/76 (13.1%)

0.15–0.2 mg/kg given as bolus, followed by continuous infusion of the drug. In a recent study, bolus midazolam (or the total dose, in cases given multiple doses) ranged from 0.03 to 1.15 mg/kg and was less than 0.3 mg/kg in 74.1% of all cases [15]. Most patients subsequently required continuous midazolam infusion (starting dose: 0.17 ± 0.20 mg/kg/hour, maximum dose: 0.04–1.2 mg/kg/hour). There was no apparent relationship between midazolam dose and treatment response, but there was great variation in the interval between onset of status epilepticus and midazolam initiation; one important finding was that cases resistant to bolus midazolam were also unlikely to show any response to continuous midazolam infusion. It was recently written that the recommended midazolam loading dose is 0.2 mg/kg, and boluses should be repeated every 5 minutes until seizures stop, up to a maximum total loading dose of about 2 mg/kg [25]. In the present study, low midazolam doses (mean dose 0.17 mg/kg) were effective in controlling 90.79% of impending symptomatic and cryptogenic convulsive status epilepticus episodes. The advantage of using repeated bolus injections rather than continuous midazolam infusion lies in the fact that treatment time is shorter and more defined than when continuous infusion is chosen. In addition, treatment at the early stage of status epilepticus probably enabled us to terminate the great majority of the events rapidly and with low doses; this protected our patients from the extended terminal half-life and tachyphylaxis that may occur with repeated doses of midazolam and possibly contributed to the low rate of adverse events in a group of patients with severe epilepsies and on multiple drugs. We believe that this is important information for those who are not familiar with this drug and for those who use continuous infusion of midazolam after the initial loading dose. This is far from a proposition to depart from the traditional approaches for defining and treating all status epilepticus events in children. It is, however, a proposition for managing patients with epilepsy with prolonged seizures that constitute early status epilepticus with a drug that gives fast, adequate, and safe control of seizures with no interference with the multiple anticonvulsants that these patients receive.

Midazolam has emerged as a highly efficacious drug in the treatment of convulsing patients, with several possible routes of administration. Before the evidence on the efficacy of intravenous midazolam appeared in the literature, it had been reported as the first water-soluble benzodiazepine that was effective when administered intramuscularly [26]; lastly, its efficacy has been recently established when administered via the buccal [27] or nasal [28] route.

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