Clinical Medicine Insights: Pediatrics

REVIEW

Nasal and Buccal Treatment of Midazolam in Epileptic Seizures in Pediatrics

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Abstract: Acute seizure and status epilepticus constitute major medical emergencies in children. Four to six percent of children will have at least one seizure in the first 16 years of life. Status epilepticus is a common neurological emergency in childhood and is associated with significant morbidity and mortality. The early application of antiepileptic treatment is very important. Because early treatment prevents the status epilepticus formation and shortens the duration of seizure activity. For this reason administration of anticonvulsant therapy in the prehospital setting is very important. Seizures generally begin outside the hospital, and thus parents and caregivers need simple, safe and effective treatment options to ensure early intervention. The only special preparation used for this purpose is rectal diazepam but has some disadvantages. Midazolam is a safe, short-acting benzodiazepin. It is suitable to use oral, buccal, nasal, im and iv routes. This provides a wide area for clinical applications. Recently there are many clinical studies about the usage of nasal and buccal midazolam for treatment of pediatric epileptic seizures. The nasal and buccal applications in pediatric seizures are very practical and effective. Parents and caregivers can apply easily outside the hospital.

Keywords: midazolam, seizure, nasal midazolam, buccal midazolam

Clinical Medicine Insights: Pediatrics 2012:6 51–60

doi: 10.4137/CMPed.S8330

This article is available from http://www.la-press.com.

Introduction

Acute seizure and status epilepticus constitute major medical emergencies in children, with an incidence ranging from 4 to 38/100,000 children per year. Prolonged seizure activity (more than 5 min) or persistent, repetitive seizure activity without recovery of consciousness between episodes is defined as status epilepticus. Status epilepticus is associated with significant morbidity and mortality. It is recommended that seizures lasting longer than 5 minutes should be treated with an anticonvulsant.[1] The administration of anticonvulsant therapy in the prehospital setting may shorten the duration of a seizure. Prolonged seizures cause an increase in metabolic rate, cerebral oxygen extraction and subsequently neuronal injury. During the first 30 min of a seizure there is massive sympathetic and parasympathetic overactivity, which may lead to tachycardia, hypertension, hyperglycaemia, hyperthermia, excessive sweating, and salivary and tracheobronchial hypersecretion. If status epilepticus persists for more than 1 hour, hypotension, hyperkalaemia, hypoglycaemia and respiratory acidosis may ensue.[2] Seizure termination is achieved by pharmacotherapy. Benzodiazepines are the first-line drugs for status epilepticus. Commonly used drugs include lorazepam, diazepam and midazolam. In children without IV access, buccal or nasal midazolam or rectal diazepam can be used.[3]

Rectal diazepam is the most commonly used medication prior to admission to hospital. The rectal route of administration is not always acceptable or convenient. Many teachers, parents and caregivers are reluctant to administer rectal medication for fear of allegations of sexual abuse. An effective treatment that can easily be administered by a more convenient route is therefore needed.[4] Nasal or buccal midazolam may be a good alternative to RD in seizure control for home treatment and when IV access is not available.

Pharmacokinetics

Absorption

Midazolam belongs to the imidazobenzodiazepines. In an acidic pH less than 4, the benzodiazepine ring is open, increasing the water solubility of midazolam. This water solubility allows midazolam to be packaged without diluents such as propylene glycol, thus decreasing venous irritation and, potentially, dysrhythmias. However at a physiological pH the benzodiazepine ring fuses shut, and midazolam becomes extremely lipophilic, accounting for its rapid onset of action.[5] Midazolam has anxiolytic, muscle relaxant, anticonvulsant, sedative, hypnotic and amnestic properties.[6,7] Midazolam is an anticonvulsive agent in the benzodiazepine group. It has a short onset of duration and is easy to use via the intravenous, intramuscular, buccal and intranasal routes.

Midazolam is rapidly absorbed from the gastrointestinal tract following oral administration.[7] Drowsiness has been observed after an oral dose, with peak effects within 30–90 min.[8] Due to first-pass metabolism, only 40%–50% of an orally administered dose reaches the systemic circulation. The duration of action following intranasal administration is similar to that after oral dosing, although the onset of sedation may be earlier.[9,10] Rectally administered midazolam has been shown to be safe and effective, with the peak plasma concentration reported 9–29 min after administration.[10] Midazolam is rapidly absorbed following intramuscular injection with an absolute bioavailability of more than 90%. The onset of sedation following intramuscular injection has been reported as early as 5 min, with peak effects seen within 15–30 min.[11] The onset of sedation is quite rapid after intravenous infusion, with clinical effects seen within approximately 3 min.[8]

Distribution

Midazolam has a volume of distribution (Vd) of 1–2.5 L/kg in healthy individuals. Obese patients have an increased Vd as a result of enhanced distribution to peripheral adipose tissue.[12] The Vd is greater in women than in men, and in the elderly and during pregnancy.[5] Midazolam is extensively bound to plasma proteins, primarily albumin, with a free fraction representing only 4% of a given dose. Midazolam has a short distribution half-life of several minutes as a result of rapid tissue uptake. Unlike the other benzodiazepines, almost no midazolam is detected in the cerebrospinal fluid following a single dose.[13] A return to baseline values for objective neurologic tests occurs 1.5 h after intravenous injection and 2 h after oral administration.[5]

Metabolism

Midazolam is biotransformed by hepatic microsomal oxidation followed by glucuronide conjugation. Initially midazolam is hydroxylated by cytochrome P450-3A4

to its primary metabolite alpha hydroxymidazolam and to a minimal extent to inactive metabolites. Alpha hydroxymidazolam is pharmacologically active and has sedative properties equivalent to midazolam. This major metabolite is produced at a higher concentration following oral administration as a result of first-pass metabolism.[8] Plasma clearance of midazolam is greater in supine patients because of a 40%–60% increase in hepatic blood flow during supination. Cytochrome P450 inhibitors such as cimetidine may profoundly reduce first-pass metabolism. Although never proven, hepatic dysfunction may impair the clearance of midazolam, resulting in accumulation.

Midazolam has a short elimination half-life of 1.5–3 h compared with >20 h for diazepam. Plasma clearance of midazolam is 5.8–9 mL/kg in healthy subjects but is lower in elderly subjects.[5] Almost 90% of an orally administered dose of radiolabeled midazolam is excreted within 24 h. The major route of elimination is the kidney. Midazolam has been associated with accumulation and prolonged sedation in patients with renal dysfunction.[14]

Dosage

The patient's response to midazolam varies widely, and the dose should be titrated accordingly. An intravenous dose of 0.02–0.03 mg/kg may be repeated at 2 min intervals while continually monitoring for the appropriate level of sedation.[15] The usual intramuscular dose for conscious sedation is 0.07–0.08 mg/kg.[16] A dose of 0.2 mg/kg oral midazolam usually provides sufficient sedation in children younger than 6 years of age for laceration repair.[17] Midazolam has a bitter taste that may decrease patient compliance when given orally, but it may be diluted in juice.[18] Intranasal administration of 0.25 mg/kg midazolam is quite effective in paediatric patients. Intranasal administration has been associated with some subjective complaints including burning and irritation and may be less favourable in some patients than parenteral routes.[19] Rectal administration of 0.3 mg/kg diluted in 5 mL of saline is an effective alternative route of administration[10,20] (Table 1).

Table 1. The dosage of midazolam.

	Conscious sedation dosing
Intravenous (IV)	0.02 mg/kg–0.03 mg/kg slowly over 2 minutes
Intramuscular (IM)	0.07 mg/kg–0.08 mg/kg
Oral	0.2 mg/kg–0.5 mg/kg diluted in juice
Nasal	0.2 mg/kg–0.3 mg/kg
Rectal	0.3 mg/kg diluted in 5 mL normal saline

Clinical Utility

Nasal treatment of midazolam in epileptic seizures

Midazolam is often used for long-term sedation and treatment of status epilepticus. It has the advantage that it can be used not only parenterally, but also orally, buccally and nasally. This is important in children with epileptic seizures. Most seizures occur out of hospital and an easy and safe anticonvulsive medication is required. For this reason nasal and buccal application of midazolam is increasing in popularity.

Jeannet et al[21] studied the efficacy, tolerance and applicability of nasal midazolam (NM) during acute seizures in children both in hospital and at home. Twenty-six children were enrolled, 11 at home and 17 in hospital. They had a total of 125 seizures; 122 seizures (98%) stopped within 10 min (average 3.6 min). Two patients did not respond to treatment in hospital and three seizures recurred within 3 hours. None had serious adverse effects. Parents had no difficulty administering the drug at home. Nine patients had been receiving RD regularly prior to midazolam and in seven (78%) of those children the parents thought that NM was easier to use and that the child had a more rapid and easier recovery.

Lahat et al[22] administered NM for epileptic seizures in children aged 6 months to 16 years. A solution of 0.2 mg/kg midazolam was dropped into both nostrils before inserting an intravenous line. Treatment was considered successful if the child's seizure stopped within 5 min, delayed if it stopped within 5–10 min, and a failure if seizures did not stop within 10 min, when 0.3 mg/kg diazepam was given intravenously. Seizure control was achieved in all children except one in whom intravenous diazepam (IVD) was ineffective and seizure control was achieved after 30 min using intravenous phenytoin. The estimated duration of seizure before the administration of midazolam was 10–25 min. The mean time to seizure control was 3.5 min (range 2.5–5). There were no recurrences of seizures within 60 min after treatment.

Table 2. The clinical studies about the usage of midazolam for epileptic seizures.

References	Patient no. Home/hospital	Seizure no.	Patients ages	Study drugs	Dosage	Success rate (%)	Treatment time (min)	Complication
Jeannet et al	26 (11/17)	125	1 month–16 years	NM	0.2 mg/kg	98%	3.6	No
Berkovitch et al	20 (0/20)	20	1 month–16 years	NM	0.2 mg/kg	95%	3.5	No
Scott et al	42 (0/42)	79	5–22 years	BM/RD	10 mg;10 mg	75%/59% respectively	Similar	No
Fisgin et al	60 (0/60)	60	2 months–14 years	NM	0.2 mg/kg	81.3%	18.7%:1 mi 43.7%:1–2 min 18.7%: 2–5 min	No
Scheepers et al	22 (0/22)	84	12–72 years	NM	50 kg ↓: 5 mg; 50 kg ↑: 10 mg	94.1%	Within 10 min	No
Kutlu et al	9 (0/9)	9	6 months–9 years	NM	0.3 mg/kg	100%	2.19	1 respiratory depression
Kutlu et al	19 (0/19)	19	1 month–15 years	BM	0.3 mg/kg	100%	3.89	No
Mahmoudian et al	70 (0/70)	70	2 months–15 years	NM/IVD	0.2 mg/kg; 0.2 mg/kg	Similar	3.58/2.94 respectively	No
Harbord et al	22 (22/0)	54	unknown	NM	0.2–0.3 mg/kg	89%	Unknown	No
Bhattacharyya et al	46 (0/46)	188	3 months–12 years	NM/RD	0.2 mg/kg; 0.3 mg/kg	96.7%/88.5%	1.93/2.96 respectiv.	No
Mclntyre et al	177 (0/177)	219	7 months–15 years	BM/RD	0.5 mg/kg; 0.5 mg/kg*	56%/27%	8/15 respectively	1.12% in BM/1.69% in RD respir. depression
Holsti et al	57 (0/57)**	57	8 months–17 years	NM/RD	0.1–0.4 mg/kg	–	11/30	1%/1% intubation
Talukdar et al	120	120	0–12 years	BM/IVD	0.2 mg/kg; 0.3 mg/kg	85%/93% respectively	1.69/1.13	No
Holsti et al	92 (92/0)	92	<18 years	NM/RD	0.2 mg/kg; 0.3–0.5 mg/kg	100%	3/4.3	No
Mpimbaza et al	330 (0/330)	330	3 months–12 years	BM/RD	0.5 mg/kg; 0.5 mg/kg*	57%/69.7%	4.75/4.35	2 patientin BM/2 patient in RD respiratory depression

Notes: *6–12 month: 2.5 mg; 1–4 years: 7.5 mg; 5–9 years: 10 mg.

Fisgin et al[23] studied NM in acute seizures in 16 children aged from 2 months to 14 years. Midazolam (0.2 mg/kg) was administered intranasally over 30 seconds using an enjector. Seizures terminated in 3 (18.7%) patients within 1 min, 7 (43.7%) patients within 1 to 2 min, and 3 (18.7%) patients within 2 to 5 min. Three (18.7%) patients did not respond to treatment. The authors thus concluded that NM administration is simple and effective.

Previous studies using midazolam as an anaesthetic agent have concluded that the drug, when given intranasally, is an effective sedative and amnestic agent.[24] Scheepers et al[25] studied NM for rescue medication in adolescent and adult patients with severe epilepsy. A dose of NM (5 mg if the patient weighed less than 50 kg and 10 mg if the patient weighed over 50 kg) was prescribed for those who had previously responded to other rescue medication. Twenty-two patients underwent 84 treatment episodes and 79 of these were considered clinically effective. Five treatment failures were recorded, three due to poor technique in delivering the midazolam. These authors improved the delivery method by using a 1 mL disposable plastic pasteur pipette; non professionally trained care staff and parents have successfully used this treatment method. Rescue medication has an important place in the treatment of severe epilepsy. NM appears to be a safe and effective rescue treatment that has a number of advantages over RD. Nasal treatment is more dignified and more acceptable to both patients and carers. This field trial confirmed that NM is effective at terminating prolonged seizures, preventing seizure clustering and reducing post-ictal behavioural complications in adolescent and adult patients with severe epilepsy.

Kutlu et al[26] treated nine patients aged 6 months to 9 years with prolonged convulsions lasting more than 10 min with NM (0.3 mg/kg). The success rate was 100%, with only one case requiring a second dose. The estimated duration of seizures was 12–30 min and the mean time elapsed until the cessation of seizures was 139.6 s. No significant adverse effects were noted except in one patient who had seizures secondary to serious CNS infection and respiratory depression following NM. These authors suggested that NM is effective and safe in children with seizures. Intranasal administration of midazolam may offer an alternative to other anticonvulsive drug applications in the acute emergency setting.

Harbord et al[27] administered NM to 22 children for a total of 54 seizures. The dose was 0.2–0.3 mg/kg rounded down to 1 or 2 of the 5 mg in 1 mL plastic ampoules, with the anticonvulsant administered into the child's nose directly from the plastic ampoule. Seizures subsequently stopped on 48 occasions, ie, 89%, and no respiratory arrest occurred. Thirty carers had given NM to a convulsing child and 27 (90%) reported no difficulty in administering NM. Fifteen people had also previously administered RD and NM was considered easier to administer than RD.

Holsti et al[28] used NM for the prehospital treatment of paediatric seizures. Patients were included if they were younger than 18 years, had a seizure in the presence of an emergency medical services provider, received RD or NM for their seizure in the prehospital setting, and arrived at the study emergency department via emergency medical services. Midazolam 0.2 mg/kg (max 10 mg) and diazepam 0.3–0.5 mg/kg (max 20 mg) were administered using a mucosal atomization device. This device comprises an applicator placed on top of a syringe that distributes midazolam in particles measuring 30-µgr, thus coating the nasal mucosa. NM administered using the mucosal atomization device should facilitate rapid nasal absorption, achieving effective plasma and cerebral spinal fluid concentrations. Of 857 seizure patients brought by the emergency medical service to the emergency department 124 (14%) patients had seizure activity in the presence of the emergency medical services and were eligible for inclusion in this study. Sixty-seven of 124 patients (54%) received no medication in the prehospital setting, 39 (32%) patients were treated with NM and 18 (15%) were treated with RD. The median seizure time noted by emergency medical services was 19 min longer for RD (30 min) when compared with NM (11 min, $P = 0.003$). Patients treated with RD in the prehospital setting were significantly more likely to have a seizure in the emergency department. The authors concluded that NM controlled seizures better than RD in the prehospital setting and resulted in fewer respiratory complications, fewer hospital and PICU admissions, and lower total hospital discharge.

Wolfe et al[29] reported that intranasal midazolam, which delivers antiepileptic medication directly to the blood and cerebrospinal fluid via the nasal mucosa, is safe, inexpensive, easy to administer by parents and

paramedics, and provides better seizure control than rectal diazepam.

Mahmoudian et al[30] compared NM with IVD for treating acute seizures in children. Seventy children aged 2 months to 15 years with acute seizures (febrile or afebrile) were administered NM 0.2 mg/kg or IVD 0.2 mg/kg. Midazolam solution (5 mg/mL) was dropped by syringe into both nostril in equal doses. In the NM group seizure control was achieved in less than 5 min in 21 out of 35 (60%) children, and within 10 minutes in the other 14; in the diazepam group, however, seizures ceased in less than 5 minutes in 28 out of 35 (80%), and within 10 min in the other 7. NM and IVD were equally effective. The mean time taken to control seizures was 3.58 min in the midazolam group and 2.94 min in the diazepam group, not counting the time required to insert the intravenous line. No significant side effects were observed in either group. No patient required intubation or mechanical ventilation. In this study the time from seizure onset to treatment was shorter in the midazolam group but seizures were controlled more rapidly in the diazepam group.

Bhattacharyya et al[31] studied 188 seizure episodes in 46 children who were randomly assigned to receive treatment with RD and NM at doses of 0.3 mg/kg and 0.2 mg/kg body weight, respectively. The efficacy of the drugs was assessed according to drug administration time and seizure cessation time. The mean time from the arrival of the doctor to drug administration was 68.30 ± 55.12 sec in the diazepam group and 50.60 ± 14.10 sec in the midazolam group. The mean time from drug administration to seizure cessation was significantly less in the midazolam group. 10 minute, and 30 minute intervals after administration of drugs in both groups, revealed that mean heart rate and blood pressure changes were not statistically different. However, the respiratory rate differed significantly between the RD group and the NM group at 10 minutes and 30 minutes after drug administration. The mean oxygen saturation after 5, 10 and 30 minutes of NM administration did not vary, whereas the mean oxygen saturation in the RD group decreased at 5 minutes and 30 minutes after administration of the drug from the mean predrug value. This difference was again statistically significant. Hypoxia was observed in one child treated with RD who required oxygen inhalation for 7 hours. No significant hypoxia was observed in the midazolam group. Seizures ceased within 10 minutes of drug administration in 85 out of 96 episodes (88.5%) treated with RD, whereas seizures ended in 89 out of 92 episodes (96.7%) treated with NM. Seizures were not controlled in 11 episodes (11.45%) in the RD group or in 3 episodes (3.26%) in the NM group. Seizures recurred in 6 out of 96 episodes (6.25%) within 60 minutes of administration of RD, and in 3 out of 92 episodes (3%) after administration of NM. The difference was not statistically significant. Side effects such as vomiting and excessive drowsiness were observed in 10 out of 96 episodes (10.4%) in the RD group, whereas no such side effects were observed in the midazolam group. The authors concluded that NM is preferable to rectal diazepam in the treatment of acute seizures in children, as it is easy to administer, has a rapid onset of action, has no significant effects on respiration and oxygen saturation, and is socially acceptable.

Haan et al[32] compared midazolam nasal spray and diazepam rectal solution in adult patients, using a device to deliver 2.5 mg midazolam per 90 µl of spray. Two puffs of midazolam were administered in each nostril as the study medication (administering a total of 10 mg midazolam). The outcome was compared with that of diazepam 10 mg rectal solution. Treatment with RD was successful in 56 out of 63 episodes (89%) and with NM in 50 out of 61 episodes (82%). The mean time before cessation of seizure activity was 4.6 ± 3.4 min with NM and 4.3 ± 3.4 min with RD. The number and severity of side effects were comparable between drugs. More than half of the patients were sedated following administration of the study medications. It is not clear how much this sedation was due to the postictal loss of consciousness. Local irritation (sneezing, coughing, dry mouth, tear flow) was reported in 17 out of 59 (29%) events with NM. The authors concluded that NM appeared to be no less effective than RD solution in the residential treatment of seizure exacerbations in the majority of patients.

Holsti et al[33] compared NM with rectal diazepam for the home treatment of acute seizures in paediatric patients with epilepsy. A total of 358 paediatric patients who visited a paediatric neurology clinic were prescribed a home rescue medication for their next seizure. A total of 92 caregivers gave the study medication during a seizure (50 NM, 42 RD). Caregivers were randomized to use either 0.2 mg/kg

of NM (maximum, 10 mg) or 0.3 to 0.5 mg/kg of RD (maximum, 20 mg) at home for their child's next seizure that lasted longer than 5 minutes. Caregivers who were present at the clinic visit watched a 5-minute instructional video on how to use their prescribed medication. They were instructed to give only one dose of study medication and call "911." If the seizure persisted, the emergency medical service could then give a second medication and transport the patient to an emergency department according to their established protocol. Caregivers who gave the study medication recorded their observations using a stopwatch and timing sheets. The times of seizure initiation, medication administration, and seizure cessation were recorded, and sheets were mailed to the principal investigator. Those who gave the rescue medication were then asked a series of questions to gauge their satisfaction with the medication. Caregivers answered questions regarding the ease of administration and overall satisfaction with the study medication by rating them on an 11-point nominal scale (0, not satisfied and 10, thoroughly satisfied). Data on several other secondary outcomes were also collected (need for additional medical support, hospitalization, length of stay, disposition, repeated seizures within 12 hours). The median time from medication administration to seizure cessation for NM was 1.3 min less than for RD. The mean time to medication administration was 5 min for each group. No differences in complications were found between groups. Caregivers were more satisfied with NM and reported that it was easier to give than RD.

Buccal Treatment of Midazolam in Epileptic Seizures

Buccal application of midazolam is a good alternative to nasal midazolam for emergence treatment of epileptic seizures. Kutlu et al[34] used BM for prolonged seizures in children. Nineteen previously unreported children, aged from 1 month to 15 years, were treated with a 0.3 mg/kg dose of BM; 13 had prolonged seizures and 6 had status epilepticus, with a duration of 5–45 min (mean 2 min). Sixteen out of 19 seizures (84.2%) stopped within 10 min of administration of BM. The drug efficacy in patients with status epilepticus was 50%. However patients with convulsions shorter than 30 min showed a perfect response (100%). Convulsion episodes stopped within 3.89 ± 2.22 min. Seizure duration was correlated with the cessation of seizures. No clinically important side effects were seen in any patient. The authors concluded that a 0.3 mg/kg dose of buccally administered midazolam might offer an effective treatment in children of all ages.

In a randomized controlled study 120 children presenting with convulsions to the emergency department were treated randomly with either BM (0.2 mg/kg) or IVD (0.3 mg/kg). Partial seizures, generalized tonic, clonic and tonic-clonic convulsions were included irrespective of duration or cause. Only one episode per child was included. The frequency of overall control of convulsive episodes within 5 min was 85% and 93.3% in BM and IVD respectively. The mean time required to control convulsive episodes following the administration of the drugs was significantly less with IVD. The mean time taken to initiate treatment was significantly less with BM. The mean time required to control the convulsive episodes after noticing these first was significantly less with BM, probably due to the longer time required to initiate treatment with IVD, including preparing the injection and establishing an IV line. There were no significant side effects in either group. In conclusion BM can be used as an alternative to IVD especially when establishing an IV line is difficult. In fact, in situations in which establishing an IV line is a problem, BM may be the first choice.[35]

Scott et al[36] compared RD and buccal midazolam (BM) for the treatment of prolonged seizures in childhood and adolescence. Forty-two young people were enrolled. Continuous seizures of more than 5 min duration were randomly treated with BM or RD. If the seizure did not stop within 10 min additional medication was administered. BM was used to treat 40 seizures in 14 children and rectal diazepam was used to treat 39 seizures in 14 children. Midazolam stopped 30 (75%) out of 40 seizures and diazepam 23 (59%) out of 39. The time from administration to the end of the seizure did not differ significantly between groups. No clinically adverse cardiorespiratory events were identified in the two groups. The authors concluded that the use of BM has clear practical and social advantages over RD. The oral mucosa provides a route into the systemic circulation that is easier to access in acute seizures than the rectal or nasal mucosa. Seizures commonly occur in public places

and carers do not like to administer rectal medication in public view. The nasal route has been suggested as an alternative to the rectal route for the acute administration of medication before admission to hospital. Nasal administration of midazolam decreases interictal epileptiform activity and early evidence shows efficacy in the treatment of seizures.[37] They discussed the effect of increased nasal discharge and mucous production on midazolam absorption from the nose is unknown and breathing may discharge drugs given via the nasal route. The nose is a smaller orifice than the mouth and, therefore, is more difficult to access than the mouth in a patient having continuous seizures. The practice of placing an object between the teeth to avoid biting of the tongue is no longer acceptable. However, they said that the method used for buccal administration of midazolam did not require the teeth to be parted. Placement of the nozzle of the syringe between the cheek and teeth is easy, even in tonic seizures. The volume of fluid is small and, therefore, aspiration is not a risk. Aspiration of saliva during convulsive status epilepticus, compromise. Ease of buccal access, physical similarity between the oral and the rectal mucosal, and efficacy of BM support the use of the buccal route. They concluded that convenience of administration and social acceptability may lead to BM becoming the preferred emergency treatment for status epilepticus.

The bioavailability of BM was shown to be 75%, and the peak plasma concentration is reached at 10 min. In a pharmacodynamic study, electroencephalographic changes were demonstrated within 5 min of administration.[38] The speed of the cerebral effect of BM seemed to be more rapid than expected from the blood level of midazolam. There is increasing evidence that the longer seizures persist, the more difficult they are to stop. Lowenstein and Alldredge[39] found that first-line therapy stopped seizures in 80% of patients when begun 2 h or less after the onset of the seizure, but in less than 40% of patients when begun 2 h or more after the onset of the seizure. Animal studies have also shown that status epilepticus becomes progressively less responsive to therapy as the seizure continues.[40]

Mclntyre et al[41] compared BM with rectal diazepam for the emergency treatment of seizures in children. Finding consent was obtained for 219 episodes involving 177 patients. The dose of BM or RD to be administered was determined by the child's age and was designed to supply about 0.5 mg/kg (2.5 mg for children aged 6–12 months; 5 mg for 1–4 years, 7.5 mg for 5–9 years, and 10 mg for 10 years and older). Both treatment groups would therefore be expected to show similar variation around the estimated 0.5 mg/kg dose. If the child was still having a seizure after 10 min and intravenous access had been established, then intravenous lorazepam (100 μg/kg) was administered and additional medication was given based on each participating hospital's protocols or guidelines. The requirement for lorazepam or another anticonvulsant drug at this stage indicated treatment failure. The therapeutic success rate was 56% (61 out of 109) for BM and 27% (30 out of 110) for RD. The rate of respiratory depression did not differ between groups. When centre, age, known diagnosis of epilepsy, use of antiepileptic drugs, prior treatment, and length of seizure, BM was more effective than RD.

In another study BM and RD were compared in Ugandan children. This study included 330 paediatric patients aged 3 months to 12 years. Treatment failure occured in 71 (43%) out of 165 patients who received RD compared with 50 (30.3%) out of 165 patients who received BM. Malaria was the most common underlying diagnosis (67.3%). For children without malaria BM was superior (55.9% vs. 26.5%). Respiratory depression was rare in both treatment groups. In conclusion BM was as safe as and more effective than RD for the treatment of seizures in Ugandan children, although its benefits were limited to children without malaria.[42]

There are some limitations to the use of midazolam out of hospital by non healthcare providers. It can be abused because of its amnestic effects. For this reason the use of midazolam by caregivers and parents requires constraints and should be monitored.

Summary

Approximately 10% to 20% of childhood epilepsy is refractory to medications, resulting in frequent breakthrough seizure episodes. Most of these seizures are brief and resolve without treatment. However, if they persist for more than 5 min, prompt intervention is recommended.[43] Early antiepileptic intervention in an actively seizing patient reduces seizure duration,

decreasing both morbidity and mortality.[44] Because most episodes of prolonged seizure activity begin outside the hospital, parents and caregivers need simple, safe, and effective treatment options to ensure early intervention.

In conclusion the nasal and buccal application of midazolam in paediatric patients is safe, easy, effective, and more socially acceptable than rectal applications for seizure control.

Author Contributions

Conceived and designed the experiments:AÜ. Analysed the data: AÜ. Wrote the first draft of the manuscript: AÜ. Contributed to the writing of the manuscript: RA. Agree with manuscript results and conclusions: CB. Jointly developed the structure and arguments for the paper: CB. Made critical revisions and approved final version: RA. All authors reviewed and approved of the final manuscript

Funding

Author(s) disclose no funding sources.

Competing Interests

Author(s) disclose no potential conflicts of interest.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest. Provenance: the authors were invited to submit this paper.

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