Seizure Rescue Medications for Out-Of-Hospital Use in Children

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For the past 2 decades, rectal diazepam (Diastat) has been the sole US Food and Drug Administration (FDA)-approved medication for treatment of bouts of seizures in the out-of-hospital setting for patients with epilepsy. Clonazepam also has been used frequently off-label for acute, repetitive seizures, as well as other indications. In the past year, the FDA has approved 2 new formulations as seizure rescue medications: intranasal midazolam (Nayzilam), and intranasal diazepam (Valtoco) (**Table**). Seizure rescue medications are rapidly acting antiepileptic drugs that help to stop a seizure quickly before it progresses to a medical emergency, such as status epilepticus. Children who present with seizures to a child neurologist, primary care provider, or emergency medicine physician often are prescribed a seizure rescue medication. Here we review the most commonly used rescue medications for children in the US: rectal diazepam and clonazepam, as well as the 2 new intranasal formulations of diazepam and midazolam. Buccal formulations of diazepam, lorazepam, and midazolam also are used infrequently in children[1] but are outside the scope of this update, as well as the use of seizure rescue medications outside the US.

Indications

Rescue medications are indicated when a seizure becomes an emergency or is unlikely to stop without the administration of the medication. The standard treatment of choice for seizure clusters and status epilepticus is benzodiazepines.[2,3] It is important for families and caregivers for children with epilepsy to have rescue medications available to administer at home to treat seizures within a timely manner. Over the years, several formulations of benzodiazepines have been manufactured for this purpose.

Before 2019, the only FDA-approved rescue medication for out-of-hospital use was diazepam (Diastat) rectal gel.[4] The FDA recently approved 2 intranasal benzodiazepines (Nayzilam, Valtoco) for clusters of seizures in children. The FDA indication for these intranasal medications is "the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (ie, seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy.[5,6]" Beyond this approved indication, seizure rescue medications often are used to treat status epilepticus and also prescribed for febrile seizures and catamenial epilepsy.[7,8]

Status Epilepticus

Traditionally, status epilepticus had been defined as greater than 30 minutes of continuous seizure activity or repeated seizures without a return to clinical baseline between seizures.[2] This was based on the finding that long-term consequences, such as neuronal injury, are more likely to occur at 30 minutes of seizure activity.[9] However, by current definition and treatment protocols, a seizure lasting 5 minutes or longer meets the definition for status epilepticus and is considered a medical emergency that requires acute treatment.[9,10] This definition is based on the observation that a seizure lasting 5 minutes or more is less likely to stop without medical intervention, typically a benzodiazepine rescue medication.[11]

Seizure Clusters

Clusters, or bouts, of seizures are characterized by brief acute, repetitive seizures. These clusters also often require medical intervention to slow down or stop the seizures. What might be considered a seizure cluster varies from patient to patient with regard to the number of seizures occurring in given time frame, and this underscores the need for individualized seizure action plans. The lack of a consistent definition for seizure clusters across a population of children or adults with epilepsy has complicated the ability to perform research on seizure clusters. Many studies define a seizure cluster as 2 or more seizures in 24 hours and others use shorter periods.[3]

Febrile Seizures

Febrile seizures are the most common type of childhood seizure, defined as seizures provoked by fever, without central nervous system infection, occurring in children between 6 months and 5 years old.[12] In cases in which febrile seizures cluster or are prolonged, or access to nearby medical care is limited, children often are prescribed a rescue medication for their seizures.[7] In addition, there are some patients with epilepsy who have severe seizure exacerbations with every febrile illness. In such circumstances, providers may prophylactically prescribe a 2- to 5-day scheduled benzodiazepine "bridge" to alleviate the seizure burden.

CYP	Cytochrome P450
FDA	Food and Drug Administration
IV	Intravenous
T_{Max}	Time to maximal concentration

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Table. FDA-approved rescue medications for seizure clusters

Brand names	Generic name	Route	FDA-approved for age, y	Time to peak concentration, min	T½ elimination, h	Metabolism	Cost
Diastat	Diazepam	Rectal	≥2	90	45-46	CYP2C19 CYP3A4	$271-400 per kit
Nayzilam	Midazolam	Intranasal	≥12	7.8-28.2	2.1-6.2	CYP3A4	$550 per box
Valtoco	Diazepam	Intranasal	≥6	90	49	CYP2C19 CYP3A4	$560 per box

Catamenial Epilepsy

Some female adolescents experience a cyclic increase in seizure frequency associated with their menstrual cycles due to changes in estrogen and progesterone levels, which can lower the seizure threshold. For some, hormonal therapy can be helpful. In other cases, rescue medications or scheduled benzodiazepines have been used to alleviate seizure burden.[8]

Routes of Administration

In the hospital, rescue medications are typically administered intravenously (IV) because this route has the fastest onset of action. However, as highlighted previously, it is important for patients to have the ability to receive rescue medications at home, especially if they have a history of prolonged seizures or clusters of seizures. Home medications are available in the following routes: intranasal, rectal, buccal, sublingual, and enteral.

Intranasal

Intranasal rescue medications have several advantages. The drug is rapidly absorbed via the highly vascular nasal mucosa. Medication also avoids first-pass metabolism. The intranasal route is relatively easy for caregivers to administer and is more socially acceptable, compared with per rectum.[13] However, until recently, intranasal administration of generic midazolam, referred to as "generic intranasal midazolam," required caregivers to draw up and measure liquid from an IV formulation, remove the syringe needle, attach an atomizer, and then administer the medication. This process was time consuming, and for many, unfamiliar and stressful. Caregivers had to undergo education by a pharmacist or nurse before being able to obtain the medication. Patients also reported a nasal burning sensation as a side effect. However, in a cross-sectional survey of caregivers at a tertiary-care medical center, caregivers preferred generic intranasal midazolam over rectal diazepam with respect to ease of use, effectiveness, and side effects.[14] The 2 new FDA-approved formulations alleviate the step of drawing up the medication, although not all patients will meet the age and weight-based dosing guidelines, and affordability also may be a barrier to usage for some patients.

Rectal

The most commonly prescribed rescue medication for prolonged seizures is rectal diazepam (Diastat).[1] Advantages of the rectal route include an easily used, prepackaged product and its rapid absorption. The greatest barrier is that many providers and families prefer to avoid the rectal route of administration when possible to avoid unnecessary embarrassment. Rectal drugs can also be challenging to administer in larger patients or in patients with limited mobility, such as those in a wheelchair or with spasticity.[1,14,15]

Other

Buccal and sublingual routes of administration are not FDA-approved for prolonged or repetitive seizures. Their advantages include ease of administration, rapid absorption (though slower than the rectal and intranasal routes), and ability to dissolve easily upon administration. Enteral administration (by mouth or feeding tube) has slower absorption and can be useful when a more prolonged effect is desired, without the need for a rapid onset. The disadvantages include undesirable taste, risk of aspiration, risk of caregiver injury (eg, being bitten during seizure), difficulty opening the mouth, and requirement for refrigeration of some liquid preparations.

Benzodiazepines

Mechanism of Action

The commonly used rescue medications are structurally similar, 1,4-benzodiazepines (midazolam, diazepam, lorazepam, and clonazepam). Benzodiazepines activate the gamma-aminobutyric acid type A receptor, causing an influx of chloride, leading to hyperpolarization of the neuron, and thereby decreasing excitability. Individual medications are then chosen based on potency, time to maximal concentration (T_{Max}), elimination half-life, absorption, distribution, and lipid solubility.[16,17]

Adverse Effects

The most common side effects experienced with benzodiazepine use in adults and children include central nervous system depression, sedation, lethargy, ataxia, respiratory depression, or cognitive impairment.[2] In children, IV benzodiazepine use is associated with respiratory depression and sedation, although the risk of respiratory depression is lower in children than in adults.[2] Tolerance, dependence, and withdrawal are all potential risks, especially with long-term use. In terms of drug interactions, there is a potential for benzodiazepines to augment the effect of other drugs that cause central nervous system depression, but when used only intermittently for abortive therapy in emergent situations, this is less of a concern. There is a boxed warning against the

concomitant use of benzodiazepines and opioids because this combination of medications can result in severe respiratory depression and dependence.[16,17] Despite concern for respiratory suppression with rescue medicines, status epilepticus itself also can cause respiratory suppression. The rate of respiratory suppression in patients with convulsive status epilepticus is lower when treated with a benzodiazepine than with placebo.[2] Benzodiazepine usage is contraindicated for individuals with acute narrow-angle glaucoma, as rarely these drugs also can raise intraocular pressure.[4-6] More specific side effects to each drug are discussed in detail to follow.

Oral Clonazepam

Clonazepam (Klonopin) can be used as a daily medication to treat epilepsy, with FDA approval for this indication since 1976.[18] This medication is not frequently used as a daily anti-seizure drug due to concerns about tolerance, dependence, as well as withdrawal seizures.[19] Clonazepam is used particularly in some absence and myoclonic seizures.[20] It does not have FDA approval for status epilepticus or acute repetitive seizures, but the IV formulation is anecdotally used for this.[20,21] In addition, oral clonazepam wafers are also used as rescue treatment for prolonged seizures,[22] seizure clusters,[1] and febrile seizure prophylaxis.[23]

The concept of a "clonazepam bridge" refers to the use of scheduled doses of clonazepam to provide additional protection from breakthrough seizures during times of illness, while a new medication is titrated and reaches a therapeutic level, or when other medication changes are necessary. Typically, twice or thrice-daily doses of oral clonazepam pills or wafers are prescribed for a finite number of days or until an illness resolves and the seizure threshold returns to the baseline level. This approach has not been proven to be effective, and there are some drawbacks. For example, patients may not experience seizures with every febrile illness, and therefore this approach could lead to prescribing an unnecessary medication and subsequent side effects.[7] Other uses for oral clonazepam include when premonitory symptoms occur, which provide an opportunity to prevent seizures, especially when seizures are known reliably to follow specific symptoms. If rapid onset of intranasally or rectally administered formulations is not necessary, the somewhat slower onset of clonazepam can be used.

Clonazepam can be associated with hypersalivation, so if increased secretions are part of a prolonged seizure, this medication could be unsafe.[19] The oral formulation is also contraindicated in convulsive status epilepticus because of the risk of aspiration or injury during administration. In a survey of pediatric epileptologists, oral clonazepam wafers were a common choice for seizure clusters, likely related to the ease of administration, long duration of action, and inexpensive cost,[1] with 30 generic orally disintegrating tablets having a retail price of approximately $50.[24] Approximately two-thirds of families of children who were treated with both rectal diazepam and oral clonazepam felt clonazepam was as effective as rectal diazepam.[22]

Adverse Effects and Interactions

Drowsiness and fatigue most often lead to discontinuation of clonazepam.[25] There have been no clinical trials testing oral clonazepam as a rescue medication, but when IV clonazepam has been used to treat status epilepticus, no significant respiratory depression was noted.[21] Clonazepam is not known to alter the metabolism of other medications; however, drugs that induce cytochrome P450 (CYP), such as phenytoin, phenobarbital, or carbamazepine, can reduce levels of clonazepam because they induce clonazepam metabolism.[19-21,26]

Pharmacokinetics

Oral clonazepam is rapidly absorbed with peak plasma concentrations within 1 to 4 hours after administration.[19,26] The drug is highly protein bound, at about 85%, and it is 90% bioavailable. The half-life is reported to be between 20 and 60 hours, which may explain prescribers' preference to use it for seizure clusters or repetitive seizures.[1] Clonazepam is metabolized through the liver via CYP3A4 but does not have active metabolites.[19,26]

Administration

Clonazepam is available as an oral tablet and oral disintegrating tablet/wafer.[22] Dosing for treatment of status epilepticus or seizure clusters is not standard. The recommended dose for daily treatment is between 0.01 and 0.03 mg/kg/d, divided into 2 or 3 doses.[19] Anecdotally, a rescue dose is approximately between 0.01 and 0.02 mg/kg for patients not already taking another benzodiazepine. Some use a "rule of man" dose based on the size of child. A baby carried in a parent's arms is prescribed 0.25 mg, a child as tall as a man's knee 0.5 mg, one as tall as a man's waist 1 mg, and adult height a 2 mg wafer.[22] The oral disintegrating tablet/wafer is placed on the buccal mucosa with dry hands for absorption and does not require water to be swallowed.[19,22]

Rectal Diazepam

Diazepam rectal gel (Diastat) was the first FDA-approved at-home therapy for "rectal administration in the management of selected, refractory, patients with epilepsy, on stable regimens of anti-epileptic drugs, who require intermittent use of diazepam to control bouts of increased seizure activity[4]" in patients who are 2 years of age or older.[27,28] The gel is available now as a generic drug, which is identical in composition to the brand-name version. The pediatric data combined from 2 large double-blind, placebo-controlled trials of acute repetitive seizures showed that rectal diazepam-treated children had a significant reduction in median seizure frequency compared with the placebo group (0.00 vs 0.25 seizures per hour), and that 59% of the diazepam-treated group remained seizure-free for the 12-hour observation period.[29] Another large double-blind, placebo-controlled trial also found that rectal diazepam significantly reduced seizure frequency in patients with acute repetitive seizures.[30] An open-label study of patients with seizure clusters or prolonged seizures found that

77% of rectal diazepam administrations prevented further seizures in the 12 hours after treatment.[31]

Adverse Effects and Interactions

Respiratory depression from rectal diazepam in children has ranged from 0% to 6.4%.[2] In a review of respiratory adverse and deaths reported to Xcel Pharmaceuticals, out of more than 2 million doses of rectal diazepam, there were 9 respiratory events and 3 deaths, all of which occurred in the context of prolonged seizures.[32] Rectal diazepam is not generally recommended for infants younger than 6 months of age because prolonged central nervous system depression has been reported in this age group.[28]

Pharmacokinetics

Rectal diazepam is rapidly absorbed. In a study of healthy adult males who received 15 mg of rectal diazepam, the plasma concentration reached 200 ng/mL within 15 minutes (therapeutic blood level range of 150 ng/mL and 300 ng/mL) and the bioavailability was 90.4%.[33] In children, the absorption may be even faster; in a study of 6 children, the therapeutic blood level was achieved within 5 ± 2 minutes after administration of 0.5 mg/kg of rectal diazepam and remained in this range for 6 ± 3 hours.[34] Diazepam undergoes liver metabolism over several hours, specifically via CYP3A4 and CYP2C19.[27] Other agents that induce these enzymes can decrease diazepam concentrations, and those that inhibit these enzymes can increase diazepam concentrations. Diazepam can interfere with the metabolism of other drugs that are substrates of the same enzymes by competing for the enzyme.

Administration

The recommended dose of rectal diazepam is 0.2 mg/kg to 0.5 mg/kg depending on age: 0.5 mg/kg for ages 2-5 years, 0.3 mg/kg for ages 6-11 years, and 0.2 mg/kg for ages 12 years and older.[28] For children ages 6 months to 2 years, although the safety and efficacy have not been rigorously established in large trials, doses of 2.5-5 mg depending on weight could be considered. The rectal gel is supplied in 2.5-mg, 10-mg, and 20-mg delivery systems. The pharmacist can set the dose to 2.5 mg (2.5 mg delivery system); 5 mg, 7.5 mg, or 10 mg (10 mg delivery system); or 12.5 mg, 15 mg, 17.5 mg, or 20 mg (20 mg delivery system).[28] Rectal diazepam ranges in price from $271-$400 for a package of 2 doses, depending on the vendor and dosage.[35]

Intranasal Diazepam

In January 2020, the FDA approved intranasal diazepam (Valtoco, from Neurelis, Inc) as a seizure rescue medication for use in patients age 6 years and older. The approval was based on section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, which allows the application to use information from previous studies done by others. In this case, the application used efficacy studies of rectal diazepam as the reference drug because of its long history of use after FDA approval in 1997. The FDA also deemed that Valtoco is clinically superior to rectal diazepam because of the advantages with an intranasal route of administration.[36]

Pharmacokinetics

Although there have not been any studies that aimed to test directly the efficacy of intranasal diazepam, several studies have demonstrated safety, bioavailability, and pharmacokinetics of the nasal formulation. A crossover study performed in 24 healthy adults evaluated the safety and pharmacokinetics of intranasal diazepam compared with an IV formulation.[37] The absolute bioavailability of intranasal was comparable with the IV formulation (97%), and the T_{Max} was 1.5 hours. The elimination half-life was 49 hours, similar to that of the IV formulation (56 hours). Another crossover study in 36 healthy adults examined plasma concentrations of diazepam and the active metabolite nordiazepam at defined time points for 24 hours after dosing.[38] These data demonstrated dose proportionality in 5-, 10-, and 20-mg single doses, as well as two 10-mg doses separated by 4 hours. The T_{Max} for single doses was again found to be around 1.5 hours. The results from additional studies showed comparable pharmacokinetics between Valtoco and Diastat in healthy adults. In 57 subjects with epilepsy aged 6-59 years, there were comparable pharmacokinetics for Valtoco given during a seizure vs interictally. These studies were presented as abstracts at national meetings but have not yet been published in peer-reviewed journals.

One challenge in delivering intranasal medications is that the volume delivered needs to be low, and this can be problematic when dissolving a therapeutic amount of medication. Valtoco uses vitamin E in the formulation to improve solubility. In addition, bioavailability can be a challenge with nasal delivery; alkyl saccharides in the formulation result in increased transmucosal absorption to improve bioavailability.[39]

Adverse Effects and Interactions

In safety studies thus far, there have not been any serious treatment-emergent adverse events related to the study medication. In healthy subjects, the most common adverse events were mild epistaxis, somnolence, headache, and mild nasal discomfort.[37] In an open-label study of patients with epilepsy, 190 individuals age 6 years and older received intranasal diazepam; the most common local (nasal) adverse reactions were nasal discomfort (6%), nasal congestion (3%), epistaxis (3%), and dysgeusia (2%).[6] There were no serious treatment-emergent adverse events, and respiratory depression was not reported. Although the medication is not approved for neonates and infants, the benzyl alcohol in the formulation can result in "gasping syndrome," which is characterized by metabolic acidosis, central nervous system depression, and gasping respirations.[6]

Administration

Intranasal diazepam is dosed by age and weight (0.3 mg/kg for 6-11 years and 0.2 mg/kg for ≥12 years). It is available

in 5-mg, 7.5-mg, and 10-mg forms, and is sprayed intranasally into 1 nostril. At greater doses of 15 or 20 mg, 2 nasal spray devices are used. A second dose may be administered 4 hours after the first if needed. The nasal spray device is the same that is used for Nayzilam.

Intranasal Midazolam

Generic intranasal midazolam was initially used as a preanesthetic agent. However, given its rapid onset of action, generic intranasal midazolam has also been widely used to abort seizures when an IV line is not present.[40] In May 2019, proprietary intranasal midazolam (Nayzilam, from UCB, Inc) was approved by the FDA for abortion of seizure clusters, for adults and children aged 12 years and older.[5]

The safety of generic intranasal midazolam in children has been studied for more than 20 years[41] and has been found to dramatically reduce epileptiform activity on an electroencephalogram.[42] Subsequently, a randomized controlled trial was performed, comparing generic intranasal midazolam administration with intravenous diazepam to abort seizures for seizures at least 10 minutes in duration at time of arrival to the emergency department; there was equal efficacy found in both groups.[43] Given the convenience of intranasal administration, many families prefer intranasal over rectal administration.[44]

A comparison study of generic intranasal midazolam (0.2 mg/kg divided between nostrils; maximum 10 mg) and rectal diazepam (0.3-0.5 mg/kg) for the use of pediatric seizures prehospital (by emergency medical services) demonstrated generic intranasal midazolam to be superior to rectal diazepam.[45] In the patients who received generic intranasal midazolam, the median seizure time was 19 minutes shorter than those who received rectal diazepam ($P = .003$). Furthermore, in the patients treated with rectal diazepam, they were more likely to have a subsequent seizure once they arrived in the emergency department, and were more likely to require intubation, hospitalization, or admission to the hospital and intensive care unit.[45]

Initial phase I clinical trials for Nayzilam were performed in patients with epilepsy ages 12 years and older.[46] An initial total of 292 patients were given two 5-mg doses of Nayzilam, separated by 10 minutes. Those who tolerated (N = 201) went on to the comparative phase of the trial (ARTEMIS-1).[46] A 5-mg dose of Nayzilam was administered during a seizure cluster, defined as ≥2 stereotyped seizures, lasting >10 minutes, unique from the patient's non-cluster seizures, with another seizure occurring within 6 hours of seizure cluster onset. In comparison with placebo, patients who received the medication had a greater chance of termination of the cluster within 10 minutes (80.6% compared with 70.1%). Patients who received Nayzilam were more likely to not have seizure recurrence in the subsequent 10 minutes to 6 hours (53.7% vs 34.3%, *P*-value .011).[46] In the open-label study for Nayzilam (ARTEMIS-2) in which participants used the nasal spray for seizure clusters, 55.5% of seizure clusters stopped after just one dose, and 80.2% of clusters responded to a second dose.[47]

Nayzilam was studied for treatment of seizure clusters and has not been studied specifically for status epilepticus, in distinction to previous studies of generic intranasal midazolam. Furthermore, the dosages used in studies for generic intranasal midazolam were weight-based and had a maximum of 10 mg,[45] doubling that of the Nayzilam studies. Therefore, it is possible that the FDA-approved 5-mg dose of Nayzilam is not adequate for treatment of status epilepticus.

Pharmacokinetics

The onset of action when given intranasally is within 10 minutes (5.55 ± 2.22 minutes).[48] The half-life is 2-7 hours, and T_{Max} is 17.3 minutes.[49] With a relatively short half-life, repeated doses of generic intranasal midazolam are less likely than diazepam to result in drug accumulation, which can result in brainstem depression, bradypnea, or respiratory arrest.[43] As midazolam is metabolized by CYP3A4, medications that induce CYP3A4 metabolism can reduce midazolam levels by up to 26%.[5]

Adverse Effects and Interactions

The most common side effects from intranasal midazolam include hypersomnolence, rhinorrhea, headache, nasal discomfort, throat irritation, and impaired awareness.[46] The adverse effects from use of intranasal midazolam in women who are pregnant are unknown, but there is concern that prenatal exposure to benzodiazepines may be harmful.[5]

Administration

Nayzilam is given as a 5 mg dose, and a second 5 mg dose may be administered 10 minutes after the initial dose is given if there is a lack of response and no respiratory suppression.[5] The dose is not weight-based, different from how most providers prescribe generic intranasal midazolam, and also different from rectal and intranasal diazepam. This dosing does not allow for adjustments required for children less than 25 kg who would receive less than 5 mg at a standard 0.2 mg/kg/dose. Nayzilam comes in a prefilled nasal spray bottle, which allows for ease of use. However, this preparation comes at a higher cost; generic intranasal midazolam is less than $13 per dose[50] and Nayzilam costs between $550 and $660 for a box of two 5-mg doses.[51,52]

Potential Future Directions

With Nayzilam and Valtoco recently becoming available for use in the US, several areas of research over the next few years could improve the use of rescue medications for seizures in children. As generic intranasal midazolam has been used as early as infancy, a study of safety and efficacy of Nayzilam in children <12 years old could help expand its usage. In addition, because the studies on safety and efficacy of Nayzilam were for seizure clusters, a study of its effectiveness in treating status epilepticus may help determine whether the FDA-approved dosing is adequate to treat status epilepticus. For intranasal midazolam, studies on generic intranasal midazolam reached up to 10 mg, whereas Nayzilam is dosed at

5 mg. As there were no studies to test directly the efficacy of Valtoco, a real-world efficacy study would be helpful. A randomized, controlled trial comparing efficacy and safety of Valtoco vs Nayzilam could help determine superiority of one of these medications, but such a trial would likely need a large number of participants for adequate power and would be quite expensive.

There are several seizure rescue medications in the development pipeline, including inhaled alprazolam. Inhaled delivery of medications provides rapid absorption through the lungs and can be administered with the onset of a seizure cluster or a focal aware seizure but cannot be used after loss of awareness. A phase IIa study showed that inhaled alprazolam results in a rapid decrease in epileptiform activity in photosensitive patients.[53] An unpublished phase IIb study demonstrated that inhaled alprazolam stopped seizures in 30 seconds on average.[54] In addition, auto-injectable intramuscular and buccal soluble film formulations of diazepam are under development.

Conclusions

After over 2 decades of having only a single FDA-approved seizure rescue medication for children, this past year has seen the addition of FDA-approved intranasal midazolam and intranasal diazepam. The FDA-approved indication for Diastat is worded differently from that of Nayzilam and Valtoco, but in essence, these rescue medications are approved for acute treatment of seizure clusters that are distinct from a patient with epilepsy's usual seizure pattern. These medications were not approved for use in status epilepticus specifically, because the clinical studies that led to FDA approval were not designed around treatment of status epilepticus. Nonetheless, these medications are often prescribed for off-label use as a rescue medication for out-of-hospital treatment of status epilepticus.

Several factors may influence the decision of which rescue medication to prescribe for a given patient, including the age of the patient, the desired pharmacokinetics, and route of administration. The ideal seizure rescue medication would have rapid and enduring action, ease of administration, and minimal to no adverse effects. However, the benzodiazepine class of medications all share adverse effects including somnolence, and a longer duration of therapeutic action of the medication is also associated with a longer duration of undesired effects. For situations that do not require a rapid effect but would benefit from a sustained effect from the medication, off-label use of oral clonazepam might be appropriate. For acute repetitive seizures requiring rapid treatment, rectal diazepam, intranasal diazepam, or intranasal midazolam would be appropriate choices. For individuals 2-5 years of age, only rectal diazepam is FDA-approved. For 6-11 years of age, both rectal and intranasal diazepam are FDA-approved, and any of the three medications can be used for 12 years and up. Intranasal is often preferable over rectal administration because it is less invasive. The clinician and the patient/caregiver's previous experience with rectal diazepam or generic intranasal midazolam also can be factors.

There are no head-to-head efficacy studies comparing the 2 intranasal formulations, but their pharmacokinetics and dosing differ. Intranasal midazolam has a shorter time to maximum concentration and may have a more rapid effect than intranasal diazepam. However, intranasal midazolam has a shorter half-life (2-7 hours) than intranasal diazepam (49 hours); therefore, the effect to prevent progression to a seizure emergency may not be as sustained, but adverse effects may also resolve more rapidly. The dosing of the drugs differs, as intranasal midazolam has a single 5 mg dose that can be repeated in 10 minutes, whereas intranasal diazepam has an age- and weight-based dose that can be repeated in 4 hours. The costs for Valtoco and Nayzilam are similar.[49] ■

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