Having parents and other caregivers administer abortive medication for breakthrough seizures is usually recommended for a relatively narrow spectrum of pediatric seizure patients. This group includes children with a history of status epilepticus or recurrent complex febrile seizures or those with poorly controlled epilepsy who are prone to develop prolonged or clustered seizures. For children with first-time seizures, recurrent simple febrile seizures, or controlled epilepsy, the recommended components of home management for breakthrough seizures include reassurance, seizure education, safety instructions, and use of emergency medical services if needed. This approach appears effective in part because most children with seizures have a favorable prognosis and because previously available delivery systems had limitations, including cost and safety concerns. However, the inherent unpredictable nature of seizures and recent study findings that raised concerns about possible deleterious effects of short-duration seizures and seizure clusters point to an expanded role for in-home abortive medication. The demonstrated safety and effectiveness of rectal diazepam and nasal midazolam, along with improved delivery systems, should enhance use of this therapeutic option.

**First-Time Seizures**
Most first-time seizures do not recur, and if they do, they are not prolonged or clustered. Analysis of various risk factors allows some predictability regarding future episodes of febrile and unprovoked seizures. Yet, there is no way to eliminate the possibility of a second or more serious seizure event for a particular child after a first-time seizure. In general, first-time febrile seizures that are complex may also be prolonged at recurrence. These patients may be candidates for abortive therapy.

Current practice guidelines rightly recommend not prescribing daily anticonvulsant medication for recurrent febrile seizures or after a first-time unprovoked seizure. Reassurance and education for parents are important components of the initial evaluation of these children. However, in spite of this conservative approach, repeat seizures trigger anxiety and fear in most parents. This may lead to unnecessary, costly visits to the emergency room, adding to parental frustration. Additional morbidity and expense may occur when seizures are treated inappropriately in the emergency department. This is a particular problem in rural areas and in small community hospitals. Although an abortive seizure therapy plan may not always be needed after first-time seizure events, it should be discussed with parents and may be appropriate in many cases.

**Established Epilepsy**
Despite significant advances in medical and surgical management, 25 to 30% of children with epilepsy remain...
intractable. These patients are at higher risk for prolonged seizures or seizure clusters. Even when epilepsy is apparently well controlled, breakthrough seizures may occur. Although less common, breakthrough seizures in this group may become prolonged or repetitive, or develop into status epilepticus. Breakthrough seizures may occur as the result of illness, sleep deprivation, or missed medication. Medication adjustment or planned medication withdrawal may also produce periods of vulnerability. For established epilepsy patients, an abortive home therapy plan is very important for those with intractable seizures, but it is also useful for those with established control who occasionally experience periods of vulnerability.

**Morbidity from Prolonged Seizures**

The potential for brain injury from convulsive status epilepticus is well known, although most pediatric patients have good outcomes. Findings from recent animal studies and magnetic resonance imaging in children have revealed acute and long-term alterations in hippocampal structure after recurrent seizure clusters or, in some cases, after seizures lasting less than 30 minutes. Effects on brain function from these changes may not be recognized early or easily in at-risk populations. At present, long-term follow-up studies of epilepsy patients and of those with febrile seizures do not indicate that preventing additional seizures or prolonged seizures prevents later development of epilepsy. Yet, the reported association of temporal lobe epilepsy in adults with a history of complex febrile seizures during childhood is of concern. Change in neuronal function and synaptogenesis in the hippocampus after recurrent or prolonged febrile seizures in certain at-risk patients is one explanation for this association that has not been ruled out.

**Administering Abortive Medication**

Terminating acute repetitive seizures and those extending beyond 5 minutes may prevent status epilepticus. Patients with intractable complex partial epilepsy who typically experience seizure clustering are at significantly higher risk for convulsive status than are patients with nonclustered seizures. In one population study that included both children and adults, 57% of those with febrile seizures lasting 10 minutes failed to stop without antiepileptic drug treatment. Early intervention for acute breakthrough seizures also facilitates eventual control.

Studies of benzodiazepine use during status epilepticus in animals have revealed a relatively short time window for efficacy, owing to evolving γ-aminobutyric acid receptor insensitivity during continuous seizure activity. In some cases, this window is as short as 10 to 15 minutes. This may be one reason why benzodiazepines lack efficacy when administration is delayed or inadequate doses are used. Optimally, abortive medication should be administered approximately 5 minutes after seizure onset. In most cases, this terminates seizures within 5 to 10 minutes. Avoiding continuous seizure activity longer than 15 minutes may prevent benzodiazepine resistance, hippocampal injury, and development of status epilepticus. Optimal timing for termination of seizure clusters varies and depends on a child’s seizure history. In general, we recommend administering abortive medication after the third convulsive seizure in 1 hour, regardless of length.

**Training Parents and Other Caregivers: Tips and Pitfalls**

The need to administer abortive medication within 5 to 10 minutes after onset of seizure activity precludes reliance upon paramedics or the hospital emergency department. Adequately training parents and other caregivers is crucial to the safe and effective use of abortive seizure medications, and there are some pitfalls to avoid.

Once the diagnosis of a seizure disorder or epilepsy is established, parents should be counseled as much as possible regarding cause, risk of recurrence, and what to do during the next episode. The need for an abortive therapy plan will depend upon several variables. These include the nature of the initial event, recurrence risk, parental anxiety, access to emergency medical care, and compliance with taking daily medication. In some areas, consultation with a child neurologist may take several weeks; thus, an abortive medication plan is particularly useful after a first or second unprovoked seizure, while the family waits for more testing and consultation. This is often a better option for primary care physicians because they can avoid prematurely placing a child on medication, which might not be needed or could potentially worsen an emerging epilepsy if the wrong drug is chosen.

In addition to discussing routine seizure safety measures, parents should be counseled to record details of future seizure events. These include date, time of onset, presence of fever, abortive medication used, medication dose, and seizure duration. Other details, such as bladder incontinence, oral trauma, and localizing features, should be included if present. If possible, home video of the seizure should be recorded. Instructions should be written in a clear, stepwise format and reviewed with parents and other caregivers, such as grandparents. Appropriate personnel at school, camp, or other venues should also be trained. Instructions should include when to use abortive medication, at what dose, and when to repeat a dose. Use of nasal midazolam for in-home abortive therapy is off-label, and this should be discussed. A number of sources
for preprinted instructions that include many of these points exist. We recommend in-office teaching for nasal midazolam administration and use of the available Diastat® training video as a way to ensure successful medication administration. Parents should be counseled that calling paramedics or transporting a child to the emergency department is not necessary if seizures are controlled and the child is otherwise stable. Anyone administering rescue seizure medication should learn cardiopulmonary resuscitation (CPR) for children, although it is rarely, if ever, needed. Rescue breathing and airway maintenance are the two components of pediatric CPR most likely to be used. A follow-up phone call to parents 2 to 4 days after initiating a home management plan is another technique that can improve success. Common pitfalls to avoid include unclear instructions, administering an inadequate dose, excessive delay of administration, parents failing to fill or refill the prescription, and leaving medication at home when traveling. The plan should be reviewed at each office visit and modified as needed.

Medication Options

Benzodiazepines (namely diazepam) given rectally and midazolam administered via the nasal or buccal route are currently available options for rapid termination of breakthrough prolonged seizures or acute repetitive seizures at home or school. The demonstrated efficacy and safety of diazepam and midazolam used for the control of status epilepticus, prolonged seizures, and seizure clusters is supported by numerous studies and years of clinical experience. The relatively aqueous insolubility of parenteral diazepam makes it unsuitable for nasal or buccal administration. Use of intermittent oral diazepam tablets or solution for febrile seizures may be an option in selected cases. A dose of 0.3 to 0.5 mg/kg is used and repeated every 8 to 12 hours if a patient’s temperature is 38°C or more. A maximum of four to five doses is given per illness. A potential drawback of intermittent medication is that a seizure could occur before fever is noticed.

Other orally administered benzodiazepines, clonazepam, lorazepam, and oral loading with Dilantin® may be considered for breakthrough seizure clusters in exceptional cases of intractable epilepsy if other measures are ineffective. The usual sublingual dose for lorazepam is 0.05 to 0.15 mg/kg. Lorazepam is absorbed more rapidly when given sublingually than orally or intramuscularly, and peak plasma levels are achieved no later than 60 minutes after administration. Disadvantages with oral or buccal lorazepam include irritability and occasional vomiting. This problem and the slow rectal absorption of lorazepam make it unsuitable for rapidly terminating seizures at home. In-home loading with intramuscular fosphenytoin (Cerebyx®) for intractable cases of recurrent status epilepticus is another off-label technique used occasionally. Fosphenytoin requires a large volume when used intramuscularly, which limits its use in infants and small children. Use of Cerebyx® in this manner is rarely indicated and usually reserved for families living far from emergency medical care. Such use requires close supervision and careful training.

Although rectal diazepam is effective for all ages, in general it is best suited for infants and toddlers. Rectal diazepam can be difficult to administer to patients using wheelchairs or during a tonic seizure, and constipation or bowel movements can interfere with absorption. Rectal administration becomes more socially unacceptable to preteens and older children. In addition, school officials are often uncomfortable with rectal administration. For these reasons, we believe nasal or buccal midazolam is the preferred option for school-age children, adolescents, and young adults, although its use in this way is off-label at this time. In one study, 83% of parents or caregivers preferred intranasal or buccal midazolam to rectal diazepam. In a few limited studies, midazolam had a slight edge over diazepam in overall efficacy and speed of action. Whether this observation is clinically significant is not clear.

Rectal Diazepam

Diazepam is a 1,4-benzodiazepine available in tablets, oral solution, parenteral solution, and a rectally administered gel format (Diastat®). For abortive therapy using diazepam, rectal administration is preferred. A rectal gel preparation can be compounded by many pharmacies, and the parenteral solution can be diluted and given via a small, lubricated tube inserted rectally. However, the commercial preparation Diastat® is preferred, because of reliable dosing, absorption characteristics, and a well-designed, easy-to-use administration system. At present, Diastat® is the only commercially available preparation of rectally administered diazepam available in the United States. It is also the only Food and Drug Administration–approved medication for in-home therapy to abort acute seizures. It is approved only for the management of selected refractory patients with epilepsy 2 years of age and older on stable regimens of antiepileptic drugs who require intermittent use of diazepam to control bouts of increased seizure activity. However, its off-label use for patients younger than 2 years and for other acute seizure situations as described earlier is widely accepted and appropriate.

Diastat® rectal delivery system is a nonsterile diazepam gel containing 5 mg/mL of diazepam provided in a prefilled unit dose rectal syringe. It comes packaged with two doses and has a shelf life of 3 years. It does not have to be refrigerated. Available dose sizes are 2.5 mg, 5 mg, 10 mg, 15 mg, and 20 mg. Dosing is based on body weight and age. The recommended doses for ages 2 to 5 years is
0.5 mg/kg, ages 6 to 11 years, 0.3 mg/kg, and ages 12 years and older 0.2 mg/kg. Because Diastat® is supplied in a fixed-unit dose, the prescribed dose is obtained by rounding up to the next available size. More precise dosing may be obtained by using combinations of the various dose sizes. Plasma concentrations of diazepam, necessary for acute seizure control, are achieved in infants and children within 2 to 4 minutes after rectal administration of 0.5 to 1 mg/kg diazepam. After single-dose rectal diazepam administration, acute prolonged seizures resolved in 60 to 96% of cases, depending on the study. We instruct parents to administer a second dose if seizures continue more than 15 minutes after the first dose. Because of its long half-life, rectally administered diazepam may provide seizure control for up to 12 hours. Parents are told Diastat® may be used more than once in a 24-hour period if needed, but they should call the office if this is necessary. Serious adverse effects from the proper use of Diastat® are exceedingly rare. As of September 2003, 1.6 million rectal gel syringes have been prescribed and more than 1.2 million doses are estimated to have been administered. Thus far, only seven spontaneous reports of respiratory adverse events have been reported. In our own practice, no cases of serious respiratory depression requiring additional medical intervention have been encountered, with approximately 400 doses being administered.

Intranasal Midazolam

Midazolam, another 1,4-benzodiazepine, has an imidazole ring that is open at low pH (3.3), which allows it to dissolve in water; at physiologic pH, the ring closes, which renders it lipophilic, allowing rapid penetration of the central nervous system. Beta activity can be seen on an electroencephalogram 2 to 5 minutes after intranasal administration. The low pH causes nasal irritation and burning or a bitter taste when given buccally but is of no consequence in a seizing child. The mean lag time of midazolam after intranasal administration is 0.84 ± 0.74 minutes. A mean peak concentration is reached after 14 ± 5 minutes. Mean bioavailability is 0.87 ± 0.19 minutes after intranasal administration and 0.24 to 0.45 minutes after oral administration. Mean initial and terminal half-lives are 8.4 ± 2.4 and 79 ± 30 minutes, respectively. Intranasal or buccal administration allows rapid absorption into the systemic circulation, bypassing the portal circulation and avoiding the high first-pass metabolism of midazolam, which occurs after oral administration. Although the half-life of midazolam may be short, its longer duration of effectiveness is likely owing to early interruption of prolonged seizures, seizure clusters, or status epilepticus.

For many years, intranasal midazolam has been used by anesthesiologists as a preanesthetic for children and by dentists for sedation. Buccal midazolam appears to be as effective as rectal diazepam in reducing time to seizure cessation. In one study, intranasal midazolam was found to be more effective than rectal diazepam in terminating status epilepticus in children. In the diazepam group, the seizures of 60% of the patients stopped at 10 minutes, whereas 87% of the seizures stopped in the intranasal midazolam group at 10 minutes.

Since 1994, we have used intranasal midazolam as an alternative to rectal diazepam for the home treatment of acute seizures. Disadvantages of intranasal midazolam include small nares and nasal congestion in infants, which would require alternative buccal administration or use of rectal diazepam. The cost of midazolam is approximately 10 to 20% that of rectal diazepam. Usually 0.5 to 0.8 mg/kg is given after a certain length of seizure, usually 5 minutes. For children who always or almost always have status epilepticus or prolonged seizures, it may be given immediately. Midazolam for intravenous use is available in 5 mg/mL, 1 or 2 mL vials and is usually given in 5 mg aliquots (ie, 5, 10, 15, and 20 mg). To avoid the use of needles, parents can use a blunt plastic cannula (Becton Dickinson Inc. order No.303345) (Figure 22-1), to withdraw the midazolam from the vial; then remove the cannula from the syringe, attach the MAD® atomizer, (Figure 22-2) (available from Wolfe Tory Medical Inc., www.wolfeitory.com), and administer the midazolam intranasally. Do not allow the pharmacist to prefill the syringe because the stability of the midazolam once placed in the syringe is uncertain. If the child has severe nasal congestion, the midazolam can be applied to the buccal mucosa and gums. Specific parent directions of administration are provided in Table 22-1. We have found intranasal midazolam to be an extremely effective treatment for acute seizures. It has a rapid onset of action and we have encountered no significant respiratory suppression in thousands of treatments.

**FIGURE 22-1.** Blunt plastic cannula.  
**FIGURE 22-2.** MAD® atomizer.
TABLE 22-1. Sample Intranasal Midazolam Instruction Sheet

| Dose: ______mL (_____mg) to be given after ____ minutes of seizure or ____________________________.

Midazolam is a very potent anticonvulstant that is rapidly absorbed into the bloodstream through the membranes in the nose and mouth. It will usually stop a seizure within 2 to 10 minutes. Midazolam is a short-acting medication. If seizures recur, follow your neurologist’s instructions. Midazolam may produce a burning sensation in the nose, but most children are not aware of it during a seizure. Common side effects of midazolam are similar to those caused by a seizure and include drowsiness, dizziness, slurred speech, and loss of memory. If breathing slows or stops, stimulate by gently shaking the child until breathing resumes. It is recommended that caregivers know cardiopulmonary resuscitation (CPR). If a child’s nose is very congested or if any midazolam remains in the atomizer, it can be poured between the cheek and gum.

Equipment
1. Midazolam solution for injection (5 mg/mL concentration), supplied in 1 mL or 2 mL vials.
2. 3 mL syringe with attached MAD® atomizer and a blunt plastic cannula (needle) to remove the midazolam from the vial.

Instructions for using the MAD® atomizer
1. Remove the plastic cap from the midazolam vial.
2. Unscrew the MAD atomizer device and remove it from the 3 mL syringe.
3. Remove the plastic protector from the blunt plastic cannula (needle) and screw the cannula onto the end of the MAD atomizer syringe.
4. Holding the midazolam vial upside down, push the plastic cannula (needle) tip through the rubber stopper of the vial and withdraw ______ mL of midazolam into the MAD atomizer syringe.
5. Remove the cannula from the syringe and replace it with the MAD atomizer device.
6. The child’s head can be in any position for administration.
7. Place the tip of the atomizer into one nostril and press the plunger until one-half of the midazolam has been atomized, and then atomize the remainder into the other nostril.

Suggested Readings


Practitioner and Patient Resources

Diastat.com
http://www.diastat.com
Information on Diastat® from Xcel Pharmaceuticals.