

## Neurology in Practice

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### **Epilepsy**

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## Rescue Medications for Home Treatment of Acute Seizures

Peter Wolf<sup>1</sup> and Rūta Mameniškienė<sup>2,3</sup>

<sup>1</sup>Danish Epilepsy Centre, Dianalund, Denmark

<sup>2</sup>Clinic of Neurology and Neurosurgery, Faculty of Medicine, Vilnius University, Vilnius, Lithuania

<sup>3</sup>Epilepsy Centre, Department of Neurology, Vilnius University Hospital Santariškių Klinikos, Vilnius, Lithuania

Epilepsy is a chronic disease and is treated with continuous medications aiming at sustained complete seizure control. However, in its course, emergency situations may sometimes arise that require acute interventions. In some epileptic conditions, seizures occur only occasionally but in series or prolonged states. These require rapid action, whereas continuous treatment may not be indicated. Rescue medication (RM) can also be used to prevent seizures when risk is perceived.

### ★ TIPS AND TRICKS

The home use of RMs can often help patients avoid emergency hospital admissions.

hippocampal sclerosis with the consequence of chronic temporal lobe epilepsy. It is therefore highly important that FS be treated as early and effectively as possible to prevent prolonged seizures. FS are often a once-in-a-lifetime event and not considered an indication for continuous antiepileptic drug (AED) treatment. However, recurrence occurs in up to one-third of children.

### ★ TIPS AND TRICKS

The risk of recurrence of FS is high enough that parents of a child who has had one should be provided with an RM and instructed how to administer it.

### Conditions requiring acute drug administration

#### Febrile and nonfebrile serial seizures of childhood

Febrile seizures (FS) are the most frequent type of acute epileptic seizures and occur at the ages of 6 months to 5 years. There is a strong genetic predisposition. Although simple, uncomplicated FS have no sequelae, febrile status epilepticus has been correlated with the development of

Recurrent prolonged and serial seizures unconnected with febrile illness are much more common in children than in adults and, in some patients, have a high risk of status epilepticus. RM should be made available.

#### Epilepsies with habitual clusters of seizures

In some patients with epilepsy, seizures habitually occur in clusters of several seizures on one or subsequent days. These clusters may affect ability to work, independence, and life quality much more

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than single seizures. In many cases, clusters can be effectively prevented by self-application of an RM after the first seizure.

### Prodromes and auras

Some patients have “warnings” before their seizures. These can be auras—that is, subjective symptoms that seem to precede the seizure but actually are the first seizure symptoms. These are quite common but usually last only seconds or fractions of seconds, too short for any drug intervention. In some patients, however, the auras last on the order of minutes, and a rapidly acting drug can possibly interrupt these.

A more rare kind of warning is the prodrome, which precedes a seizure for periods from 30 min upwards. Sometimes prodromes represent increased subclinical seizure activity or very mild forms of nonconvulsive status epilepticus, and sometimes their background cannot be clarified. They may be registered by the patients themselves or observed as behavioral changes by others. They are an indication for RM only if they stand out clearly from the habitual interictal state. In these cases, an oral benzodiazepine (BZD) can prevent an imminent seizure.

#### CAUTION!

Prodromes may impair a patient’s ability to use RM as prescribed. It may therefore be necessary to have a family member or caregiver to administer it.

### Stress convulsions, provoked and lifestyle seizures, and social indications

Sleep disturbances increase the risk of seizures in many patients, especially when combined with excessive alcohol intake. Some patients with infrequent seizures even have exclusively provoked seizures that may also result from excessive psychophysical stress. They may be aware of the relationship but not necessarily willing to change their lifestyles. Prophylactic intake of an oral BZD at perceived risk can protect them against seizures. Prophylactic BZDs may also be recommended in cases of predictable sleep disturbances caused by overnight or transcontinental travel. People who travel a lot or have experienced a provoked seizure should have a small supply of a suitable BZD available.

Likewise, seizures can be prevented in socially important or potentially stigmatizing situations such

as church services, the theater, concerts, and sports events, or when the patient is in the spotlight, as when performing at cultural, political, or scientific events, applying for a job, or presenting a project to a committee.

### Reflex epileptic seizures (e.g., hot water epilepsy)

Reflex epilepsies are conditions where epileptic seizures habitually are precipitated by qualitatively, often even quantitatively, well-defined sensory or cognitive stimuli. Most patients also have spontaneous seizures that require continuous AED treatment. Others have only provoked seizures, or treatment controls the spontaneous but not the reflex seizures. If the seizure trigger cannot be avoided or attenuated (such as by the use of dark glasses to avoid photosensitive seizures), RM can be applied before the patient is exposed to the trigger. The best-known example is hot water epilepsy, a condition particularly common in South India, in which complex partial seizures habitually are provoked by pouring hot water over the head. In most cases, the application of 5–10 mg clobazam (CLB) 60–90 min before taking the head bath fully controls the seizures even without continuous AED treatment.

### Drugs for acute anticonvulsive intervention

#### Benzodiazepines (BZDs)

Whereas BZDs are rarely used for sustained epilepsy treatment because of frequent development of secondary tolerance, they are clearly the first-line rescue medicines due to their rapid action and high anticonvulsant effect. The principal adverse effects are sedation and respiratory suppression, but these effects have not been reported to cause serious problems in studies of home RM. BZDs are differentiated from each other mainly by their pharmacokinetic properties.

#### CAUTION!

Persistent administration of BZDs often leads to tachyphylaxis that will limit their effectiveness.

#### *Diazepam (DZP)*

Diazepam (DZP) was the first BZD for which a solution for rectal use was introduced for home treatment as an alternative to IV administration. It has been extensively studied in both children and adults in



double-blind, placebo-controlled studies. Absorption is rapid and complete, with peak concentrations attained within 5–15 min and a half-life of 20–40 h.

#### *Clonazepam (CLZ)*

Oral clonazepam (CLZ) (tablets of 0.5 and 2 mg, orally disintegrating tablets of 5 strengths between 0.125 and 2 mg, or oral liquid of 2.5 mg/mL) is absorbed rapidly, with an absorption half-life of 24 min and without substantial differences between the formulations. Elimination half-life is 35–40 h. Rectal administration of CLZ has been investigated, and peak values were reached after 10–30 min, but no commercially available formulation for rectal use has been developed.

#### *Clobazam (CLB)*

Clobazam is used almost exclusively for oral administration in tablets of 5, 10, and 20 mg, although rectal administration has been investigated and a liquid preparation is available in some countries. It is rapidly and completely absorbed, reaching peak levels after 1–3 h, and is metabolized with a half-life of 20–25 h. It has an active metabolite, desmethyloclobazam, with a half-life of 36–46 h, so repetitive administration even at intervals of 2–3 days can be expected to produce accumulation to a steady state especially of the metabolite.

#### *Midazolam (MDZ)*

Midazolam (MDZ) is a short-acting BZD developed in the 1970s, with rapid absorption and an elimination half-life of 1–4 h. It is available in tablets of 7.5 and 15 mg and in injectable form as ampoules of various sizes. Administration by the intranasal or the buccal route (absorption via the gums and cheek) as an alternative to rectally administered DZP is becoming increasingly popular for the emergency treatment of seizures because of high effectiveness for suppression of seizure activity and good tolerability. However, the main difficulty with the use of MDZ is tachyphylaxis, which becomes a problem within 48 h of initiation. A variety of liquid preparations for buccal and nasal administration are available. MDZ is absorbed directly via the mucosa into the bloodstream within 5–10 min.

#### *Lorazepam (LZP)*

Oral, sublingual, and buccal administration of lorazepam (LZP) tablets (0.5, 1, or 2 mg) has been

studied in several investigations. The absorption is rapid but too slow when immediate intervention is required. Absorption from a nasal spray is faster, and this formulation was not inferior to IV LZP in terminating acute seizures. LZP has a half-life of about 12 h, significantly longer than MDZ.

#### **Other**

##### *Acetazolamide (AZM)*

Acetazolamide (AZM) is a carbonic anhydrase inhibitor with antiepileptic properties that is not well established as an AED for sustained treatment, probably because of secondary tolerance. It has been used as interval therapy for catamenial epilepsy, with unconvincing results. There are no studies of AZM as RM for epilepsy, but it may be a possible alternative to BZDs if these are contraindicated, as in patients with a history of paradoxical reactions to BZDs, BZD addiction, or muscular weakness with increased risk of respiratory deficiency.

#### **Procedures**

Home treatment normally excludes parenteral applications. RMs are available for oral, rectal, buccal, and nasal administration. The choice of route depends upon required speed of action, practicality, and availability, the latter differing much from country to country.

#### **Rectal**

Diazepam is available in some countries as suppositories (5 or 10 mg) and in others as microclysmic gels (5 or 10 mg). DZP rectal gel is provided as unit doses of 2.5, 5, 7.5, 10, 12.5, 15, 17.5, and 20 mg, and the rectal delivery system includes a plastic applicator with a flexible, molded tip available in two lengths.

Leaking and defecation are potential obstacles to reliable rectal administration, especially as the application may provoke defecation. This is one of the reasons why other routes are now usually preferred when available.

#### **Buccal and nasal**

The liquid formulation of MDZ for buccal administration can also be applied intranasally. The dose is given in two halves, one to each side. Traditionally, the liquid is provided in bottles from which the required dose is taken with a syringe and then delivered to the patient. For easier use and to improve speed of delivery, new ready-packed



formulations are increasingly becoming available in some countries. LZP for nasal use comes with an atomizer or spray pump.

With buccal administration the patient must abstain from swallowing for 2 min. Nasal administration requires detailed instructions, and supporting materials are available, for example, at [www.intranasal.net](http://www.intranasal.net).

### Intramuscular

In some countries home treatment potentially includes intramuscular (IM) administration, which usually delivers the exact quantity of drug desired. For most AEDs, IM injection results in greater than 90% absorption, but the rate of absorption is highly variable. Formulations for IM administration are available for DZM, CLZ, MDZ, and LZP. Some patients and relatives prefer this rather than the rectal route. However, IM medications are absorbed more slowly than rectal formulations. Therefore, IM RM is used rarely, the alternative in most cases being oral administration. This may change in the future when autoinjectors that are under development for DZM, MDZ, and LZP become available.

### Strategies

#### ★ TIPS AND TRICKS

The rapidly absorbed buccal MDZ, nasal LZP, and rectal DZP will be used as interventions:

For FS and habitually prolonged nonfebrile seizures in childhood

To interrupt incipient recurrent status epilepticus (convulsive or nonconvulsive)

In patients with habitual series of seizures occurring at short intervals; intervention is made at onset of a series, after the second or even the first seizure

In patients at perceived risk of an imminent seizure (e.g., at aura onset)

In most instances, the buccal or nasal routes of administration will be preferred, especially if RM may be required out of the house. LZP acts longer than MDZ, which may determine individual choice depending on whether shorter action is desired to minimize side effects or longer action for more sustained therapeutic effect. In a semiconscious patient who could fight against buccal application

#### ⚠ CAUTION!

Rapidly acting BZD can produce a fall in blood pressure. Therefore, to prevent syncope, patients should rest in a recumbent position for some time after administration.

or when hypersalivation is present, the nasal route may be more reliable. Patients with a tendency toward resumption of seizure series or status after temporary interruption may benefit most from rectal DZP, which has the longest action of the three. This drug may also be easier to apply in bedridden and unconscious patients.

For recommended doses see Table 16.1.

#### ★ TIPS AND TRICKS

Oral CLB, DZP, and CLZ are indicated when onset of effective protection after 20–30 min is acceptable and sustained action is desired. This is the case when the RM is given to prevent seizures when risk is perceived, as with the following:

- Prodromes
- Seizures occurring in clusters
- Lifestyle-provoked seizures
- Overnight and transcontinental travel
- Social situations
- Reflex seizures

The time at which the preventive RM is taken depends on the time indicated by the individual's history. The therapeutic effect with all three drugs given orally starts approximately 20–30 min after intake, rapidly reaching its maximum. All three have sedation and drowsiness as unwanted effects, most pronounced with CLZ. CLB is the RM with which the most experience is available.

Most events that require RM end on the same day, but seizure clusters such as those in temporal lobe epilepsy may extend over two or more days. In these cases, doubling of the usual dose (such as 20 mg instead of 10 mg CLB) should be considered, and it may be necessary to repeat RM on the morning of the second day. These schemes may require adaptation in individual cases.

Some patients at perceived seizure risk may spontaneously take an extra dose of their regular AED,



**Table 16.1.** Recommended doses.

Drug	Children	Adults	Remarks
DZP rectal gel	0.5 mg/kg	10–20 mg	20 mg for cluster
Oral		10 mg	prevention
CLB oral	5 mg for <30 kg; 10 mg for >30 kg body weight (for children more than 2 years old)	10 mg	20 mg for cluster prevention
CLZ oral	0.02 mg/kg (from 0.01 to 0.03 mg/kg)	1 mg	
MDZ buccal	0.2 mg/kg	10 mg	Rest recumbent after
Oral	0.2 mg/kg	10 mg	application
LZP nasal	0.1 mg/kg	2 mg	Rest recumbent after application
AZM oral	8–30 mg/kg	500 mg	

AZM, acetazolamide; CLB, clobazam; CLZ, clonazepam; DZP, diazepam; LZP, lorazepam; MDZ, midazolam.

but the effect of this is doubtful and has not been established by any study.

Interventive, as well as preventive, RM is used only when a seizure is highly likely to occur. In some patients, however, the need for RM recurs rather frequently. The typical risks with repetitive administration of BZD, which accumulate because of a long half-life, are the development of tolerance and of drug dependence, so the question arises as to how often RM can be applied. This has been little discussed, but no such problems have been encountered with CLB used one to two times per week or even more frequently in the case of hot water epilepsy. No reports are available on DZM or on CLZ, which both may have a higher potential of dependence. In the case of reflex epilepsies, when frequent intake of RM may be required to provide protection only for brief periods, oral short-acting MDZ is probably the best option.

With some indications, the patients themselves can apply the acute medication. In most cases, however, the assistance of others is needed, and all should receive detailed instructions, which may need to be given repeatedly to ensure they are well understood and applied. The decision of whether or not to apply RM may be difficult and require a learning process before full success can be achieved. Camfield and colleagues recommend RM as the standard home treatment for FS “for a well-organized family.”

Instructions to patients need to address the possibility that the RM might not have the desired effect and the seizures could thus continue or resume. In such

instances, the most typical approach will be to repeat the RM one time along with calling an emergency doctor or an ambulance. Therefore, instructions should specify when the first RM should be considered unsuccessful, if and how often it can be repeated, and with what dose. Also, “home” treatment may include related situations such as school or kindergarten, where the immediate caretakers may be teachers or other nonmedical staff, unless a school nurse is available. These caregivers may have legal concerns about this responsibility and will usually feel more comfortable with buccal or nasal rather than rectal administration, which, in uninstructed observers, has raised suspicion of sexual assault. Questions such as how the RM may be stored where it is safe but rapidly accessible need to be discussed. Some issues may arise that cannot be resolved between the parents and caretakers and therefore need advice from the doctor. These matters have been discussed from a European perspective by Wait and colleagues.

## Conclusions

Several rapidly acting AEDs, especially BZD, are now available for rectal, buccal, nasal, and oral administration. This makes them applicable as RMs for home treatment by patients and caregivers. The advantages of RM are that emergency situations such as seizure clusters and status epilepticus can be stopped more rapidly, that patients at perceived risk can prevent seizures, and that emergency hospital admissions can be avoided.

## Bibliography

- Camfield PR, Camfield CS, Eriksson KJ. Treatment of febrile seizures. In: Engel J, Pedley TA, eds. *Epilepsy: A Comprehensive Textbook*, 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2008, 1345–1349.
- Meghana A, Sinha S, Sathyaprabha TN, Subbakrishna DK, Satishchandra P. Hot water epilepsy clinical profile and treatment – A prospective study. *Epilepsy Res* 2012; **102**(3):160–166.
- Wait S, Lagae L, Arzimanoglou A, et al. The administration of rescue medication to children with prolonged acute convulsive seizures in the community: What happens in practice? *Eur J Paediatr Neurol* 2013; **17**(1):14–23.
- Wolf P. Acute administration of benzodiazepines as part of treatment strategies for epilepsy. *CNS Neurosci Therap* 2011; **17**:214–220.
- Wolf P. Acute drug administration in epilepsy. A review. *CNS Neurosci Therap* 2011; **17**:442–448.