

# Fits

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## Introduction

The remote-area nurse or Aboriginal health worker may have to deal with the stressful emergency of the fitting child or adult, with no medical backup other than telephone advice. The main goals of treatment are:

- Maintain adequate vital functions (oxygenation and circulation)
- Prevent systemic complications
- Terminate the seizure rapidly
- Minimise side effects of treatment
- Evaluate and treat any underlying causes.

Many seizures will terminate spontaneously, but drug treatment should be initiated if fitting persists. Rapid control of fitting results in fewer complications. As a general rule, this should be done if a fit lasts for more than three minutes in children or five minutes in adults. There are no specific data to support the use of these times: they are the recommendations of neurologists. In individual patients whose pattern of fits is well understood, it may be appropriate to wait longer if, for example, they usually stop fitting within say ten minutes. Such patients should have an individualised management plan in their case notes.

Recommended protocols should therefore be easy to follow, involve only one or two drugs and have simply-calculated dosage regimens. Drugs should be administered by socially/culturally acceptable routes.

As a general rule, a doctor should probably be consulted after any fit unless an individual management plan indicates otherwise. The degree of urgency can vary. If the fit is not controlled with one dose of anti-convulsant, or fitting is recurrent, consultation should be immediate. If the fit ceases spontaneously, or is controlled with a single dose, some time can be spent in taking a history and doing some investigations (e.g. blood glucose) as per 'Further Management'.

Specialist medical terminology has been avoided where possible, or explained if it is used. Cross-references have been given to other topics in the CARPA STM (e.g. Resuscitation, Meningitis) rather than duplicate material unnecessarily.

This revised protocol follows the previous version where no change is necessary or advisable. However, since the publication of the previous edition of the manual there have been developments in the management of seizures, which are changing recommended practice.

## When should a fit be treated?

The recommendation of the Working Group on Status Epilepticus of the Epilepsy Foundation of America is that fits lasting more than 10 minutes should be treated. Australian neurologists associated with the Epilepsy Society of Australia recommend three minutes in a child and five minutes in an adult. These times are based on expert opinion and not on specific data.

In practice, it may take several minutes for fitting patients to get to the clinic or for health personnel to reach the patient. The protocol therefore recommends that once health personnel are in attendance, drug therapy be started after three minutes in a child or five minutes in an adult.

Most self-limiting generalized convulsions stop within 3 minutes, and almost all stop by 5 minutes from onset. Furthermore, early therapy is far more effective than is delayed therapy, so the longer the seizures persist, the more difficult they are to stop. Therefore, patients seizing for 10 minutes should be treated on the assumption that they are in (status epilepticus).<sup>3</sup>

### **The ‘demise’ of paraldehyde**

All injectable paraldehyde products have been discontinued in the USA due to lack of demand (RDH Pharmacy database), and it is likely that this will also follow in Australia. Royal Darwin Hospital Pharmacy currently supplies about 60–70 ampoules per year to remote-area clinics and the NT Aerial Medical Service. This probably represents replacement of expired unused stock. RDH Pharmacy anticipates difficulty in future supply of paraldehyde. The perceived ‘safety’ of paraldehyde is probably incorrect; it seems just as capable of causing respiratory depression as the benzodiazepines (RDH Pharmacy database, MIMS Annual). Its intramuscular use when diazepam could not be used in this way was a major rationale for its use in previous editions of the manual. The availability of midazolam makes paraldehyde redundant.

### **The ‘rise’ of midazolam**

Control of fitting is not one of the current listed indications for midazolam in Australia. It is, however, a potent anti-epileptic as well as anaesthetic/sedative, and there is a large volume of current literature dealing with its use for this purpose. It is widely used throughout Australia for the control of fitting. At the Women’s and Children’s Hospital in Adelaide there is a program to train parents, other carers and teachers to use intra-nasal midazolam to control fits that occur outside of hospital.

Intravenous or intra-osseous administration produces the quickest onset of action, and is the preferred route in ideal circumstances. However, in contrast to diazepam, midazolam is water-soluble at its preparation pH (3.5) and is therefore well absorbed after intra-muscular injection and also across mucous membranes (oral, nasal or rectal). Its low pH causes pain/burning when given intra-nasally in the conscious patient but this is of decreased relevance in a convulsing subject. It has an unpleasant taste when given orally, but this is unlikely to be appreciated by a fitting patient.

At physiologic pH, midazolam becomes extremely lipophilic<sup>3</sup> and therefore crosses the blood–brain barrier readily for a rapid onset of action. Effects on the EEG have been reported within minutes of IV administration, and control of fitting has also been achieved within minutes. Elimination half-life is short (1.5–3.5 hours). Its metabolites are pharmacologically inactive.

Midazolam has successfully terminated seizures when other benzodiazepines have failed to do so, and has also reportedly succeeded when barbiturates have been ineffective. It is not yet widely accepted as a first-line drug, but increasing numbers of studies are advocating its use in this respect.

Midazolam has a generally good safety record with respect to respiratory depression, but can cause this, especially when combined with opioids or other CNS depressant drugs. Incidence of side effects, when used on its own for sedation in the Emergency Department, is of the order of 2%. This is mainly transient respiratory depression, occasionally requiring short-term bag-and-mask ventilatory support.

Medline searches on midazolam in fitting:

- 'effects can be seen within 1 to 5 minutes of administration, and its anti-convulsive effects are apparent as early as 5 to 15 minutes after administration' in refractory status epilepticus<sup>a</sup>
- 'Seizure arrest is usually attained within 5 to 10 min' after IM use<sup>b</sup>
- Efficacy in controlling seizures is 79% (intranasal), 93 to 100% (intramuscular) and 100% (intravenous) – (v) 28.6 to 100% (rectal) and 54 to 100% (IV) for diazepam<sup>c</sup>
- 'Midazolam is relatively free of side effects when used alone'.<sup>d</sup>

### Midazolam: cost and shelf life

Midazolam is supplied in the several preparations including:

15 mg in 3 ml	Box of 5	\$34.85 or \$37.10	\$6.97 to \$7.42 per amp
5 mg in 5 ml	Box of 10	\$11.65 or \$15.30	\$1.12 to \$1.53 per amp
5mg in 1 ml	Box of 10	\$15.30	\$1.53 per amp

The 5mg in 1 ml preparation comes in both glass and plastic ampoules. The plastic ampoules are those recommended by the Women's and Children's Hospital in Adelaide for use by lay persons, as the top can be removed easily and the midazolam dripped into the patient's nose.

Only one concentration should be stocked, to minimise confusion in calculation of dose and dilution. Therefore, either the 15 mg in 3 ml or 5 mg in 1 ml preparations are recommended, as the volumes required are more suitable for nasal, buccal or IM injection.

One box should be sufficient stock, if this can be replaced readily by regional pharmacy. Shelf life is four years at 25°C, if protected from light (store in cupboard or drawer). Health centres that do not use it within four years could arrange to exchange their stock with the local hospital emergency or anaesthetics departments so that in-date stock is maintained without extra expense.

### What dose to use?

The doses recommended in this protocol are slightly conservative with respect to those cited in journals. Most journal articles deal with therapy in hospitals or epilepsy centres. The CARPA STM is intended for a remote-area situation, where expertise in managing respiratory depression may be limited. A lower dose will often terminate the fit, is less likely to cause respiratory problems, and can be repeated after discussion with a doctor, if seizures continue or recur.

Drug doses are best calculated for children on the basis of body surface area; the next best measure is body weight, which does not always correlate well with age. However, it is usually difficult to weigh a fitting child and a recent weight may not be known. Therefore, for this protocol, drug doses are presented in both a weight and age table. For the age table, weights are assumed as given in the following table. In many remote communities, a high proportion of children are lighter than children in urban settings.

Age	Approx weight
3 mths to <6 mths	6 kg
6 mths to <1 yr	8 kg
1yr to <2 yrs	10 kg
2 yrs to <3 yrs	12 kg
3 yrs to <4 yrs	14 kg
4 yrs to <5 yrs	16 kg

### **Is there still a place for diazepam?**

'Diazepam is highly lipid soluble, and appears in the brain as quickly as 1 minute after (IV) injection, with a median time to terminate a seizure of two minutes'.<sup>3</sup> Its anti-epileptic effect lasts for 20–30 minutes, and the dose may have to be repeated, or a longer-acting agent (phenytoin or a barbiturate) given for recurrent fitting.

It is not well absorbed after IM injection. It is effective rectally, and guidelines for rectal use have been published by a combined group of organisations with interest in epilepsy. However, its onset of action is slower than via the IV route, and the incidence of respiratory depression may be unacceptably high. Norris et al. reported that diazepam is associated with a 9% incidence of respiratory depression (no doses quoted). 'The use of diazepam as first-line therapy for children with acute seizures needs to be reviewed'.<sup>10</sup>

The impression of working practitioners is that while rectal delivery of diazepam is (barely) acceptable in children, it is not so in adults. Midazolam given either IM, nasally or buccally is likely to be much more socially acceptable to most clients.

Diazepam in oral form should still be retained in the community pharmacy, for sedation of disturbed/psychotic patients.

### **What is the most suitable route of drug administration?**

Intravenous administration undoubtedly gives quickest onset of action and quickest control of seizures, regardless of which anti-convulsive agent is used. An intravenous cannula should be inserted in any fitting patient as soon as possible, but this may be difficult until the fit is controlled.

Intra-osseous needles are becoming increasingly available in remote communities, as are staff who are trained to insert them. These needles may be an equally rapid and more reliable alternative to IV in a fitting infant or child. They should be regarded as an interim emergency measure, and IV access should be obtained as soon as possible.

When using IV or intra-osseous anti-convulsants, it is advisable to dilute the drug and give a larger injected volume, thus overcoming the problem of having to flush the drug in with saline, etc.

Intramuscular injection can be used for midazolam and phenobarbitone. Many remote-area health staff would be comfortable with giving IM injections. Several articles now report success of IM midazolam at least equal to IV diazepam. Five relevant articles are summarised below. Full references are given at the end of this document.

#### **Chamberlain JM et al.**

24 children (age from birth–18 years) presenting to emergency departments with seizures longer than 10 minutes were randomly allocated to receive either IM midazolam 0.2 mg/kg (maximum 7 mg) or IV diazepam 0.3 mg/kg (maximum 10 mg). Both regimens were effective (one treatment failure in each group), but time to stopping seizures was 3.3 +/- 2.0 minutes for IM midazolam versus 7.8 +/- 3.2 minutes for IV diazepam. The reason given was that without the need to obtain IV access, administration was more rapid.

*[Editor: This study was done in hospital emergency departments, where IV expertise may be higher than in a remote-area health centre. The IM route will probably perform even better in the remote setting]*

**Lahat E et al.**

(Abstract only sighted)

Midazolam was given IM in 60 episodes of epilepsy in 48 children (four months to 14 years). In 64 episodes, seizures stopped 1–10 minutes after injection. Its use is suggested 'specifically when attempts to introduce an intravenous line in convulsing children are unsuccessful'.

Nasal midazolam is generally well absorbed. There is some concern that absorption could be decreased by nasal secretions, as in URTI, but this does not seem to happen in most cases in practice.<sup>5</sup> The dose is drawn up into a syringe and any needle discarded. The drug is 'dripped' alternately into both nostrils, or 'injected' over 30 seconds. Midazolam 'burns' when given nasally, but that should not be a problem in a fitting patient.

Buccal (oral) administration of midazolam is probably better; absorption is also good. The dose is drawn up into a syringe, any needle discarded, and the end of the syringe inserted between the cheek and the teeth for injection. The surface for absorption is larger than the nasal surface, and the volume of fluid used should not be a problem in the oral airway. There is a small risk of mucosal damage from the end of the syringe, and therefore blood in the airway; loose teeth could also be knocked out with rough handling. The bitter taste would not be noticed by a convulsing patient.

**Scott RC et al.**

79 episodes of severe epilepsy in 18 young people (5–22 years) in a residential centre were treated with either rectal diazepam (10 mg) from a commercially-prepared pack, or buccal midazolam (10 mg). Some patients received both drugs in different episodes. Midazolam was effective in 75% of episodes (diazepam 59%) in median time six minutes (diazepam eight minutes). However, there was no significant difference between the drugs for efficacy, time to drug administration, from administration to end of seizure, or total seizure length. The buccal route was found to be more acceptable than rectal.

*[Editor: Camfield PR: Journal of Pediatrics 1999; Vol 135: No.3: p 398–9 finds the study 'sufficiently convincing that I will slowly begin to alter my [neurological] practice'.]*

**Jeannet PY et al.**

26 children treated (11 at home and 17 in hospital; two treated in both locations) for total of 125 seizures. 122 seizures (98%) stopped within 10 minutes (average 3.6 minutes). No serious adverse side effects. Parents with experience of rectal diazepam found that nasal midazolam was easier to use and that post-ictal recovery was faster.

**Lahat E et al.**

47 children (six months–five years) with febrile seizure lasting at least 10 minutes in a paediatric emergency department were given either nasal midazolam 0.2 mg/kg or IV diazepam 0.3 mg/kg (maximum dose of each 10 mg). Both drugs are equally effective at controlling seizures, but mean time to starting treatment was significantly shorter with midazolam (3.5 +/- 1.8 minutes) than diazepam (5.5 +/- 2.0 min). Time to cessation of seizures is also two minutes shorter with midazolam (although IV diazepam acts more quickly, it takes longer to obtain IV access and administer drug). No significant side effects in either group.

Rectal administration can be used for diazepam, midazolam or phenytoin. A modified device, such as a butterfly needle with the 'wings' removed, must be used. There is a small risk of rectal perforation. The nasal or buccal routes seem easier than rectal in a fitting patient (especially adult), and more socially acceptable. The rectal route may be abandoned in the future.

Most studies on IM, oral and nasal midazolam involve small numbers of patients and are not statistically strong (insufficient power due to low numbers of patients, difficulties with randomisation in an emergency situation, etc.). Larger trials are needed before the evidence basis for change is statistically strong. [Editor: Or perhaps a meta analysis.] However, clinicians and departments are starting to alter their practice and protocols, and this would seem to be sufficient

reason for recommending a CARPA protocol that is simpler to administer, equally effective, and possibly safer than the former edition.

### **When are other drugs needed?**

Phenytoin (Dilantin) is the drug of choice for patients who fit after a head injury. Phenytoin can be given IV, but must be given slowly (with ECG monitoring) to prevent cardiac arrhythmias. It should probably be given only on the advice of a doctor, with careful specific instructions. It is therefore not included in the flow chart. Phenytoin is about 50% effective in stopping seizures when used on its own. The propylene glycol solvent can cause fitting and other side effects in very young children.

Fosphenytoin (a phenytoin prodrug) is well absorbed after IM injection and is less irritant if extravasation occurs via the IV route.

Some paediatricians prefer phenobarbitone as a first-line anti-convulsant in neonates and young babies. Recommending phenobarbitone would introduce another drug to the community pharmacy, which has a lower safety margin than midazolam in relatively inexperienced hands.

### **Evans D, Levene M**

Detection and treatment of the underlying cause of the seizure is most important. The authors' practice is to give anticonvulsants if there are three seizures per hour or more, or if any one seizure lasts for three minutes or more. First-line treatment in their hospital is still phenobarbitone. Second-line drug is clonazepam but 'other benzodiazepines are also popular . . . Diazepam has an extremely short duration of action with a risk of sudden respiratory depression and its use should be avoided'. IV lignocaine may be effective.

Refractory status epilepticus may need large doses of barbiturates or propofol for control. This will cause profound respiratory depression, needing endotracheal intubation and ventilatory support, and so is generally unsuitable for community use.

### **The current protocol**

The major change to this edition of the manual advocates nasal or buccal midazolam as the first-line treatment for a fitting patient. The rationale for this is as follows:

1. Evidence from the literature that these routes are safe, effective and as quick or even quicker in controlling fits than intravenous or intramuscular administration.
2. Increasing experience in a number of centres in Australia of these routes of administration, which supports the literature.
3. The experience of the program in Adelaide where parents, other carers and teachers are effectively and safely using nasal midazolam in out of hospital settings.

Paediatricians and adult physicians at both Royal Darwin and Alice Springs hospitals have reviewed the protocol and consider it appropriate for use. Advice has also been received from consultant neurologists, Prof Sam Berkovic and Dr Michael Harbord, who have considerable experience with these uses of midazolam in both in and out of hospital settings.

Intramuscular or intravenous administration can still be used if practitioners feel more confident with those routes and dosage recommendations are provided.

Diazepam is no longer recommended. There appears to be no advantage to the use of diazepam and several in favour of midazolam.

It is recommended for known epileptics, particularly children, that a test dose of midazolam be

given in a controlled setting to establish the safety of the dose. Ideally, this would be done in a hospital ward or outpatients but it could also be done in a community clinic with a doctor present and the facilities to support respiration. The appropriate dose can then be written into a management plan for the individual.

The dosages recommended in the table of doses according to age are based on a 0.2 mg/kg dose for nasal or buccal administration, a 0.1 mg/kg for the intramuscular route and a rather low estimate of the weight of a child in that range. This relatively lower dose was chosen to minimise the risk of overdose. In addition, according to practitioners experienced in the use of nasal or buccal midazolam, a relatively lower initial dose often suffices to control a fit, and if it does not a small extra dose can be given.

### **Individual management plans**

People with known epilepsy should have an individual management plan documented in their casenotes. This should include details of how long to wait before initiating drug therapy, specific doses to give, whether to always consult a doctor or not and instructions for follow-up observations.

### **When should fits be investigated?**

There is no body of evidence indicating a clear direction as to whether and when fits should be investigated. Specialist opinion varies somewhat and may change. As a result of discussion with specialists at Royal Darwin and Alice Springs hospitals, the following is recommended:

- Anyone who has had a fit for the first time should be sent to hospital for investigation
- Always talk to a doctor immediately
- The doctor should talk with the specialist on-call at the regional hospital about how soon the patient should go in.

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