

# Impact of a protocol using intranasal midazolam for managing seizures

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**M**idazolam was first used in 1982 (O'Regan, Brown & Clarke, 1996). Unlike rectal diazepam (RD), which has a number of disadvantages including the need for privacy, intranasal midazolam (INM) can be easily administered in the community. Scheepers, Scheepers & Clough (1998) also claimed that fear of RD administration has been cited as a reason for truancy among older children with epilepsy. Additionally, they pointed out that the long half life of 20-40 hours may result in drowsiness which in itself may paradoxically lower the seizure threshold, leaving the patient more susceptible to further seizures.

Nasal administration of midazolam results in rapid absorption from an area rich in blood supply, cerebrospinal fluid concentrations peaking 5-12 minutes after administration. INM does not have the disadvantage of being processed through the liver, unlike buccal administration, and has a mean elimination half life of two hours in healthy subjects.

## Statistics of status epilepticus (SE)

Aicardi (1994) demonstrated that the outcome of SE was worse in children (especially those less than 3 years of age), with neurologic sequelae in 20%, and death in 3-7%, a claim supported by Wilson, McLeod & O'Regan (2004). Soon after an episode of SE, magnetic resonance imaging studies demonstrated regions of focal cerebral oedema which resolved, but later changes of cerebral atrophy appeared in those regions (Meierkord, Wiesmann, Niehaus, &

Lehman, 1997). Young (1996) noted seizure duration to be the single major predictor of mortality, with a 10% mortality rate if SE was controlled within 10 hours, but rising to 85% mortality rate if SE persisted for more than 20 hours.

## Timing of administration of emergency anticonvulsants

Although it is now generally accepted that prolonged seizures can cause neuronal injury, there is considerable uncertainty regarding the duration and intensity of seizures required before injury occurs (Alldridge & Lowenstein, 1999), largely due to an extremely limited ability to validate in humans the findings of experimental models. Lowenstein & Alldredge (1993, 1998) showed that treatment of SE within 30 minutes of onset was associated with an 80% response rate to first line anti-epileptic drugs (AEDs), but only 40% if the seizure had persisted for longer than 2 hours. Walker (2003); Gilbert, Gartside & Glauser (1999); Hirsch & Claassen (2002); and Livingston (2004) all claimed treatment in the premonitory stages of a seizure is more likely to be successful than treatment in the later stages, with Hirsch & Claassen (2002), and Livingston (2004) advocating treatment by caregivers at home to allow extremely fast treatment, prevent SE, and reduce the need for emergency room visits. Hirsch & Claassen (2002) were of the opinion that failure to treat aggressively in the early stages increased the likelihood of refractory SE (RSE), which Gilbert, Gartside, & Glauser (1999) demonstrated in a meta-



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analysis to have a mortality rate of 16%. This is an important recommendation, considering approximately 5% of adults and 10-25% of children with epilepsy will have at least one episode of SE (Shorvon, 2001), and 13% of all patients with SE will have a further episode of SE (Fountain, 2000).

## Studies involving pre-hospital treatment of SE

Alldredge, Wall & Ferriero (1995) in a prospective study reported that pre-hospital treatment of SE not only reduced the seizure duration, but also reduced the incidence of respiratory complications. Holsti, Sill, & Firth et al, (2004) compared 25 paediatric patients administered either INM or RD by emergency services before being transported to a paediatric emergency service in Salt Lake County. The first 17 children were administered RD, with a subsequent 8 administered INM. Children given INM had less need for bag-valve-mask ventilation (0% versus 31%), or endotracheal intubation (0% versus 33%), were less likely to have further seizures prehospital (0% versus 22%), or in the emergency department (60% versus 78%), and less likely to require hospitalisation (40% versus 88.8%). A study by ambulance paramedics in New South Wales (Rainbow, Browne, & Lam, 2002)

found respiratory depression to be significantly less frequent with IV or IM midazolam than with IV or rectal diazepam.

### Studies involving the use of INM for SE

O'Regan et al (1996) dripped midazolam into the nasal passages of 19 children, with 79% improvement in the EEG pattern of 15 within 2-5 minutes, and cessation of fits in another 3 (statistically significant  $p < 0.01$ ). One child had brief self-corrected desaturation to 87%, another a paradoxical reaction, but there were no episodes of apnoea or slowing of the pulse rate.

Jeannet, Roulet, & Maeder-Ingvar et al (1999) reported INM administration to treat acute seizures in home and hospital, with response within 10 minutes, and no adverse side effects. McGlone and Smith (2001) administered 0.5 mg/kg INM to two children in whom they were unable to obtain IV access, with no adverse effects ( a higher dose than the 0.2-0.3 mg/kg we used). Conroy, Morton & Dixon et al (2000) reported all 5 children with seizure duration less than 10 minutes responded to INM, compared with only 3 of 13 children with seizure duration over 30 minutes.

Wilton, Leight, Rosen & Pandit (1988) administered INM for pre-anaesthetic management of 45 preschool aged children, and Latson, Cheatham, & Gumbiner et al (1991) sedated 15 children for echocardiography with no adverse effects. Jeannet et al (1999), Lahat et al (2000), McGlone and Smith (2001), and Holsti et al (2004) also reported no adverse effects from the administration of INM. Fisgin, Gurer, & Tezic (2002) demonstrated that for a seizure of more than 5 minutes, response to INM was 87%, compared with 60% for RD.

Based on the statement from the Epilepsy Foundation of America Working Group on SE (1993) which stated that practically speaking, any person who exhibits persistent seizure activity or who does not regain consciousness for 5 minutes or more after a witnessed seizure should be considered to have SE, the fact that many of the students we were supporting

already had a history of SE, and in consultation with the ambulance service, we specified administering a rapidly acting anticonvulsant for a seizure lasting 3 minutes. An alternative to commencing treatment is waiting for an ambulance or medical attention, but in times of high demand the delay before treatment might be longer than the desired 30 minutes. It was important to train all staff to the same standard time frame to avoid confusion, but at the same time orders could be individually varied in writing by the specialist on clinical grounds.

### RD and INM

Scheepers, Scheepers & Clough (1998) reported significant benefit for a 25 year old female with learning difficulties. Within two weeks of substituting INM for RD, her prolonged seizures reduced, she was alert, bright, no longer requiring a wheelchair, and even managing to play football. Wilson, MacLeod, & O'Regan (2004) contacted 40 parents whose children had been given nasal or buccal midazolam at home for prolonged seizures, with 83% control of seizures. Twenty four parents had also used RD, with 20 (83%) preferring to use midazolam in the future.

### Training for the administration of INM

Following overseas reports of the successful use of midazolam for managing prolonged seizures, an interagency working party convened by the Department of Education and Children's Services (a South Australian Government Agency) developed a protocol incorporating the use of INM (education staff were prepared to give INM but not buccal midazolam). Although the initial training program was developed for use in educational settings, the program is also being instituted in child care and adult settings.

The development of the protocol involved 4 stages:

#### 1. Seizure management training package

A one hour training on seizure management presented by first aid agencies, allowing for whole of school or group participation. Information is

then given about midazolam, precautions for using it (test dose, plastic ampoule), effects and side effects, management of a seizure using INM, and a reminder to keep the empty ampoule to show the ambulance officers (in South Australian educational settings an ambulance is to be called if INM is administered).

A 7 minute video is then shown, illustrating both the main types of seizures, and the administration of INM.

#### 2. Precautions and doses for INM used for prolonged seizures.

To minimise risk of an adverse reaction to INM, parents and carers do not give it in the community until the person has had midazolam by any route without adverse effects. If midazolam has not previously been given, a test dose is given as an out-patient under observation in hospital, not necessarily when the person is seizing. Only the 5 mg in one ml plastic ampoule is used, as the drops can be administered directly from the inverted ampoule, without requiring a syringe or drawing up, and the person only carries a single labelled dose in the community.

The INM doses are based on 0.2-0.3 mg/kg but rounded to use complete ampoules where possible. Table 1 shows the recommended doses based on weight, and the approximate age ranges these apply to. We have not yet trialled INM in children less than one year old in the community.

**Table 1. Recommended doses of INM**

Weight	Approximate age range	Dose
Up to 16kg or 35lbs	1-4 years of age	2.5 mg (half ampoule of 5 mg in 1 ml)
16-32kg or 35-70lbs	4-10 years of age	One ampoule of 5 mg in 1 ml
Over 32kg or 70lbs	Over 10 years of age	Two ampoules of 5 mg in 1 ml generally

Some people over 32 kg respond to the one ampoule (particularly people with autism). Where the 2.5 mg dose is ordered, with each ampoule generally containing 16 drops, we recommend dropping out 8 drops first into a tissue, then giving the remaining 8 drops to avoid the risk of overdosage. Even if 9 drops are accidentally dropped out, this should still be adequate to control or at least reduce the severity of the seizure.

### 3. Additional training for those volunteering to administer INM

Staff are required to have first aid training including resuscitation. After completing the training outlined above, they practice squeezing drops of water from the ampoule, to reduce the anxiety of not knowing what it will be like controlling the ampoule when giving INM to a person having a seizure. Volunteers are then familiarised with forms and information in the Yellow Folder which travels with the child (in South Australia we are using yellow folders to distinguish them from health care plans which are generally in blue or black folders).

### 4. A yellow folder containing information specific to the person ordered INM

The Yellow Folder contains the INM order signed by specialist and parent specifying dose, length of seizure after which INM is to be given, and when an ambulance is to be called (generally INM is given at 3 minutes in children and 5 minutes in adults, at the same time as an ambulance is called in educational settings). Parents and carers in the community still use INM at the specified time, but only call an ambulance if they are concerned about the severity or length of a seizure. The folder also contains forms identifying location of the midazolam in that setting; record of administration by all who give it including parents so they have a complete record to show the specialist; seizure care plan; a first aid flow chart for seizures indicating midazolam has been ordered; and a seizure observation log using numbers to describe features of the seizure.

### Participants

Following Research Committee approvals, questionnaires were distributed to parents of children prescribed INM to manage prolonged seizures, also to education and support staff trained to administer INM to those children. Parents of younger children attending a neurologist privately were also offered the questionnaire. Eighty adult residents in a large institution were also identified as having been administered INM for a prolonged seizure.

### Results

There were 65 children administered between one and ten doses of INM, and 80 adults given between 1 and 20 doses for prolonged seizures. Seizures were controlled in 138 of the 145 persons (95.3%), increasing to 140 (96.5%) when a higher dose based on weight was administered. There were no instances of respiratory arrest, and only one report of apparent shallow breathing. Some people complained of discomfort or a burning sensation in the nasal passages, but only when they were awake for the test dose.

### Problems encountered

One mother previously used INM successfully, but after an episode in which her son snorted back the INM she decided to return to using RD.

Difficulty getting midazolam from the plastic ampoule into a syringe was overcome by instructions to drip directly into the nose from the ampoule. To prevent others having the same difficulty, a pamphlet with pictures is enclosed with each new pack of INM from the hospital pharmacy.

Slowing of respiration when given for a seizure due to an upper respiratory infection. After a repeat test dose requested by the mother had no adverse effects, the mother happily resumed using INM.

Parents have reported that community pharmacists have provided glass ampoules even when plastic has been clearly specified on the prescription, or simply stated inability to obtain the plastic ampoules. To prevent ongoing difficulties, manufacturers have proposed listing the plastic ampoules in pharmaceutical catalogues.

### Preferences for RD versus INM

331 questionnaires were completed by parents, and carers and education staff. Education staff do not give RD, and most carers had only recently been trained to give INM, so the responses analysed are only those from parents. Fifty-five parents had given RD, 65 had given INM, and 52 had administered both. Table 2 illustrates the preferences of the 52 parents who had administered both INM and RD, with 73% preferring INM, and a further 10% happy to use either. Only two preferred to wait for an

ambulance rather than administer any medication.

**Table 2. Parent preferences**

Preferred option	No. of respondents n=52	% of respondents
Preferred to wait for an ambulance	2	4%
No preference for either	5	10%
Preferred RD	7	13%
Preferred INM	38	73%

Parents stated intranasal midazolam was less intrusive, gave greater privacy, was easier to administer even with a person in a wheelchair, and was faster in onset of response and for the effects to wear off after resolution of the seizure.

Comments from parents included:

- From the mother of a 5 year old boy: *He had a seizure in the shopping centre. The INM controlled his seizure, so I waited until he was starting to wake up then got a taxi home. His seizure wouldn't have settled as quickly with RD so I would have had to call an ambulance, and wheelchairs don't fit in ambulances.*
- From the father of a 33 year old female: *For 20 years of using RD, my daughter's seizures didn't respond fast enough, so we had to call an ambulance (up to 18 times in one year), with transfer to hospital. In the past 3 years we have used INM, with the seizure settling within about 2 minutes, so we haven't needed an ambulance or hospital. We can now confidently fly interstate to visit relatives rather than endure a long drive.*

### Perceived time of response with INM and RD

Parents were also asked their perceptions of how long INM and RD took to control the seizure. Of note is the perception that over 2/3 of seizures responded to INM within 5 minutes of administration, compared with less than 1/3 of those given RD. Almost half of those given RD took over 10 minutes to respond, compared with none of those given INM (Table 3).



**Table 3. Parent perception of time for RD and INM to take effect**

Perception of time to take effect n=52	Rectal diazepam	Intranasal midazolam
Effect within 2 mins	7.6%	38.5%
Effect within 5 mins	25%	34.6%
Effect within 10 mins	19.2%	26.9%
Effect over 10 mins	48%	0

## Discussion

The rate of control of seizures using INM in our study is higher than in other reported studies. However, bearing in mind the number of researchers and clinicians who have advocated early treatment for prolonged seizures, the success of our study might be due to the early instigation of treatment with INM.

It is difficult to compare the various studies, as duration of seizure is variably quoted from the time of arrival at the hospital, or time from the administration of the AED. Critics could quite rightly claim that we might be administering an AED for a seizure that would have settled spontaneously. The risk of administering INM for a seizure that might still resolve spontaneously has to be balanced against the risk of waiting to see if the seizure settles, by which time the first AED alone may not be effective in controlling the seizure. Failure to respond to the first AED renders the patient liable to require another one, if not two, AEDs, with possible hospitalisation, and even intensive care.

Midazolam is a powerful drug which needs to be used carefully according to the protocols, but used correctly is very effective in controlling prolonged seizures. Some oppose parents and carers having access to this drug in the community, because of the potential to be used for illegal purposes. A person ordered INM only carries a single dose, and midazolam is only available on prescription, which limits availability, and reduces the potential for abuse. Scott was of the opinion that stinging in the nose when awake signified damage to the nasal mucosa, yet none of the 145 people given INM, many on multiple occasions, have reported any increase in nasal symptoms.

## Conclusion

Intranasal midazolam is a practical and acceptable anticonvulsant for managing prolonged seizures in both children and adults, with parents, carers and

educational staff feeling comfortable about administering it in the community. INM gives parents and carers a sense of both control and freedom if our protocol is carefully adhered to, and reduces the risk of SE, but adequate training is imperative.

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