J. Paediatr. Child Health (2004) **40**, 556–558

Use of intranasal midazolam to treat acute seizures in paediatric community settings

MG Harbord,[1] NE Kyrkou,[2] MR Kyrkou,[3] D Kay,[4] and KP Coulthard[5]

Departments of [1]Paediatrics and Child Health, Flinders Medical Centre, [2]School of Disability Studies, Flinders University, Bedford Park, [3]Child and Youth Health, [4]Education and Children's Services, Adelaide and [5]Pharmacy Department, Women's and Children's Hospital, North Adelaide, South Australia, Australia

Objectives: To evaluate the acceptability of intranasal midazolam (INM) in acute seizure management in the community.
Methods: Parents and staff in residential and educational settings were trained in first aid and seizure management and the administration of INM. Feedback was obtained from those who had given INM over the 30-month period September 2000–March 2003.
Results: Intranasal midazolam was administered to 22 children for a total of 54 seizures (range 1–6 seizures each). The dose was 0.2–0.3 mg/kg rounded down to 1 or 2 of the 5 mg in 1-mL plastic ampoules, with the anticonvulsant instilled into the child's nose directly from the plastic ampoule. Seizures were effectively stopped on 48 occasions, i.e. 89%, while no respiratory arrests occurred. Thirty carers had given INM to a convulsing child and 27 (90%) reported no difficulty in administering it. Fifteen people had also previously administered rectal diazepam and INM was considered easier to administer than rectal diazepam by 13 while a preference to use INM rather than rectal diazepam was indicated by 14.
Conclusion: This study has shown that INM is an acceptable treatment option as a first aid response for acute seizures. We believe that INM should be considered as the preferred alternative in the community setting, as it is easier to administer and is more dignified for the patient than rectal diazepam.

Key words: children; community; midazolam; seizure.

Tonic clonic status epilepticus is a medical emergency that is defined as prolonged or recurrent seizure activity persisting for 30 min or more.[1] It occurs in 5% of adults and 10–25% of children with epilepsy.[1]

The mortality rate of this condition in childhood is 3–6% while permanent neurologic sequelae, i.e. neurologic deficits or intellectual disability occurs in up to 30%, with the highest risk occurring in younger children.[2] Brain imaging studies with MRI have demonstrated regions of focal cerebral oedema occurring soon after an episode of status epilepticus.[3] Although the oedema resolved, changes of atrophy and gliosis subsequently appeared in the same regions.

Urgent treatment is required for status epilepticus as neurologic complications are directly related to the duration of the seizure.[1] In addition the sooner that treatment is commenced, the more likely it is that it will be effective. Lowenstein[4] showed that treatment of prolonged seizures within 30 min of onset was associated with an 80% response rate to first line anticonvulsants, compared with less than a 40% response rate if the seizure had persisted for more than 2 h.

Since most generalized tonic clonic seizures usually last less than a few minutes, Holmes[5] and Lowenstein[6] have proposed an operational definition of status epilepticus as continuous seizures lasting more than 5 min, or two or more discrete seizures not separated by complete recovery of consciousness.

It therefore seems desirable that once a seizure has continued for more than 5 min, then treatment should be commenced with a quick acting anticonvulsant.

In the community setting the current options for acute seizure management are limited to waiting for an ambulance to arrive or giving rectal diazepam. Rectal diazepam has been used for the prehospital acute treatment of seizures for over 20 years.[7] It is usually effective, but concerns have been raised about the physical difficulty of administering rectal medication to a convulsing patient, as well as the ethical considerations in regard to maintaining privacy and the potential for allegations of sexual abuse.[5]

Interest has recently been raised in using intranasal midazolam (INM), which has an equally rapid onset of activity compared with rectal diazepam, but is easier and more socially acceptable to administer.[8] Midazolam is now available in a plastic ampoule at a strength of 5 mg in 1 mL, which enables nasal instillation of the midazolam directly from the ampoule.

OBJECTIVES

The aims of this study were to evaluate the acceptance of INM for acute seizure management in the community when given by parents, carers, teachers and first aiders.

METHODS

Consecutive children with epilepsy from the first author's epilepsy clinic at Flinders Medical Centre, Adelaide, South Australia (SA) and his private practice were approached for involvement in the study between September 2000 and March 2003. The inclusion criteria were an age between 4 and 18 years and at least one primary or secondarily generalized tonic clonic seizure lasting two or more minutes. Parents were informed about the availability of INM and those who elected

Correspondence: Dr M Harbord, Department of Paediatrics and Child Health, Flinders Medical Centre, Bedford Park, SA 5042, Australia. Fax: +61 8 8204 3945; email: michael.harbord@flinders.edu.au
Accepted for publication 7 April 2004.

to be trained were enrolled in the study. The child's teacher and care worker were also invited to be trained as well, with parental permission. The study was approved by the Ethics Committee of the South Australian Department of Education and Children's Services, while parents of all children gave informed consent.

A standardized management procedure was developed for directly giving INM using the 5 mg in 1-mL plastic ampoule, i.e. without the need for drawing the dose up into a syringe first. Although various intranasal administration devices are available, we opted to use the plastic ampoules on the grounds of cost and stability of the drug in the ampoule. Preparations were made to give INM if a generalized tonic clonic seizure had lasted more than 3 min, which is similar to the method used in a recent comparative trial of buccal midazolam and rectal diazepam by Scott.[9] The children were moved onto their backs for instillation of the midazolam, with 1–3 drops squeezed gently from the ampoule into each nostril until the ampoule was empty, i.e. 15–16 drops in all. This took 30–60 s and they were immediately rolled onto their sides into the recovery position once the dose had been given.

The prescribed dose was 0.2 mg – 0.3 mg/kg, which was rounded down to one or two of the 5 mg ampoules. In general children aged 4–10 years had one ampoule and those older than 10 had two ampoules. All children had been given an interictal test dose of INM in a hospital outpatient clinic prior to its use in the community, to ensure that there were no side-effects of respiratory depression with the dose prescribed. Feedback about the use of INM was then obtained by a questionnaire, coupled with direct interviews of parents and carers in the outpatients clinic.

RESULTS

No family refused to be involved in the study. Over the 30-month study period training was given to 43 parents, 41 teachers and 30 care workers. INM was administered to 22 children for 54 Seizures (range 1–6) at home or school. The clinical and demographic information about the children and their epilepsy is listed in Table 1. Seizures were effectively stopped in 48 episodes (89%) meaning that further administration of an anticonvulsant by an ambulance officer or in hospital was not required.

In two of four children whose seizures did not respond to INM a successful response did occur on subsequent occasions when the dose was increased to 0.3 mg/kg with two rather than one of the 5 mg ampoules used. Although shallow breathing was reported in one case, no respiratory arrests occurred.

Questionnaires were completed by all those who had given INM, i.e. 30 parents, school assistants and teachers. Twenty-seven (90%) reported no difficulty in administering the medication.

Fifteen people also had experience administering INM and rectal diazepam (either as a suppository or rectal solution) with 13 considering INM easier to administer than rectal diazepam. A preference to use INM instead of rectal diazepam was reported by 14.

Once they had been trained to give INM, 80% of people preferred to use it rather than wait for an ambulance, with 100% of parents, 79% of teachers and 58% of school assistants expressing this intention. The most frequent comments about the use of INM were that it was less intrusive, gave greater privacy and was more suitable for use in the community compared with rectal diazepam.

Table 1 Clinical and demographic features of 22 children administered intranasal midazolam

Age range	4–18 years
Males	10 (45%)
Intellectual disability	20 (91%)
Aetiology of epilepsy syndrome	
Symptomatic	13
Idiopathic	9

DISCUSSION

This study has shown that INM is an acceptable anticonvulsant for acute seizure treatment in the community setting. The technique for administering INM was considered to be easier than for rectal diazepam and less intrusive. It was also perceived that INM was more effective than rectal diazepam, although this was not objectively evaluated in the study.

There is a steadily growing volume of literature on the use of INM to treat seizures. Lahat[10] compared the safety and efficiency of INM with IV diazepam in children presenting to the emergency department with prolonged febrile seizures, which had lasted at least 10 min. Both INM and IV diazepam were equally effective, but the authors noted that the mean time to control the seizures was shorter in the midazolam group, as there was no delay in having to obtain intravenous access before administering the drug.

Kutlu[11] and Fisgin[12] found that INM at a dose of 0.2–0.3 mg/kg effectively stopped seizures in over 80% of children within 5–8 min. In a later study Fisgin[13] reported that the response rate to INM for seizures lasting more than 5 min was 87%, compared with 60% for rectal diazepam. Conroy[14] found that only three of 13 children whose seizure had lasted more than 30 min responded to INM 0.2 mg/kg compared with five of five children whose seizure duration was 10 min or less.

Jeannet[8] reported the use of INM in 26 children who had acute seizures, either when in hospital (17 children) or at home (11 children). The dose was 0.2 mg/kg and the midazolam had been drawn up beforehand in a 1-mL syringe. All the seizures treated at home responded within 10 min and no serious adverse side-effects occurred, with two children being administered the INM on over 25 occasions. Parents of nine children had previously used rectal diazepam at home, and for seven of these children their parents considered that INM was easier to use and that their children had recovered more rapidly.

Wilson[15] reported a telephone survey of 40 parents whose children had been administered nasal or buccal midazolam at home for prolonged seizures. Midazolam was considered effective for 33 children (83%). Rectal diazepam had previously been used for seizures in 24 children and parents expressed a preference for using midazolam in 20 of these. Reasons for preferring midazolam included that it was more dignified and socially appropriate, it was easier to administer in wheelchair users and a response occurred more quickly than with rectal diazepam.

Some anticipated problems with INM did not eventuate. No difficulties were encountered with airway obstruction during the brief period of 30–60 s during which the children were on their back for INM administration.

Training emphasized that the children must be turned onto their side into the recovery position once the dose has been given. INM was well absorbed despite some children having a runny nose. Occasionally nasal irritation was reported when the trial dose was given in the waking state, but this was not a

problem in clinical use as the children were unconscious during the generalized seizures.

Midazolam appears to be better tolerated than diazepam.[16] A recent comparative study of IV or IM midazolam with IV or rectal diazepam by ambulance paramedics in New South Wales found that respiratory depression was significantly less frequent with midazolam.[17] No episodes of apnoea occurred secondary to INM administration in the current study but the authors consider that it is desirable to give a test dose of INM in the hospital or clinic prior to its use in the community.

Carers and parents frequently commented that INM was easier to administer and was more dignified for the child, particularly for adolescents. This issue has previously been raised in the 1995 Australian Position Statement on Rectal Diazepam[18] in which it was recognized that the physical difficulty of rectal diazepam administration and issues of privacy, dignity and consent limited enthusiasm for its use in adolescents and adults.

Once they had been trained to give INM, parents and caregivers showed a willingness to treat seizures rather than just wait for an ambulance to arrive. This study has shown that INM is an acceptable treatment option as a first aid response for acute seizures. We believe that INM should be considered as the preferred alternative to rectal diazepam in the community setting.

ACKNOWLEDGEMENT

The authors thank Ms Kylie Bailey for assistance in collecting data.

REFERENCES

1 Shorvon S. Tonic clonic status epilepticus. *J. Neurol. Neurosurg. Psych.* 1993; **56**: 125–34.
2 Pellock JM. Status epilepticus in children: update and review. *J. Child Neurol.* 1994; **9** (Suppl.): S527–S535.
3 Meierkord H, Wieshmann U, Niehaus L, Lehmann R. Structural consequences of status epilepticus demonstrated with serial magnetic resonance imaging. *Acta Neurol. Scand.* 1997; **96**: 127–32.
4 Lowenstein DH, Alldredge BK. Status epilepticus at an urban public hospital in the 1980s. *Neurology* 1993; **43**: 483–8.
5 Holmes GL. Buccal route for benzodiazepines in treatment of seizures? *Lancet* 1999; **353**: 608.
6 Lowenstein DH, Alldredge BK. Status Epilepticus. *NEJM* 1998; **338**: 970–6.
7 Knudsen FV. Plasma diazepam in infants after rectal administration in solution and by suppository. *Acta Paediatr. Scand.* 1977; **66**: 563–76.
8 Jeannet P, Roulet E, Maeder-Ingvar M, Gehri M, Jutzi A, Deanna T. Home and hospital treatment of acute seizures in children with nasal midazolam. *Eur. J. Paediatr. Neurol.* 1999; **3**: 73–7.
9 Scott RC, Besag FMC, Neville BGR. Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomised trial. *Lancet* 1999; **353**: 623–6.
10 Lahat E, Goldman M, Barr J, Bistritzer T, Berkovitch M. Comparison of intra nasal midazolam with intravenous diazepam for treating febrile seizures in children: prospective randomised study. *BMJ* 2000; **321**: 83–6.
11 Kutlu NO, Yakinci C, Dogrul M, Durmaz Y. Intranasal midazolam for prolonged convulsive seizures. *Brain Dev.* 2000; **22**: 359–61.
12 Fisgin T, Gurer Y, Senbil N *et al.* Nasal midazolam effects on childhood acute seizures. *J. Child Neurol.* 2000; **15**: 833–5.
13 Fisgin T, Gurer Y, Tezic T *et al.* Effects of intranasal midazolam and rectal diazepam on acute convulsions in children: prospective randomised study. *J. Child Neurol.* 2002; **17**: 123–6.
14 Conroy S, Morton R, Dixon H, Porter A, Choonara I. A prospective study of intranasal Midazolam for children with acute seizures. *Paediatr. Perinat. Drug Ther.* 2000; **4**: 52–7.
15 Wilson MT, MacLeod S, O'Regan ME. Nasal/buccal midazolam use in the community. *Arch. Dis. Child* 2004; **89**: 50–1.
16 Koren G. Intranasal midazolam for febrile seizures. *BMJ* 2000; **321**: 64–5.
17 Rainbow J, Browne GJ, Lam LT. Controlling seizures in the pre-hospital setting: diazepam or midazolam? *J. Paediatr. Child Health* 2002; **38**: 582–6.
18 Somerville ER, Antony JH. Position statement on the use of rectal diazepam in epilepsy. *Med. J. Aust.* 1995; **163**: 268–9.