

A Prospective Study of Intranasal Midazolam for Children with Acute Seizures

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Abstract

Objective: *To evaluate the use and safety of intranasal midazolam when used as first-line treatment for children with acute seizures.*

Study design: *Prospective study of 20 children over the age of six months presenting with an acute seizure to the emergency department of a 70-bed children's hospital in the UK. All children were treated with intranasal midazolam in a dose of 200 micrograms/kg. Efficacy and toxicity were assessed.*

Results: *Midazolam controlled the seizure within 15 minutes in 10 patients (50%). A further five patients (25%) showed a partial response. Five children showed no response to midazolam. No adverse reactions were seen.*

Conclusion: *This efficacy rate is lower than that shown in other studies. All studies to date have been small. It is suggested that larger, controlled studies are required to establish the place of midazolam, and alternative routes of administration, such as the intranasal route, in the treatment of children with acute seizures.*

Key words: Midazolam – Seizure – Nasal route

Introduction

The treatment of acute seizures constitutes a medical emergency until spontaneous resolution or control by pharmacological means¹. The ideal drug for treating acute seizures should act rapidly, have a sustained duration of action, be safe, simple to administer, and acceptable to the patient and their carers. Rectal diazepam has been first-line therapy recommended for children presenting with acute seizures². Although diazepam is quick acting, recent

doubts over its safety have been expressed³. It can be both difficult and embarrassing to administer, and unacceptable to many patients and their carers.

Midazolam is effective as an anticonvulsant when given by the intramuscular and intravenous routes of administration. The intramuscular route is painful and is not recommended for children¹. The intravenous route of access can be difficult to obtain in a convulsing child even when in hospital, and becomes a much greater problem if the child

is convulsing outside the hospital setting. Midazolam given intranasally has been shown to produce dramatic improvements in the EEG and cessation of attacks in children with intractable seizures⁴. Rapid absorption of midazolam administered by the intranasal route has been demonstrated. A sedative plasma concentration is achieved 2.5 minutes after administration and is sustained for an hour⁵, and at lower doses when compared with the rectal and oral routes⁶. When compared with rectal diazepam, the intranasal route is a more acceptable and accessible route of administration, making treatment of the convulsing patient easier and less distressing for all involved, whether therapy is needed in the hospital or the community setting.

This study was designed to evaluate the use of midazolam by the intranasal route in children with acute seizures presenting to the emergency department.

Method

All children over the age of 6 months presenting with a seizure to the emergency department of the Derbyshire Children's Hospital were entered into the study. Data were collected for a period of 12 months. Children were included in the study even if they had received rectal anticonvulsant medication at home or during transportation to hospital. On arrival in hospital, intranasal midazolam was used as first-line therapy. The doses used are shown in Table 1. This was based on a desired dose of 200 micrograms/kg. This dose had been demonstrated to be safe and effective in the treatment of acute seizures in children in several studies^{4,7,8}. The required dose was drawn from an ampoule of the injectable form of the drug using a filter needle. The needle was removed and the solution dripped slowly (over about a minute) into the nostrils (approximately half the dose into each nostril) from the syringe. It was recommended that the child's head be maintained in a neutral position during administration to facilitate absorption. This, however, was not practical in all convulsing children; restraint was not used.

Table 1. Patients' ages and doses of intranasal midazolam prescribed

Age of patient	Dose of intranasal midazolam (10 mg/2 ml)
6–12 months	2 mg (0.4 ml)
1–2 years	2.5 mg (0.5 ml)
3–4 years	3 mg (0.6 ml)
5–7 years	4 mg (0.8 ml)
8–11 years	5 mg (1 ml)
12 years and over	10 mg (2 ml)

Children who failed to respond to intranasal midazolam after 5 minutes were given rectal diazepam. Any further treatment required was prescribed according to the emergency department policy, rectal paraldehyde being the next line followed by intravenous diazepam, if necessary.

Temperature, pulse, respiratory rate, oxygen saturation and blood glucose (measured by reagent sticks and meter) were recorded on arrival at the emergency department. Pulse, respiratory rate and oxygen saturation were also measured one minute after midazolam administration, and every five minutes for 15 minutes thereafter. Other details noted were whether the child had had a seizure in the past, known medical conditions, regular drug therapy and preliminary diagnosis. The time of administration of the medication, commencement and termination of the seizure were recorded.

Efficacy and toxicity were assessed by:

- The time taken for the convulsion to stop after administration of the drug. This was sub-divided as follows:
 - Complete recovery within five minutes.
 - Partial recovery – either:
 - Seizure settling but still ongoing at five minutes, or
 - Seizure stopped within five minutes but recommenced within one hour.
 - No recovery.
- Whether rectal diazepam was required.
- The total number of seizures occurring in the first 24 hours of admission.
- The development of respiratory depression – this was defined as poor respiratory effort, reduced respiratory rate, the requirement of intubation during the seizure, or a fall in oxygen saturation requiring oxygen by facemask in the post-ictal phase. (All patients were given high-flow facial oxygen while actually convulsing.)

Ethical permission for the study was obtained from the local Ethics Committee. Informed consent was *not* obtained from carers of patients as it was agreed that this was impractical in an acute situation.

Results

Patients

Twenty consecutive patients were entered into the study; details of these patients are shown in Table 2. The median age was 2 years 6 months (range 10 months to 11 years 9 months). Eleven patients had febrile convulsions; the remaining nine were known to have had epilepsy with or without associated disorders such as autism, cerebral palsy and developmental delay. The actual dose of midazolam

Table 2. Patient details						
Patient number (response)	Patient's age	Length of time patient was convulsing prior to midazolam (min)	Time for seizure to stop (min) after midazolam	Rectal diazepam needed?	Diagnosis	Midazolam (micro-grams/kg)
1 (CR)	4 y 8 m	25	15	No (not given – medical decision that child was improving)	Febrile convulsion	140
2 (CR)	1 y 7 m	2 (but fitting in ambulance on and off)	3	No	Febrile convulsion	230
3 (CR)	1 y 3 m	5	4	No	Febrile convulsion	240
4 (CR)	3 y 11 m	Not recorded	5	No	Epilepsy	160
5 (CR)	11 y 9 m	10 (plus 3 seizures prior to arrival)	2	No	Epilepsy	130
6 (CR)	2 y 7 m	< 1 minute	1	No	Febrile convulsion	180
7 (CR)	8 y 9 m	< 1 minute	1	No	Epilepsy	200
8 (F)	1 y 2 m	65	35	Yes – then paraldehyde	Febrile convulsion	250
9 (F)	10 m	52	8	Yes – then paraldehyde 30 min later for further seizure	Febrile convulsion	220
10 (CR)	1 y 6 m	35	8	No	Febrile convulsion	220
11 (CR)	8 y 9 m	75	1	No (2 doses were given at home without effect)	Epilepsy	200
12 (F)	2 y 2 m	45	30	Yes – then paraldehyde	Febrile convulsion	270
13 (PR)	8 y	294	36 – more settled after midazolam	(2 doses were given at home) paraldehyde was given after midazolam	Epilepsy	150
14 (PR)	2 y 6 m	40	4	Yes – for further attack 19 min after midazolam had controlled the presenting seizure	Epilepsy	190
15 (PR)	1 y 11 m	39	5	Yes – left arm still twitching	Epilepsy	260
16 (CR)	9 y 9 m	Several hours – on and off	5	No	Epilepsy	200
17 (PR)	1 y 2 m	52	3	Yes – odd movements and stiffness noticed 23 min after midazolam had controlled the presenting seizure	Febrile convulsion	250
18 (PR)	6 y 9 m	64	3	Yes – major attack; also needed paraldehyde after midazolam had controlled the presenting seizure	Febrile convulsion	170
19 (F)	2 y 2 m	230	50	(Given at home) paraldehyde x2 were given after midazolam	Epilepsy	250
20 (F)	3 y	40	35	Yes and i.v. diazepam	Febrile convulsion	210

CR = complete recovery following intranasal midazolam
 PR = partial recovery following intranasal midazolam
 F = treatment failure

administered ranged from 130 micrograms/kg to 270 micrograms/kg (median 205 micrograms/kg).

All children were convulsing at the time of midazolam administration. In some patients the seizure started while the patient was in the emergency department. The remainder had been convulsing either on and off or continuously for a prolonged time prior to hospital arrival.

Efficacy

- Ten patients (50%) made a complete recovery from their seizure following midazolam as a single drug within 5–15 minutes.
- Five patients made a partial recovery:
 - Two patients had settling seizures which were still continuing at 5 minutes, and were given further treatment to terminate the seizure

- Three patients had a further seizure within 23 minutes requiring further treatment.
- Five patients failed to respond to midazolam.

Complete Recovery

Where midazolam was completely successful, the length of time between administration and effect ranged from 1 to 15 minutes (median 3.5 minutes). Two patients were convulsing for longer than the five minutes stated in the protocol (patients 1 and 10), but the doctor decided that further drug administration was unnecessary as the patient was settling.

Three of the 10 patients making a complete recovery following intranasal midazolam administration presented with prolonged convulsions (35 minutes, 75 minutes and several hours on and off). Five of the 10 had febrile convulsions.

These patients received 130–240 micrograms/kg of midazolam.

Partial Recovery

Of the five patients making a partial recovery with intranasal midazolam, three patients (patients 14, 17 and 18) went on to have further seizures during their hospital admission. Patient 14 had two further 10-second episodes starting 19 minutes after midazolam administration; these required the administration of two doses of rectal diazepam. Patient 17 developed odd movements and stiffness 23 minutes after termination of the initial seizure, which were treated with rectal diazepam. Patient 18 had the presenting prolonged seizure controlled with midazolam, but a further prolonged convulsion started 23 minutes later, which was treated with rectal diazepam followed by rectal paraldehyde.

The other two patients (patients 13 and 15) making a partial recovery showed improvement following midazolam but required further treatment to terminate the seizure completely. All five of these patients had prolonged convulsions (median 52 minutes) before intranasal midazolam administration.

Treatment Failures

Similarly, each of the five treatment failures had prolonged convulsions (median 52 minutes) before administration of midazolam. Four of these patients had febrile convulsions; the fifth was a known patient with epilepsy.

Only one of the five midazolam failure patients

(patient 9) responded to rectal diazepam. This patient received a dose of 2.5 mg of diazepam (small dose for age) and the seizure terminated in four minutes. However, rectal paraldehyde was required to control a further seizure 30 minutes later. Three (patients 8, 12 and 20) required rectal paraldehyde or i.v. diazepam after rectal diazepam to control the seizure. The fifth patient (patient 19) had received rectal diazepam at home and required two doses of rectal paraldehyde following intranasal midazolam to control the seizure. All these patients received at least 200 micrograms/kg of midazolam; therefore rounding of doses according to age did not cause lack of response.

Eight patients were transferred to the Paediatric Intensive Care Unit (PICU) because of their overall clinical condition. The length of stay in the PICU varied from 6 hours to 48 hours (median 18 hours). The remaining patients were admitted directly to a paediatric medical ward. The total length of hospital stay ranged from 9 hours to 96 hours (median 24 hours).

Respiratory depression was not seen in any patient and no adverse reactions were observed.

Discussion

The Importance of Early Effective Treatment

Early control of acute seizures in children is the main goal of therapy. Prompt cessation of seizure activity may prevent the development of status epilepticus, reduce the risk of injury and long-term morbidity associated with recurrent seizures, and may also decrease the probability of seizure recurrence⁹.

Midazolam has a short onset of action, as at physiological pH it becomes highly lipophilic allowing penetration of the brain within 2–5 minutes⁴. Our study shows that midazolam was effective in 1–15 minutes (median 3.5 minutes). Four patients had seizures that terminated in 2 minutes or less following intranasal midazolam treatment. It is possible that these patients may have recovered without active treatment. Midazolam is quickly cleared by the liver resulting in a short elimination half-life, unlike diazepam, which has active metabolites that are present in the body for days. However, in our study, three patients who had their presenting seizures controlled with intranasal midazolam went on to have a further attack within about 20 minutes. This may reflect the short half-life of midazolam. It provided initial seizure control but this was lost within 19–23 minutes. The ideal drug for treating acute convulsions must have a rapid but sustained duration of action. Lorazepam may be the best

benzodiazepine for acute seizures, in view of the prolonged duration of action¹⁰.

Previous Studies

Previous studies of intranasal midazolam for the treatment of acute seizures have reported efficacy rates of 95% and 98%^{7,8}. This is higher than the 50% complete and 25% partial recovery rate demonstrated by our study. Differences in methodology include our inclusion of children who had received anticonvulsant medication before arrival in hospital. Two children who had received rectal diazepam at home were treatment failures in our group, and required paraldehyde to terminate the seizure; these children would have been excluded by Lahat *et al.*⁷. Jeannet *et al.*⁸ allowed 10 minutes following intranasal midazolam administration before the treatment was considered ineffective. Some patients received a second dose if the seizure had not stopped at 5 minutes, and were considered as successes if the seizure terminated by 10 minutes⁸. Our study would have termed these 'treatment failures'. All of our five treatment failures had prolonged convulsions (40–230 minutes) before midazolam administration, and four had febrile convulsions. These patients may have been resistant to treatment. However, intranasal midazolam has been shown to be effective in patients with intractable seizures⁴. Also three of our 10 complete recoveries presented with prolonged seizures and five of these 10 had febrile convulsions. It is possible that if we had waited 10 minutes, or given a second dose of midazolam at 5 minutes (as in Jeannet's study), then the complete recovery rate in our study might have been higher. Recent guidelines in the UK advise waiting 10 minutes before giving the second dose of an anticonvulsant¹¹.

Route of Administration

Rectal diazepam has been thought to be safer than intravenous diazepam, and does not require intravenous access. Therapeutic plasma concentrations are usually obtained within four minutes; however, the drug may be expelled prematurely. Maximal anticonvulsant action lasts only 20–30 minutes, as diazepam is rapidly distributed into fatty tissues and stores¹². This short-lived action may require repeated dosing for sustained control of seizures, leading to accumulation of metabolites with an increased risk of adverse effects¹⁰. The safety of rectal diazepam has also recently been questioned. Over 8% of children receiving rectal diazepam for the treatment of acute seizures resulted in respiratory depression³. Respiratory depression was not seen

in our study in any patient receiving midazolam, diazepam or paraldehyde. It has, however, been occasionally reported with intranasal, as well as intramuscular and intravenous, midazolam⁶. This would suggest that caution is required until further experience with these alternative routes of administration is gained.

Rectal administration of drugs may be embarrassing particularly to older children and their carers. They may feel it is unacceptable to administer it in a public place¹³. Teachers, nursery staff and foster parents may be reluctant to use this route⁴. Together these factors suggest that rectal diazepam is not the ideal first choice for treatment of acute seizures in children and midazolam by an alternative route may be preferable.

Seven of our children had viral upper respiratory tract infections or otitis media. This may have improved absorption of the drug by increasing blood flow to the nasal mucous membrane. Alternatively the presence of nasal secretions may have diluted the solution and impaired absorption¹⁴. Patient acceptability of midazolam by the intranasal route of administration was not assessed; however, all patients were suffering generalised convulsions and therefore were, by definition, unconscious and unaware of drug administration at that stage. Other studies have reported acceptability of this mode of midazolam administration to be high^{8,13}.

The buccal route of administration of midazolam has also been tried successfully in a limited number of patients¹⁵. These patients had established epilepsy and had experienced the use of anticonvulsant medication both chronically and in the acute setting. The youngest patient was 5 years of age. The buccal route overcomes any potential impairment of absorption in the presence of nasal inflammation and secretions, and may be an easier route of administration from a practical point of view.

Future Studies

The availability of alternative routes of administration of midazolam could dramatically improve the lives of patients regularly suffering from acute convulsions requiring treatment. The results of this small study suggest that further work is necessary to confirm or refute the efficacy of intranasal midazolam in acute seizures, its safety profile and the dose required. A multicentre randomised controlled trial comparing buccal midazolam with rectal diazepam is due to commence in the UK. Such trials are essential to ensure children receive the best possible treatment.

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