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Brief Communication

Comparison of intranasal midazolam with intravenous diazepam for treating acute seizures in children

T. Mahmoudian* and M. Mohammadi Zadeh

Department of Child Neurology, Medical University of Isfahan, Isfahan, Iran

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Abstract

Midazolam, a water-soluble benzodiazepine, is usually given intravenously in status epilepticus. The aim of this study was to determine whether intranasal midazolam is as safe and effective as intravenous diazepam in the treatment of acute childhood seizures. Seventy children aged 2 months to 15 years with acute seizures (febrile or afebrile) admitted to the pediatric emergency department of a general hospital during a 14-month period were eligible for inclusion. Intranasal midazolam 0.2 mg/kg and intravenous diazepam 0.2 mg/kg were administered after intravenous lines were established. Intranasal midazolam and intravenous diazepam were equally effective. The mean time to control of seizures was 3.58 (SD 1.68) minutes in the midazolam group and 2.94 (SD 2.62) in the diazepam group, not counting the time required to insert the intravenous line. No significant side effects were observed in either group. Although intranasal midazolam was as safe and effective as diazepam, seizures were controlled more quickly with intravenous diazepam than with intranasal midazolam. Intranasal midazolam can possibly be used not only in medical centers, but also in general practice and at home after appropriate instructions are given to families of children with recurrent seizures.

Keywords: Midazolam; Diazepam; Seizure disorder

1. Introduction

In the acute treatment of seizures, diazepam is undoubtedly the benzodiazepine most widely used, but its tendency to accumulate with repeated doses and very short duration of action are significant. Midazolam can be given intravenously, intramuscularly, and rectally, as well as via the nasal mucosa.

Midazolam acts rapidly and is less likely than diazepam to accumulate [1]. The plasma concentration of midazolam after intranasal administration of 0.2 mg/kg is 100 ng/ml at about 6 minutes [2]. O' Regan and colleagues examined the effectiveness of intranasal midazolam on seizure discharges recorded concurrently by electroencephalography (EEG). Their findings demonstrate unequivocally that midazolam 0.2 mg/kg is absorbed rapidly through the nasal mucosa and can eliminate spike activity on the electroencephalogram [1].

In this study we compare intranasal midazolam with intravenous diazepam for the treatment of acute childhood seizures.

2. Methods

The study was conducted in the pediatric emergency department of the Medical University of Isfahan, between September 1998 and October 1999. We randomly assigned 70 patients between 2 months and 15 years of age admitted to the emergency department of Alzahra Hospital in Isfahan with acute seizures.

Randomization was performed in advance with an odd and even number table by a pediatric assistant not involved in the study, and treatment allocations were sealed in opaque envelopes. Investigators were blind to these allocations. Intravenous diazepam 0.2 mg/kg was administered to patients with odd numbers after an intravenous line was introduced; midazolam solution (5 mg/ml) was dropped by syringe into both nostrils in

* Corresponding author. Fax: +98-311-6240027.
E-mail address: t_mahmoudian@med.mui.ac.ir (T. Mahmoudian).

equal doses to those with even numbers and an intravenous line was immediately introduced. Children who had received anticonvulsants before admission were excluded. The time from treatment with intranasal midazolam or intravenous diazepam to cessation of seizures was recorded. Treatment was considered successful if seizures ceased within 10 minutes. Seizures that did not stop within 10 minutes of treatment were defined as treatment failures, and intravenous diazepam was given to the midazolam group and phenobarbital to the diazepam group. During seizure activity, high-flow oxygen by mask and routine life support were provided. All children were admitted to the pediatric ward for evaluation of the etiology of seizures. The effectiveness of the drugs was tested with the χ^2 method, and the mean time required to achieve control was tested with the Mann–Whitney method.

3. Results

During 14 months, 70 patients were included in this study. In all patients, in both groups, seizure control was achieved within 10 minutes, and there was no significant difference in effectiveness between intranasal midazolam and intravenous diazepam ($P > 0.05$). The mean interval between drug administration and seizure control was 3.58 (SD 1.68) minutes for midazolam and 2.94 (SD 2.62) minutes for diazepam. The time required to insert the intravenous line was not included. There was a significant difference in the mean time required to achieve control between the midazolam and diazepam groups ($P = 0.007$). Time from seizure start to treatment was faster in the midazolam group but seizures were controlled faster in the diazepam group. None of the children had clinical signs of respiratory distress, bradycardia, or other side effects.

The overall times required for seizure control in the two groups are presented in Fig. 1. The etiology of seizures in both groups is given in Table 1. The various types of seizures are listed in Table 2.

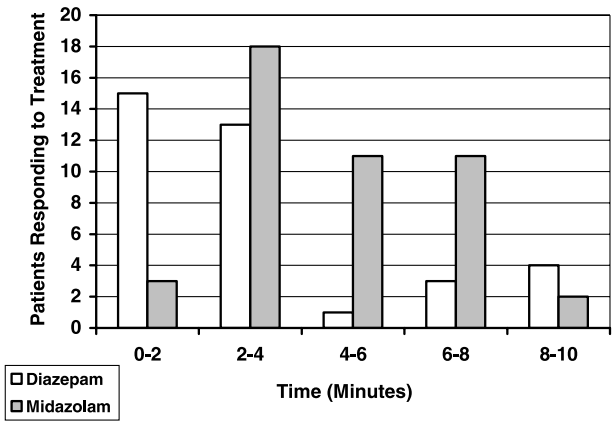

Fig. 1. Duration interval between administration of drug and response to treatment.

Table 1
Etiology of seizures

Etiology of Seizures	Midazolam	Diazepam
Hypocalcemia	2	8
Hypoglycemia	—	2
Febrile convulsions	14	1
Epilepsy	14	13
Head trauma	—	1
CNS infection	4	10
Hyponatremia	1	—
Total	35	35

Table 2
Various types of seizures

Type of seizure	Midazolam	Diazepam
GTC[a]	25	25
SPS	3	3
CPS	4	8
Myoclonic	3	2
Total	35	35

[a] GTC, generalized tonic–clonic seizures; SPS, simple partial seizures; CPS, complex partial seizures.

4. Discussion

Midazolam, a water-soluble benzodiazepine, is an effective anticonvulsant given intravenously and intramuscularly. Intranasal midazolam is a safe and effective anesthetic in children and can suppress epileptic activity [3,4]. Midazolam can be effective in the treatment of status epilepticus [5,6].

Absorption of drugs is modified by, among other things, the circulation to the site of absorption, the area of the absorbing surface to which the drug is exposed, and the concentration of the drug. It is well recognized that for many children, especially those who have febrile seizures, upper respiratory tract infections are present at the times at which acute medication to terminate seizure is required. Although the infection might help absorption by increasing blood flow to the nasal mucous membrane, the presence of nasal secretions could dilute the midazolam solution and make it more difficult for this agent to contact the absorbing surface.

The elimination half-life of midazolam is usually between 1.5 and 3.5 hours [7]. One study found that intranasal midazolam is absorbed in epileptic children; the mean time to seizure control was 3.5 (range 2.5–5) minutes and there were no recurrences of seizures within 60 minutes of treatment [3].

Lathat et al. reported that intranasal midazolam and intravenous diazepam are equally effective in children

with prolonged febrile seizures [3]. The mean time to cessation of seizures was 3.1 (SD 2.2) minutes in the midazolam group and 2.5 (SD 1.9) minutes in the diazepam group.

We showed that intranasal midazolam is effective in the management of acute seizures in children. In 21 of 35 (60%) children, seizure control was achieved in less than 5 minutes, and the other 14 within 10 minutes; in the diazepam group, however, in 28 of 35 (80%), seizures ceased in less 5 minutes, and in the other 7, within 10 minutes. The mean time to seizure control was significantly shorter in the diazepam group (2.94 (SD 2.62) minutes) than in the midazolam group (3.58 (SD 1.68) minutes). No patient had to be intubated or mechanically ventilated.

The introduction of an intravenous line may be difficult and if the time required for this procedure is added to the time to cessation of seizures, treatment with intranasal midazolam may work faster than treatment with intravenous diazepam [3].

Although acute seizures have been treated with rectal diazepam [8], the rectal route is not always reliable. Further studies are needed to determine whether intranasal midazolam can be used not only in medical centers, but also at home after appropriate instructions are given to parents of children with acute seizures.

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