

BUCCAL MIDAZOLAM USE FOR ACUTE TREATMENT OF SEIZURES

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Introduction and aim: Several studies confirmed midazolam effectiveness to control refractory seizures and especially status epilepticus (SE) in infants and children. Buccal route of use has become a preferred way during recent years. We have been using this route of application to abort seizures as an outpatient medication given to parents as well as for treatment of SE for inpatient cases in a hospital setting since year 2000. Results are presented as well as parents' response to use this kind of route.

Patients and methods: all the patients were followed-up in our outpatient department for severe forms of epilepsies for at least 2 years. Midazolam vials (Dormicum®) of 50 mg/10ml were used and a dose of 0.4 mg/kg was given to children of less than 20 kg, while all the others received a dose of 0.2 mg/kg. A special protocol was made and given to the parents for observation of possible positive as well as non-desired effects.

Results: a cessation of seizures was observed in 82.5% of all cases and no severe adverse effects were reported.

Conclusion: we strongly suggest the use of buccal midazolam in outpatient settings and believe that it is useful also for primary care paediatricians in emergent situations.

Descriptors: MIDAZOLAM-BUCCAL, CHILDREN, STATUS EPILEPTICUS, OUTPATIENT SETTINGS

Introduction

Status epilepticus or prolonged refractory seizures are the most common neurological emergencies in children. During recent years our knowledge has increased in understanding its pathophysiology, role of electroencephalography (especially with the increased use of cerebral function monitors), the long-term morbidity and mortality and its pharmacological management (1). A seizure is defined as a transient, involuntary alteration of consciousness, behavior, motor activity, sensation or autonomic function, while epilepsy describes a condition of increased susceptibility to recurrent seizures (2). The classic definition of

status epilepticus (SE) refers to continuous or recurrent seizure activity lasting longer than 30 minutes without recovery of consciousness. More recent definition has been proposed by Lowenstein et al. that a SE should be used for all seizures lasting more than 5 minutes or two or more seizures during which the patient does not return to baseline consciousness (3). The rationale for this revised definition is based on the fact that a typical, generalized tonic-clonic seizure rarely lasts more than 5 minutes, that spontaneous termination becomes less likely in seizures of >5 minutes, and that the longer the seizure continues, the more difficult the seizure becomes to control with anticonvulsive drugs, and maybe even much more important, the greater is the degree of neuronal damage (4).

Control of prolonged seizures in the past usually required transport to an emergency room and administration of intravenous anticonvulsant drugs. The inherent delay in starting treatment raised concerns about the potential morbidity and mortality of prolonged seizure

activity, about the inverse relation between seizure duration and effectiveness of acute treatment (5). The use of drugs, usually benzodiazepines, by alternative routes - rectal, intranasal, sublingual - was sometimes reported in the past, but was not common management. However since the report of Holmes GL in 1999 Lancet on efficacy of buccal routes of midazolam this option of application has become a preferred use, especially for the non-hospital settings (6-8).

Midazolam is a water-soluble benzodiazepine which has a potent anticonvulsive action. Several studies confirmed its effectiveness to control refractory seizures as well as status epilepticus (SE) in infants and children; it has even been proposed as a first-line agent in intravenous infusion for SE (9). Buccal route of use has been much more disputed about and some even disagree that it can be as effective as rectal diazepam, and that special caution should be given to those patients where SE can follow the acute attack of seizures (9, 10). Only recently studies have proven its excellent results

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with a moderate dose (0.3 mg/kg per dose) at different ages (1 month to 15 years) and no clinically important side effects (11, 12). We have used midazolam introduced into buccal cavity to abort seizures as an outpatient medication given to parents in case of short seizures treated at home, as well as for treatment of SE for inpatient cases in a hospital setting. Parents' response to use this kind of route was also studied.

Patients and methods

All the patients were followed-up by one of the 3 child neurologists and have been treated for severe forms of epilepsies for at least 2 years. Some patients have had multiple handicaps. Patients were either followed-up only in outpatient department or were also occasionally managed in the hospital settings. Midazolam vials (Dormicum®) of 50 mg/10ml were used and a dose of 0.4 mg/kg was given to children of less than 20 kg, while all the others received a dose of 0.2 mg/kg. For buccal application a special nozzle was used and the parents were instructed by three senior nurses who have a long time experiences with work on pediatric neurology units as well as in outpatient settings. All the patients were also given a special brochure where all the steps of giving the drug were meticulously described and even presented by figures. Also all the telephone numbers of treating physician were mentioned and a possibility for contact via e-mail address of the department was given (pednevro@cklj.si) were always all the parents' questions were answered with 24-hour time. The vials of 50 mg (10 ml) midazolam were given to parents who were also instructed exactly how much they should give. This data were also written down on one of the brochure's leaflets. A special protocol was made and given to the parents for observation of possible positive as well as non-desired effects. The study was approved by hospital ethical committee. Group 1 consisted of outpatient cases, while group 2 consisted of those few cases treated in hospital due to SE. All these patients have had intravenous line done in case of failure of buccal administration.

Results

In the first group 34 outpatient and in the second 8 inpatient cases were enrolled, with male to female ratios being 17/17 and 3/5 respectively. Ages were in the range of 3 years up to 24 years (mean: 8 years \pm 2.3 years). In the first group in the majority of cases midazolam was given after 1.5 to 5.0 minutes' duration of seizures (type of seizures were partial and generalized), while in 4 midazolam was given due to series of short-duration seizures. The parents' reporting was not always given properly and there was high percentage of non-compliance as only 12 of 34 (35%) questionnaires given have returned. The cessation of seizures was observed in 82.5% of all cases and no severe adverse effects were reported. In 11/12 of cases where parents' report was obtained buccal midazolam was preferred route over rectal diazepam (92%). In the group 2 (in-hospital cases) all SE were successfully stopped by buccal midazolam only and no other intravenous administration was necessary.

Discussion

Our results show that buccal midazolam is very effective in both, non-hospital and in-hospital settings. We have chosen the buccal route, because it's previously been shown that the emphasis to be on the use of buccal rather than nasal midazolam and because nasal midazolam is much more difficult to obtain (13). There have been randomized controlled trials comparing midazolam and rectal diazepam already done in the past, however one more recent one was done in four accident and emergency units in the United Kingdom and reported the treatment of 219 separate episodes in 177 children between ages 6 months and 15 years (7, 14). Buccal midazolam was more effective than rectal diazepam and here was no increased risk in terms of respiratory depression. The proportion of children that responded was only 56% in the buccal midazolam group (14). In our much smaller group with no randomization the parents reported buccal midazolam to be preferred use in 92%, while the effectiveness was 82.5%.

We also must be aware of the fact that McIntyre and colleagues believed that low proportion of effectiveness was most probably due to the strict criteria for seizure termination, and due to the fact that a third of children had already received rectal diazepam in the community setting and therefore these children may have had refractory SE that was destined to be more difficult to treat with another non-parenteral benzodiazepine (13). Our study also did not include any of the modern neurophysiological techniques to establish whether SE was also electrically well diminished or stopped. Many authors used electroencephalography for that purpose, while also amplitude integrated electroencephalography by cerebral function monitor could be used for that purpose (15, 16).

Conclusion

We strongly suggest the use of buccal midazolam in outpatient settings and believe that it is useful also for primary care paediatricians in emergent situations. As already stated before also our parents reported its good popularity especially because of non-rectal use as administration via the mouth is more socially acceptable (7, 14). However the parents' response in our study was poor and in the future the parents will be contacted personally by our nursing staff. Our study also confirmed excellent results with buccal midazolam in an emergency inpatient setting, similar to recent study where also no other measures were used and no important side effects were seen in any patient, however also some diagnostic tool should be used in the future to ascertain that the seizures were stopped also electrographically (14). As routine electroencephalography can not be performed on an all day basis, maybe the amplitude-integrated EEG would be a preferred tool in the future. We should also stress that also in our small inpatient group where for the treatment of SE buccal midazolam was used, no other measures were necessary and no adverse effects were recorded, so we would strongly recommend it also for the hospital use. It can prove especially effective mainly in the cases where non-parenteral use is the preferred route and in those cases (e. g. encephalopathy's or

non-convulsive SE) where frequent application of some of the anticonvulsant drugs is necessary.

LITERATURE

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Sažetak

PRIMJENA BUKALNOG MIDAZOLAMA U TERAPIJI KONVULZIVNOG STATUSA

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Uvod i cilj: Nekoliko istraživanja je potvrdilo učinkovitost djelovanja midazolama pri refraktornim napadajima, a posebno epileptičkom statusu u dojenčadi i djece. Tijekom posljednjih godina, bukalni način primjene se počeo smatrati najprikladnijim. Ovaj način primjene koriste roditelji za prekide napadaja kod vanbolničkih pacijenata, a mi ga od 2000. godine koristimo u liječenju epileptičkog statusa bolničkih pacijenata. Prikazujemo naše rezultate, kao i dojmove roditelja na ovaj način primjene lijeka.

Ispitanici i metode: Svi su pacijenti nadzirani u našoj ambulanti radi teških oblika epilepsije najmanje dvije godine. Ampule midazolama (Dormicum®) od 50 mg/10 ml su korištene; djeci <20 kg je ordinirano 0,4 mg/kg, a svima ostalima 0,2 mg/kg. Prikladan formular je pripremljen za roditelje s ciljem da registriraju zamijećene i moguće pozitivne ili negativne učinke lijeka.

Rezultati: Napadaj je prekinut u 82,5% svih slučajeva, a niti jedan teži negativni učinak lijeka nije registriran.

Zaključak: Preporučamo uporabu bukalnog midazolama u vanbolničkom okruženju i vjerujemo da je od koristi pedijatrija primarne prakse u hitnim situacijama.

Deskriptori: MIDAZOLAM, EPILEPSIJA, BUKALNA PRIMJENA