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Buccal midazolam vs rectal diazepam administered by parents for continuing and serial epileptic seizures: a randomised controlled trial of parental preferences

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Abstract

Aim: We aimed to undertake a small study comparing buccal midazolam and rectal diazepam in the emergency out-of-hospital treatment of prolonged or serial epileptic seizures in children. We wanted to see if the parent/carer could not only administer the emergency medication but also document the timings and outcomes of the trial. We also aimed to demonstrate parental preference for either treatment.

Methods: This was an open-label, randomised, cross-over clinical trial. The primary outcome was parental preference, secondary outcomes included therapeutic success (seizure stopped within 10 minutes of treatment with no relapse in the next 24 hours), and adverse events. Research Ethics Committee approval and appropriate written informed consent were obtained for all participants. Identical convenient age-related doses of buccal midazolam and rectal diazepam were used: for those aged 6 to < 12 months, 2.5 mg was prescribed; for those aged 1 to < 5 years, 5 mg; 5 to < 10 years, 7.5 mg; 10 years and over, 10 mg. Appropriate randomisation and statistical methods were used.

Results: Twelve children, three males, aged 2.5–8 (median 5) years, including 10/12 with developmental delay or intellectual impairment completed the trial. Each participant had between 2–4 types of epileptic seizure, was taking 2–3 different regular antiseizure medications, and had been previously on 2–9 (median 3) regular other antiseizure medications in the past. Nine of twelve parents preferred buccal midazolam, 1/12 preferred rectal diazepam ($P < 0.05$). Therapeutic success was seen in 7/12 participants with either treatment. No respiratory depression was seen in this small trial.

Conclusions: Buccal midazolam was clearly preferred to rectal diazepam by parents. This small study was not powered to show a difference in efficacy and adverse effects. The study did show that the cross-over design with parents recording trial data, including data for the outcome measures was feasible.

Keywords

Children, status epilepticus, emergency, pre-hospital, out-of-hospital, open-label

Introduction

Prompt and effective treatment of convulsive status epilepticus in children is a medical emergency. The sooner a prolonged epileptic seizure is stopped the less likely the chance of it evolving into established or prolonged status epilepticus, and the less likely the child will be damaged or require paediatric intensive care, hence the need for out-of-hospital emergency treatment [1].

When intravenous (i.v.) access is not available, rectal diazepam is an effective treatment, with marketing authorisation i.e. has been widely "licensed", e.g., by the FDA in the USA, since 1997, and the MHRA in the UK since 1982. It is still in use in many countries. In the USA, intramuscular (i.m.) and intranasal midazolam have been licensed just recently in 2022, but in Europe, in line with evolving clinical practice, buccal midazolam has been licensed in the UK by the MHRA since 2006, by the EMA since 2011, and intranasal but not i.m. midazolam since 2022. Furthermore, there is some evidence that buccal midazolam is superior to rectal diazepam in children with acute convulsive epileptic seizures lasting more than 5 minutes [2], and is more cost-effective [3]. A Cochrane review concluded in 2018, after consideration of the published evidence up to May 2017, that while i.v. lorazepam or i.v. diazepam was recommended, in the absence of immediate i.v. access, buccal midazolam or rectal diazepam was the best non-i.v. option in children [4]. All the 12 studies included in this review were undertaken in hospitals, mostly in Emergency Departments.

Much of the literature in this area focuses on the use of intranasal midazolam, which was preferred by carers, in a recent trial, although it was not more effective than buccal, or i.m. midazolam [5].

There is also evidence of the superiority of nasal midazolam compared to rectal diazepam in canine epilepsy [6].

However, we felt that in children febrile seizures are often associated with upper respiratory tract infections and nasal congestion or blockage, rendering intra-nasal administration less reliable than the buccal route [7]. The buccal fossa lies between the teeth and gums and the inside of the cheek, is outside the oral cavity, and therefore safe and accessible in an unconscious child even when the jaw is tightly shut, as can happen in some prolonged epileptic seizures.

We report a small study comparing out-of-hospital emergency seizure treatment given by parents or the usual carers (not paramedics, nurses, or doctors), comparing buccal midazolam and rectal diazepam, to see which is preferred by the parents, and to act as a pilot for a possible future larger efficacy trial.

Materials and methods

Methods

This was an open-label, randomised, cross-over clinical trial. The parents/legal guardians of children, aged 6 months to < 18 years old, attending paediatric neurology follow-up with epilepsies and a history of previous prolonged convulsive epileptic seizures lasting more than 5 minutes, were recommended out-of-hospital emergency treatment with appropriate training. They were asked to consider giving written informed consent for their child to be enrolled in this open-label clinical trial of two commonly used treatments: buccal midazolam (Hypnoval®: 10 mg in 2 mL; Neon Healthcare Ltd, UK) and rectal diazepam (Stesolid®: 2.5 mg, 5 mg, 10 mg rectal tubes; Desitin Arzneimittel GmbH, Germany; however, the 2.5 mg tubes are now discontinued).

The study was sponsored by Nottingham University Hospitals NHS Trust, and conducted in accordance with the Good Clinical Practice guidelines of the International Conference on Harmonization (ICH) and the ethical principles of the Declaration of Helsinki. The protocol was approved by the East Midlands-Nottingham 2 Research Ethics Committee (Q2090313), and written informed consent was obtained from all the participants' parents/legal guardians, as all were under 16 years of age.

We randomised which drug was to be given on the first trial occasion, and whichever was not given, was used on the next occasion. Randomisation was done at recruitment, with concealed allocation in blocks of 10.

The parents/guardians were trained in both buccal midazolam and rectal diazepam administration, and in completing the standard data collection sheet. This included demographic and clinical information on each child, and for each seizure treated indication, location such as at home, school, or outdoors, and the outcomes. Each child received each drug and acted as their own control. Identical convenient age-related doses were used: for participants aged 6 to < 12 months, 2.5 mg was prescribed; for those aged 1 to < 5 years, 5 mg; for those aged 5 to < 10 years, 7.5 mg; and for those aged 10 years and over, 10 mg. Those declining participation were offered buccal midazolam in line with our policy at the time.

As this small trial was unlikely to recruit enough children to compare the efficacy of these effective drugs (see statistical analysis below), we settled on ultimate parental preference as the primary outcome measure. Secondary outcomes included efficacy measures: discernible seizure duration (from time seizure started, and time drug was administered, to time seizure was seen to finish) was recorded; any seizure relapse within 24 hours; sleepiness; breathing difficulties; and any other adverse events seen. Therapeutic success was calculated as the proportion whose seizure stopped within 10 minutes of administration without seizure relapse within 24 hours.

Statistical analysis

The power calculation suggested that 44 participants were required to demonstrate a difference in efficacy. As this was unlikely to be achieved in such a small study, parental preference was chosen as the primary outcome. SPSS was used, and the following tests were applied as appropriate: McNemar's test, Wilcoxon matched-pairs signed-ranks test, and Chi-squared test. Two-tailed statistical tests were applied, and a *P*-value < 0.05 was considered statistically significant.

Results

Twelve children, three males, aged 2.5–8 (median 5) years at first dose, completed this trial. 10/12 had significant developmental delay or intellectual impairment, recorded in their routine hospital medical records. Each participant had between 2–4 types of epileptic seizures and was taking 2–3 different regular antiseizure medications. Each had been previously on 2–9 (median 3) regular other antiseizure medications in the past. All had had previous convulsive epileptic seizures lasting more than 5 minutes or clusters of seizures without recovering consciousness in between seizures. 5/12 had previously had at least one admission to paediatric intensive care with convulsive status epilepticus.

The first 2 treatments will be reported, one buccal midazolam and the other rectal diazepam, which were given to each child in randomised order.

Each participant received identical doses of buccal midazolam and rectal diazepam; which accounting for their body weight was 0.2–0.4 (median 0.3) mg/kg.

Of the 24 treatment episodes 16 (67%) were at home, 1 was in school, 1 was in public, 2 were in other locations, and 4 were in unspecified locations.

The main outcomes are in Table 1, 9/12 (75%) of parents/guardians preferred buccal midazolam.

Discussion

Although small, and underpowered for efficacy this trial was able to demonstrate a clear preference by parents/guardians for buccal over rectal administration which was statistically significant ($P = 0.012$). A larger study would be needed to demonstrate a difference in efficacy, however, this parental and caregiver preference is important and has not been demonstrated in a controlled trial before. The therapeutic success achieved with both treatments was in line with other studies, e.g., in paediatric emergency departments [2] and a recent retrospective report of pre-hospital use of buccal midazolam [8]. The lack of respiratory depression (0/24: 95% CI, 0 to 14%) was expected given the small participant numbers.

Table 1. Main outcomes

Outcome measure	RD	BM	*P*-value
Therapeutic success (stops seizure < 10 min, for 1 hour, without respiratory depression)	7/12	7/12	
Time from onset to administration (min)	6.0 (5–30)	6.0 (5–30)	
Time from administration to seizure cessation (min)	7.0 (3–13)	7.5 (1.5–13.5)	
Sedation	8/12	10/12	
Respiratory depression	None	None	
Ease of administration	7/12	9/12	
Ultimate parental preference	1/12	9/12	$P < 0.05$

McNemar's test, Wilcoxon matched-pairs signed-ranks test, and Chi-squared test were applied as appropriate. Ease of administration was recorded by parents as either "easy to give" or not. Blank cells indicate no statistically significant difference. RD: rectal diazepam; BM: buccal midazolam

We regret being unable to secure sufficient funding for a larger trial, however, we have shown that parents and carers can manage this cross-over trial design, and provide satisfactory data for analysis. One advantage of the cross-over design is that each child and parent acted as their own controls so that within each pair the same indications and approach to documentation was used. The cross-over design requires fewer participants than the more common parallel group design.

One disadvantage of the trial design was that the parents/guardians were not blinded. This would have required a double-dummy design, increasing the cost and complexity of the trial which was not feasible.

Given that buccal midazolam is so well established now, in the UK, we doubt that a further larger trial powered for efficacy would find funding or be worth pursuing in the UK. This is to our knowledge the only trial comparing buccal midazolam with rectal diazepam in children, out-of-hospital, administered by trained parents/carers.

Abbreviations

i.m.: intramuscular

i.v.: intravenous

Declarations

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Author contributions

HWG: Formal analysis, Writing—review & editing. EW: Project administration, Writing—review & editing. WPW: Conceptualization, Data curation, Methodology, Project administration, Supervision, Writing—original draft.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

The protocol was approved by the East Midlands-Nottingham 2 Research Ethics Committee (Q2090313), and conducted in accordance with the Good Clinical Practice guidelines of the International Conference on Harmonization (ICH) and the ethical principles of the Declaration of Helsinki.

Consent to participate

Written informed consent was obtained from all the participants' parents/legal guardians, as all were under 16 years of age.

Consent to publication

Not applicable.

Availability of data and materials

Datasets are available on request. The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

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