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Review

Benzodiazepine use in seizure emergencies: A systematic review

Sheryl R. Haut [a,*], Syndi Seinfeld [b], John Pellock [b,1]

[a] Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York City, NY, USA
[b] Virginia Commonwealth University School of Medicine, Richmond, VA, USA

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ABSTRACT

Purpose: The aim of this review was to systematically examine safety and efficacy outcomes, as well as patient/caregiver satisfaction, from clinical studies in pediatric and adult patients treated with benzodiazepines (BZDs) through various administration routes in response to seizure emergencies.
Methods: A literature search was conducted to identify articles describing the use of various routes of administration (RoAs) of BZDs for the treatment of seizure emergencies through April 21, 2015, using Embase™ and PubMed®. Eligible studies included (a) randomized controlled trials or (b) controlled nonrandomized clinical trials, either retrospective or prospective. Outcome assessments reviewed were 1) time to administration, 2) time to seizure termination, 3) rate of treatment failure, 4) prevention of seizure recurrence, 5) patient and caregiver treatment satisfaction, 6) adverse events related to BDZ treatment or RoA, and 7) respiratory adverse events.
Results: Seventy-five studies evaluated safety and efficacy using individual or comparator BDZs of various RoAs for treating seizure emergencies in all-aged patients with epilepsy. Buccal, intranasal (IN), or intramuscular (IM) BZDs were often more rapidly administered compared with rectal and intravenous (IV) formulations. Time to seizure termination, seizure recurrence rates, and adverse events were generally similar among RoAs, whereas nonrectal RoAs resulted in greater patient and caregiver satisfaction compared with rectal RoA.
Significance: Results of this systematic literature review suggest that nonrectal and non-IV BZD formulations provide equal or improved efficacy and safety outcomes compared with rectal and IV formulations for the treatment of seizure emergencies.

1. Introduction

Acute seizure emergencies – including prolonged seizures, acute seizures, status epilepticus, seizure clusters, acute repetitive seizures, and out-of-hospital seizures – require immediate action to prevent neuronal damage and other morbidities [1,2]. Benzodiazepines (BZDs) are considered first-line options among seizure rescue treatments (i.e., treatments given only if needed for specific situations) as they provide a rapid onset of action, high rates of efficacy, and minimal risk for adverse events (AEs) [3–5]. In the hospital setting, seizure emergencies are commonly treated with intravenous (IV) BZD formulations. For outpatient use, diazepam (DZP) rectal gel (Diastat®) is the only drug approved in the United States [3,4,6], while buccal midazolam (MDZ; Buccolam®) [7] and DZP rectal gel are approved in Europe.

Although currently approved IV and rectal methods of delivery are effective at terminating and preventing future seizure activity, they can be associated with challenges related to their route of administration (RoA). For example, the use of IV BZDs is recommended in the presence of a healthcare professional, which limits accessibility to rapid treatment. Even in experienced facilities, preparation and placement of an IV line can be problematic and delay the time to treatment [8]. Moreover, rectal drugs are difficult to administer in emergency situations and impose social distress for caregivers and patients, particularly adolescents and adults [3,6]. As a result of these challenges, intranasal (IN), intramuscular (IM), and buccal administration routes of BZDs have been used for prehospital seizure emergencies [4,9] and have been recommended and called major therapeutic advancements by a task force of the International League Against Epilepsy [10,11]; none of these novel RoAs, however, is currently approved by the Food and Drug Administration (FDA).

To fill this unmet need, development of nonrectal BZDs that can be administered by nonhealthcare professionals has been a research focus. Various modes of administration and novel BZD formulations that have been studied in clinical trials include IN delivery of DZP, clonazepam (CZP), and MDZ; IM delivery of DZP, MDZ, and lorazepam (LZP, by autoinjection); and buccal MDZ [3,6,12–14]. Recent publications have thoroughly reviewed these emerging non-IV and nonrectal BZD treatments and suggest that they are changing the current therapeutic landscape for patients with epilepsy, particularly with regard to efficacy and patient satisfaction [15–17]. For example, treating seizure emergencies with IN and IM BZDs is supported by pharmacokinetic and safety profiles [18] and greater social acceptability [15].

* Corresponding author at: Montefiore Medical Center, 111 East 210th St., Bronx, New York City, NY 10467, USA. Tel.: +1 718 920 4898; fax: +1 718 882 0216.
E-mail address: SHAUT@montefiore.org (S.R. Haut).
[1] Deceased: May 6, 2016.

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Despite the emerging studies and increasing interest in this area, no systematic literature review to date has been performed to collectively evaluate acute seizure management and seizure recurrence prevention in all patient types treated with investigational and approved BZD administration routes. The objective of this review was to systematically examine safety, efficacy, and patient/caregiver satisfaction data from clinical studies in pediatric and adult patients treated with BZDs through various administration routes in response to seizure emergencies.

2. Methods

A systematic literature search of clinical articles was conducted on April 21, 2015 in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [19,20]. The search was not limited by publication date or publisher and was filtered for English language.

2.1. Eligibility criteria

Eligible studies, based on predetermined criteria, were (a) randomized controlled trials (RCTs) or (b) controlled nonrandomized clinical trials, either retrospective or prospective. Study participants included patients of all ages having epileptic or nonepileptic seizure emergencies. Excluded publications included review articles, clinical pharmacology studies, case studies, and those with ≤10 subjects. Also excluded were studies that included the following patient populations: critically ill; with a specific infection, disease, or condition; pharmacoresistant; with refractory status epilepticus or types of psychogenic nonepileptic seizures; and nonresponsive to first-line therapies. Studies assessing BZDs for seizure prevention, BZDs as second-line treatments, or those in which outcome assessments could not be linked to a single BZD (because of further rescue treatment administration) were also excluded.

2.2. Search strategy and information sources

The search strategy, developed by authors in conjunction with a research specialist librarian, was performed using Embase™ and PubMed®; details are included in the supplemental materials (Supplemental methods, Tables 1 and 2). Briefly, databases were searched for the following phrases – "acute seizure(s)", "acute repetitive seizure(s)", "prolonged seizure(s)", "seizure cluster(s)", "seizure emergency(ies)", "out of hospital AND seizure", "status epilepticus", and "seizure rescue" – each in combination with one of 5 specific benzodiazepines — DZP, LZP, MDZ, clobazam (CLB), and CZP.

2.3. Selection of articles

Details of the article selection process are included in the supplemental materials. Briefly, a medical writer assessed whether articles met inclusion criteria using a 3-staged selection process: 1) Screening, 2) Eligibility, and 3) Inclusion. All steps were peer-reviewed by a separate medical writer, and the final list of articles identified for analysis was approved by all authors.

2.4. Data analysis

Each publication was assessed for study design details, efficacy and safety/tolerability results, and a risk for bias. Additional assessment details are included in the supplemental materials. Briefly, outcomes assessed were the time to administration, time to seizure termination, rates of treatment failure, prevention of seizure recurrence, adverse events, and patient/caregiver satisfaction; high or low risk for bias was assessed based on the evidence-based Cochrane risk of bias tool [21].

3. Results

3.1. Study selection

Of 1170 unique articles identified from Embase™ and PubMed®, 964 were excluded during the Screening Stage, 134 were excluded during the Eligibility Stage, and three were added during the Inclusion Stage (Supplemental Fig. 1), resulting in a total of 75 unique citations analyzed in this review.

3.2. Study characteristics

The 75 studies examined the safety and efficacy of individual BDZs, multiple BDZs in different treatment arms, or a single BZD by various RoAs in the treatment of acute seizure emergencies in patients of all ages (Supplemental Table 3). Search results included 35 studies (47%) focusing on patients with status epilepticus, 7 (9%) on prolonged seizures, 6 (8%) on acute repetitive seizures/seizure clusters, and 27 (36%) on patients experiencing nonclassified acute seizures or multiple seizure types. In addition, many of these studies explicitly described the seizure events as 'seizure emergencies'.

Twelve studies (16%) examined patients of all ages, and 7 studies (9%) exclusively examined adults (18+ years). Children (1 month–18 years) were exclusively examined in 48 studies (64%), three of which were in young children aged 1 month–6 years and 13 in children aged 1 month–12 years. The remaining eight studies (11%) examined

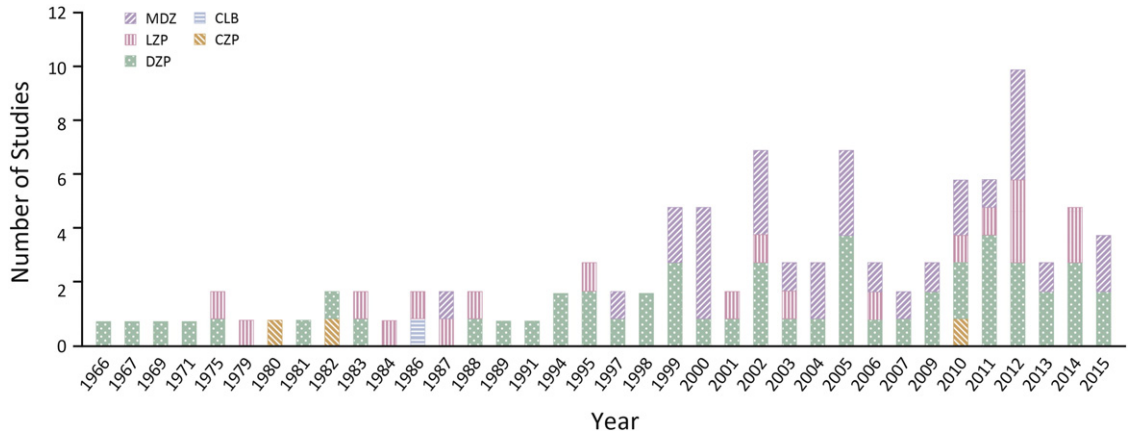

Fig. 1. Benzodiazepines studied per year as seizure rescue treatments. The number of studies, by year, that examined various BZDs for seizure rescue treatment. The bars are comprised of the 75 studies examined in this review (nonmutually exclusive); therefore, only the years that these studies were published in are displayed. Individual bars indicate the total number of BZDs studied in the given year, with each BZD differentiated by a different color (purple = MDZ; pink = LZP; green = DZP; orange = CZP; light blue = CLB).