Epilepsy & Behavior 101 (2019) 106537

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Review

Diazepam buccal film for the treatment of acute seizures

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ARTICLE INFO

Article history:
Received 1 September 2019
Accepted 4 September 2019
Available online 5 November 2019

ABSTRACT

Benzodiazepines, including diazepam and midazolam, are the mainstay of treatment for seizure emergencies, including acute repetitive seizures. Nonparenteral dosage forms are used when parenteral (intravenous or intramuscular) dosing is not feasible. Currently available nonparenteral dosage forms have limitations in terms of usability, patient and caregiver acceptance, speed of action, and portability. Diazepam buccal film (DBF) is a compact, easily administered diazepam formulation. When placed onto the buccal mucosa inside the cheek, DBF adheres firmly and then rapidly dissolves, delivering diazepam transbucally and via the gastric route. In fasted healthy male volunteers, plasma levels were achieved rapidly after DBF placement in a linear dose-proportional fashion. Bioavailability in adult patients with epilepsy was not significantly different when DBF was applied interictally or periictally (within 5 min of a seizure). Diazepam buccal film was successfully placed and generally used without difficulty, even without patient cooperation immediately after a seizure. In a cross-over comparative study with diazepam rectal gel (Diastat®) in adult patients with epilepsy, DBF performed equivalently to the rectal gel, but peak exposures were less variable. Diazepam buccal film is a convenient alternative for out-of-hospital treatment of seizure exacerbations.

Proceedings of the 7th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures.

1. Introduction

Patients with epilepsy who have worrisome seizure exacerbations outside of a medical facility may benefit from rapid treatment by a caregiver or bystander, or even from a therapy that is self-administered. Such seizure exacerbations fall on a continuum ranging from single breakthrough seizures (including a more severe or prolonged seizure than is typical for the patient), to acute repetitive seizures (ARS), and, in the most severe form, to status epilepticus [1]. Also commonly referred to as seizure clusters or seizure flurries, ARS represents a series of seizures grouped consecutively, typically with short (or shorter than usual) interictal periods [2]. More generally, ARS can be considered a change in frequency of seizures for which treatment is desired. Patients experiencing ARS have drug refractory epilepsy and experience spontaneous seizures on a recurrent basis. When ARS is identified, there is heightened concern for seizure-associated risks including postictal psychosis; injury from falls and burns; negative social and economic impact from frequent emergency department visits, hospitalizations, or missed school or work days; and importantly for status epilepticus that may lead to persistent neurological impairment or death [3]. Parenteral (intravenous or intramuscular) dosing is preferred for seizure rescue therapy, particularly in the emergency treatment of status epilepticus [4]. Alternative nonparental dosage forms are used when parenteral therapy is not feasible or when a patient has such frequent episodes that parenteral therapy is not practical [4,5]. The objective of therapy may be to prevent seizure recurrence, interrupt progression of a sequence of seizures, or terminate an ongoing seizure [4].

2. Current treatments for acute seizures

Benzodiazepines such as diazepam, midazolam, and lorazepam are considered the drugs of choice for the initial acute treatment of seizures. Shortly after the introduction of diazepam in 1963, the drug was found to be effective in the acute treatment of status epilepticus and became established as the standard of care [6–8]. Benzodiazepines have also been used off label by the oral, nasal and buccal routes for the treatment of ARS [9]. The first product approved in the United States for the treatment of breakthrough seizure clusters was diazepam rectal gel (Diastat®), which gained approval in 1997. A second product for the treatment of ARS, midazolam nasal spray (Nayzilam®), was recently approved in the United States. In the United Kingdom and elsewhere in the world, oromucosal midazolam for buccal administration [Buccolam® (midazolam hydrocholoride), Epistatus® (midazolam maleate)] has been approved for prolonged acute convulsive seizures.

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https://doi.org/10.1016/j.yebeh.2019.106537

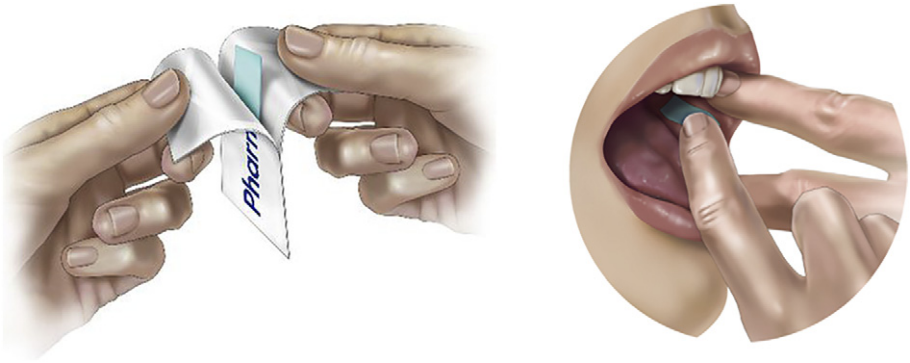

Fig. 1. Buccal film packaging and placement to the buccal mucosa inside the cheek.

Currently available products for the treatment of ARS and acute convulsive seizures have significant limitations. Rectal administration is unwieldy, may be embarrassing for patients and caregivers, and use may be restricted by social and legal constraints [4], and intranasal administration is often poorly accepted by patients, which can negatively impact compliance [10]. Most oral tablet forms of benzodiazepines such as lorazepam, diazepam and clonazepam must be swallowed with water and this is only feasible when the patient is awake and alert. Some sublingual or buccal dosage forms may also require patient cooperation. Lorazepam in an orodispersible tablet form (Temesta Expidet®) has been used sublingually in the treatment of acute seizures in children, but it and other available oral dosage forms may not act as rapidly as rectal diazepam [11].

3. Diazepam buccal film

A buccal soluble film formulation of diazepam (DBF; Libervant™, Aquestive Therapeutics) is under development that has several favorable characteristics and overcomes many of the disadvantages of other nonparenteral dosage forms used for acute seizure treatments (Fig. 1). The thin film, which is less than the size of a postage stamp, is affixed to the buccal mucosa inside the cheek. Placement can be either by the patient or by a caregiver. Diazepam is absorbed transbucally and is also swallowed, so that a portion of the dose is transported to the stomach and absorbed by the small intestine. The polymer hydroxypropyl methylcellulose is used to hold diazepam and excipients in a uniform distribution throughout the film. Because of the uniform distribution, the dose can easily be adjusted by cutting the film. The film has a mucoadhesive surface so that it adheres to the buccal mucosa. It begins to dissolve immediately on application to the mucosa releasing diazepam.

4. Studies in healthy volunteers

In studies with fasted healthy male volunteers, DBF doses of 5 mg to 15 mg exhibited rapid absorption and linear dose-proportional pharmacokinetics (Figs. 1 and 2) [12,13]. By contrast, diazepam rectal gel showed sublinear dose-proportional pharmacokinetics [13]. Recent studies in animal models indicate that plasma diazepam concentrations in the range of 70 ng/mL are associated with an elevation in seizure threshold [14]. At 15 min after application to the buccal mucosa, the mean plasma concentration following a 15-mg DBF dose exceeds levels in this range.

5. Studies in subjects with epilepsy

A study was conducted in adult male and female patients with epilepsy to determine if changes in the oral environment or other

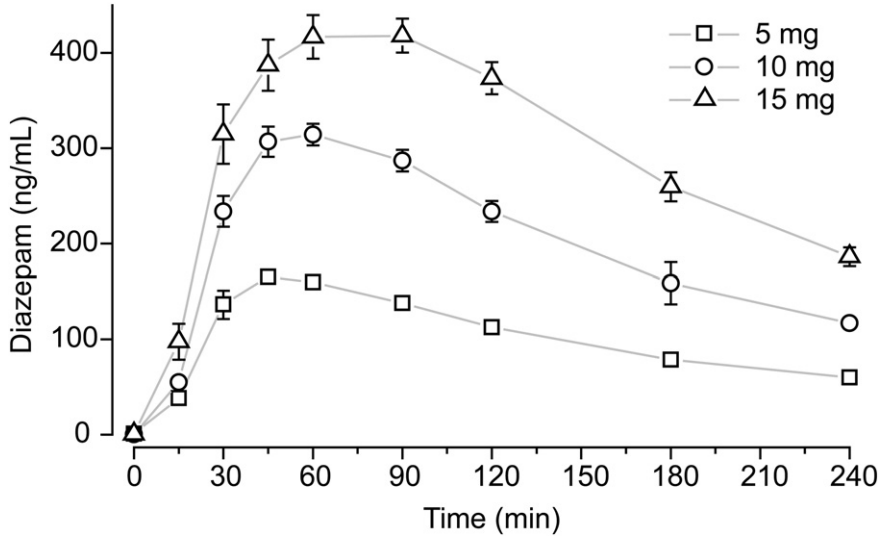

Fig. 2. Plasma diazepam concentrations in a single-dose, randomized, open-label, three-period, crossover study of diazepam buccal film (DBF) 5 mg, 10 mg, and 15 mg in 30 healthy adult male volunteers under fasting conditions. Thirty healthy adult males ages 18–55 years, body weight 83.5 ± 11.4 kg, and BMI 26.7 ± 2.2 kg/m^2 (mean ± S.D.), were administered single DBF doses containing 5-mg, 10-mg, or 15-mg diazepam under fasting conditions in an open-label, 3-period, randomized sequence crossover study with 21-day washout between treatments. Each subject received at least one DBF dose. Data points represent the mean ± S.E.M. of 25 to 30 plasma concentration measurements during the 4-h period after dosing. Error bars are not shown when they are smaller than the size of the symbols.

Table 1
Pharmacokinetic parameters obtained following administration of 12.5 mg DBF in adults with epilepsy.

Parameter	Interictal (A)	Periictal (B)	Ratio B/A (%)	90% CI (%)
C_{max} (ng/mL)	190.3	180.0	95.5	73.3–121.9
AUC_{0-4h} (h·ng/mL)	483.8	433.3	89.6	69.2–115.9
T_{max} (h)	0.77	0.53		

Pharmacokinetic parameters were derived from a single-dose, crossover study in which plasma samples for determination of diazepam concentrations were drawn at various times up to 4 h after administration of 12.5-mg DBF either when no seizure activity had been observed in the preceding 3 h (interictal) or within 5 min of a seizure (periictal). The study subjects were 35 adult men and women ages 17–65 with poorly controlled tonic–clonic seizures or focal seizures with impaired awareness. Patients were excluded from analysis if both treatments were not completed (4 subjects), critical time points were missing (6 subjects), predose diazepam concentrations were >5% of the subsequent C_{max} (2 subjects), or DBF was administered in a manner contrary to instructions (5 subjects). C_{max} and AUC_{0-4h} values are geometric means; T_{max} values are median values. 90% geometric confidence interval (CI) values were determined using ln-transformed data. Difference in T_{max} is not significant, $p = 0.5708$ (Wilcoxon signed-rank test). Values shown represent data from 18 evaluable subjects. AUC_{0-4h}, area under the plasma concentration-time curve from 0 to 4 h after dosing; C_{max}, maximum plasma drug concentration; T_{max}, time to reach maximum plasma concentration. From Rogawski et al. [15].

physiological changes that occur during a seizure impact diazepam absorption [15]. The study had a crossover design in which subjects received a single 12.5-mg DBF dose during two visits separated by no less than 14 days. In one of the visits, which was in the epilepsy monitoring unit (EMU) setting, DBF was dosed within 5 min of a seizure, referred to as "periictal dosing." In the other visit, DBF was dosed when no seizure had been observed in the preceding 3 h, referred to as "interictal dosing." Plasma samples for diazepam determination were drawn at intervals following dosing. As shown in Table 1, there was no significant difference in the exposures to diazepam in the interictal and periictal periods, demonstrating adequate performance of DBF even when administered to the buccal mucosa in the period immediately after a seizure. The straight-line interpolated C_{max} value for a 12.5-mg DBF dose in fasted healthy volunteers based on the data presented in Fig. 3

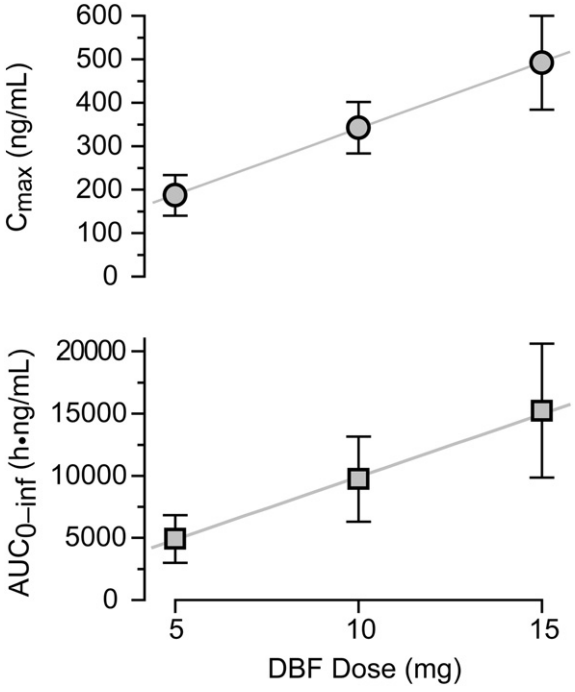

Fig. 3. Dose-proportional pharmacokinetics of diazepam buccal film (DBF) in healthy adult males. Data points represent mean ± S.D. maximum plasma concentration (C_{max}) and extrapolated area under the concentration-time curve from time zero to infinity (AUC_{0-inf}). Best fit straight lines show that both values increase linearly with dose. Same study as in Fig. 2.

Table 2
Usability of DBF in adults with epilepsy.

Outcome	Interictal (A)	Periictal (B)
Successful placement of film	33 (100%)	33 (100%)
Required more than 1 film placement attempt	0 (0%)	2 (6.1%)
Spit or blew out film	0 (0%)	3 (9.1%)
Swallowed film	2 (6.1%)	1 (3.0%)

Results of usability evaluation from interictal-periictal crossover study described in Table 1. Values indicate number of subjects out of 33; percentages are given in parentheses. From Jung et al. [17].

is 417 ng/mL, which is substantially greater than the geometric mean C_{max} values obtained in the study with subjects with epilepsy. Diazepam is *N*-demethylated by CYP3A4 and CYP2C19, so that its clearance is increased by inducers of these isozymes [16]. The lower than expected C_{max} value obtained in subjects with epilepsy could be due in part to concomitant inducing antiseizure drugs taken by many of the subjects. There was also a reduced AUC_{0-inf} consistent with CYP induction. Additional as yet undefined factors could also play a role in the reduced mean C_{max} value in subjects with epilepsy, including an effect of food on the rate of drug absorption since subjects were not fasted.

6. Adverse effects and usability

Diazepam is a sedative-hypnotic agent. According to the Food and Drug Administration (FDA)-approved label, somnolence was observed in 23% of subjects dosed with diazepam rectal gel compared with 8% receiving placebo. In the interictal–periictal crossover study, 6% (2 of 35) of subjects exhibited somnolence in at least one of the treatment periods; somnolence was rated as severe in one subject. There were no serious adverse events related to study drug, and no patient withdrew because of an adverse event. In this study, DBF was successfully placed on the first attempt in most subjects (Table 2). Occasionally the film was not placed correctly on initial attempt, but this was readily corrected. Rarely subjects swallowed the film, which is not expected to markedly affect performance.

7. Crossover study with diazepam rectal gel

To further characterize the performance of DBF in patients with epilepsy a crossover study was conduced in 31 adult male and female patients who were dosed DBF according to a weight-based regimen with a maximum dose of 17.5 mg. The subjects were also dosed diazepam rectal gel (Diastat®) according to the weight-based regimen in the FDA-approved label. Because food can delay absorption of oral diazepam and reduce the C_{max} level, subjects were dosed within 30 min of the start of a moderate fat meal to provide an evaluation under challenging "real world" conditions. In this study, DBF performed equivalently to diazepam rectal gel. The geometric mean C_{max} value obtained with DBF was 204 ng/mL. However, DBF was more consistent than diazepam rectal gel inasmuch as 3 subjects exhibited low diazepam exposures (C_{max} < 70 ng/mL) with rectal gel whereas such low exposures were not observed in any subject when challenged with DBF. The median T_{max} value for DBF was 1.0 h whereas the median T_{max} for rectal gel was 0.52 h. It is noteworthy that therapeutic levels may be achieved before T_{max}. Variability in the data and uncertainty as to the required therapeutic level precludes a conclusion as to whether the onset of action of either treatment would tend to occur more rapidly.

8. Conclusions

Diazepam buccal film provides a convenient alternative to other benzodiazepine-based acute seizure treatments. With appropriate dosing, DBF results in diazepam peak levels and overall exposures that are similar to those obtained with the diazepam rectal gel legacy formulation. Moreover, DBF performs more reliably than diazepam rectal gel.

A rigorous pharmacokinetic study has demonstrated that recent seizure activity and the concomitant changes in the oral milieu do not affect DBF performance. Diazepam buccal film can be self-administered or alternatively a caregiver can administer DBF without cooperation of the subject. Application of DBF to the inner wall of the cheek avoids the teeth, so there is a low risk of a bite or damage to the teeth. Diazepam buccal film is a compact, easily carried, dosage form that could represent a versatile treatment for acute seizures and might be used in a variety of circumstances where other dosage forms are problematic.

Declaration of competing interest

Both authors have served as consultants to Aquestive Therapeutics. The company had no role in the decision to publish and did not participate in writing, editing and reviewing the manuscript. The authors received no specific funding for the work.

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