NEW NON-INTRAVENOUS ROUTES FOR BENZODIAZEPINES IN EPILEPSY: A CLINICIAN PERSPECTIVE

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ABSTRACT

Benzodiazepines (BDZs) represent first line treatment for the acute management of epileptic seizures and status epilepticus. The emergency use of BDZs requires timely administration and considering that most seizures occur outside of the hospital, there is a significant need for easy to use delivery methods that can be given quickly and safely by nonclinical caregivers. In addition, the ideal route of administration should be reliable in terms of absorption. In the US, rectal diazepam is the only licensed formulation, while in the EU rectal diazepam and buccal midazolam are currently licensed. However, both the rectal and buccal administration are not ideal as the absorption can be sometimes unpredictable. Several alternative routes are being explored and are currently under investigation. This is a narrative review of available data about delivery methods for BDZs alternative to the intravenous and oral routes for the acute treatment of seizures. Unconventional delivery options such as the direct delivery in the central nervous system or inhalers are reported. Available data shows that intranasal diazepam or midazolam and the intramuscular auto-injector for midazolam are as effective as rectal or intravenous diazepam. Head to head comparisons with buccal midazolam are urgently needed. In addition, the majority of trials focused on children and adolescents and further trials in adults are warranted.

1. Introduction

Benzodiazepines (BDZs) remain first-line agents for the acute management of convulsive seizures and status epilepticus [1,2] while their use in the long-term prophylactic treatment of epilepsy has been historically limited by two major problems: side-effects, especially sedation, and the high potential for tolerance [3]. According to the NICE guidelines, children, young people and adults with epilepsy should receive emergency care in case of prolonged (lasting more than 5 minutes) or repeated (three or more in an hour) convulsive seizures [4]. Diazepam (DZP), lorazepam (LZP) and midazolam (MDZ) are the most widely used drugs in both adults and children. They have different pharmacokinetic profiles [5,6] and are available in different pharmacological formulations [1,7] (Table 1). For many years, rectal diazepam has been a very popular rescue medication and still represents the only out of hospital treatment approved in the US, but this rout of administration is problematic and most of the time socially unacceptable, especially in adults [8]. In the EU, buccal midazolam is also licensed for this indication and is now a widely used treatment in the community for patients with prolonged or repeated convulsive seizures. However, this rout is also not ideal as the absorption can still be unpredictable and if the drug is swallowed, it will then be subjected to metabolism and first-pass effect (Table 2).

The emergency use of BDZs requires timely administration and considering that most seizures occur outside of the hospital, there is a significant need for easy to use delivery methods that can be given quickly and safely by nonclinical caregivers at home, school, work or any institution. In fact, initiating an IV infusion system can be challenging, requiring specially trained and competent personnel as well as various supplies. At the moment, several alternative routes are being explored and are currently under investigation. This is a narrative review of available data about non-intravenous delivery methods for BDZs in the acute treatment of seizures. References have been identified through Medline searches until June 2016 using the terms “epilepsy”, “benzodiazepines”, “acute repeated seizures”, “status epilepticus”, “clinical trial”. Additional publications were hand searched if relevant for the discussion.

2. Intranasal delivery

There are three distinct functional areas in the nasal cavity: the vestibular, olfactory and respiratory zones. Due to the rich vascularization, the olfactory and in particular the respiratory zone, with a total surface of approximately 145 cm2, may serve as an efficient absorption surface for topically applied drugs [9]. The intranasal administration of BDZs became rapidly attractive because the nasal cavity is easily accessible and the nasal absorption is not subjected to the hepatic first-pass effect [10][11]. In addition, the absorption through the cribriform plate can lead to a rapid increase in drug concentrations in the CSF as compared to other delivery methods and this is obviously crucial for a brain disorder like epilepsy [12]. However, the intranasal administration is limited by a number of factors: i) the extent of the nasal mucosa; ii) blood flow of the nasal mucosa; iii) potential mechanical drug

loss anteriorly and posteriorly (Table 2). For all these reasons, the delivering technology becomes crucial for an effective absorption. In fact, in case of liquid formulations or drops, the head of the patient should be maintained in a specific position in order not to lose the drug in the throat or outside the nasal cavity (i.e. the patient should be turned on back with head slightly hyperextended, if in wheelchair head back hyperextended). It is evident that this is not always possible during a convulsion especially if prolonged. For this reason spray or atomised pumps have been developed in order to reach the best mucosal distribution.

Clinical studies on the use of intranasal BDZs for the acute management of seizures are available for MDZ [13–22] and LZP [23,24] suggesting that, in both cases, the intranasal delivery is a potentially efficient alternative root of administration (Table 3) and ad hoc technologies are currently under investigation. In particular, there are two intranasal DZP formulations currently under development by Neurelis (10 mg) and Acorda Therapeutics (20 mg) and a MDZ intranasal formulation by Upsher-Smith Laboratories (2.5 mg, 5 mg, 7.5 mg) [10]. Intranasal MDZ is the one at the more advanced stage as it is already under Phase III while DZP studies are still in Phase I for Neurelis and Phase II for Acorda [10]. Pharmacokinetic data showed that absorption is more reliable and efficient than using the injectable solution but data in patients with epilepsy in "real life" settings are still lacking.

A number of trials compared intranasal MDZ with either rectal DZP or intravenous DZP [13-22] (Table 3). Available data suggests that intranasal MDZ is effective, safe and more efficient that rectal DZP in controlling seizure activity [7] (Table 3). In general terms, as compared to DZP, MDZ has the advantage of a faster absorption but the lower bioavailability and the shorter half-life may be potentially associated with an increased risk of recurrence [10]. Future studies comparing purpose-developed intranasal formulations of MDZ will be of interest.

Data about intranasal LZP are limited to two studies (Table 3) showing similar efficacy as compared to paraldehyde [24] and intravenous LZP [23]. However, paraldehyde is not a useful comparator as it is not generally considered first line agent and LZP is less lipophilic than MDZ, making it not ideal for intranasal delivery.

3. Buccal delivery

The buccal administration is another transmucosal route like the intranasal and rectal ones. It is, therefore, characterised by the same advantages such as a rapid absorption and no first-pass effect (**Table 2**). In addition, it has the advantage of an easier administration as compared to the intranasal and rectal roots. However, it is usually more suitable for drugs administered at small doses because if any part of the dose is swallowed that proportion should be treated as an oral dose and subject to liver metabolism (**Table 2**). MDZ is the most popular buccal formulation and has been investigated in a number of clinical trials [25–33], demonstrating to be more effective than rectal DZP in aborting seizure activity [34]. When compared to intravenous DZP the mean time for controlling seizures was shorter for intravenous DZP but, as it happens for intranasal MDZ, the mean time from initiation of

treatment to seizure control was shorter with buccal MDZ [29]. Buccal MDZ is currently approved in the EU for the treatment of prolonged convulsive seizures in children and adolescents. It is available as Buccolam® by Shire Services and Epistatus® by Special Products Limited. Buccolam® contains MDZ Hydrochloride and comes in pre-filled oral syringes while Epistatus® contains MDZ Maleate and comes in pre-filled syringes as well as a 5 ml (10 mg/ml) bottle with four syringes in the package. Suggested dosages range from 2.5 mg for patients aged between 6 and 12 months to 10 mg in patients aged more than 10 years.

No studies compared directly buccal and intranasal MDZ. An indirect comparison meta-analysis suggested no difference in efficacy and in the occurrence of serious adverse events between the two transmucosal formulations of MDZ [35]. Despite the limitations of an indirect meta-analysis, similarities are easy to explain. In fact, it is the same compound and the two roots of administration are both transmucosal, with the same pros and cons. In fact, as well as with intranasal MDZ, buccal MDZ is limited by the potential risk of seizure recurrence given the short half-life. However, head-to-head comparisons are needed as well as studies in adults.

4. Sublingual delivery

The sublingual delivery is another root of administration within the oral mucosal cavity. The buccal and sublingual roots are slightly different with the latter being considered more permeable and capable of producing an even more rapid onset of action [36] and this is based on the relative thickness and degree of keratinization of these tissues. In fact, although both of them are non-keratinized tissues, the sublingual mucosa is thinner than the buccal ones [36]. In this regard, it is important to point out that the drug should be administered in different areas of the oral cavity in the sublingual and buccal routes. Sublingual medications are given under the tongue while buccal medications should be placed towards the back of the mouth between the upper or lower molars and the cheek.

Although the sublingual delivery has a very good bioavailability, the absorption can be very slow [37] and the administration always requires the cooperation of the patient (Table 2). It appears, therefore, evident that the sublingual delivery is not ideal for patients having a convulsive seizure and this is further supported by the only published randomised controlled trial in 436 children showing that sublingual LZP is less efficacious than rectal DZP in controlling seizures [38].

5. Intramuscular auto-injection

Although the intramuscular root cannot be considered innovative, the development of new devices for the auto-injection of BDZs represents a novel delivery method permitting a timely treatment of epileptic seizures. Both intramuscular LZP and DZP are absorbed slowly while intramuscular MDZ exhibits a faster absorption (Table 1). In addition, the use of LZP

in non-hospital settings is limited by the need to be refrigerated. For all these reasons, studies on the intramuscular root focused on DZP and MDZ.

Interestingly, the first auto-injector device for DZP was developed by the U.S. Army in the early 1990s for the immediate treatment of soman-induced seizures [39]. A Phase I study investigating bioequivalence and dose proportionality showed that DZP 10 mg auto-injection in the anterolateral thigh was bioequivalent to DZP injected with a conventional syringe [40]. In addition, this study also suggested that the site of injection is important because the gluteus or the deltoid muscles may lead to inconsistent absorption. A specific device was developed by Pfizer and a double-blind, randomised, placebo-controlled Phase III study showed that DZP auto-injection is safe and easy to use with significant reduction in time to next seizure as compared to placebo but did not prevent hospitalisation or need for further medical care [41]. The open label extension study showed that 78% of injections resulted in no subsequent seizures or rescue during the post-dose follow-up period [42]. Head-to-head comparisons with buccal MDZ would be of great value.

A few studies suggested that intramuscular MDZ is as effective as intravenous diazepam in the acute management of seizures in children [43,44] but data on safety and efficacy of the auto-injector device for MDZ come mainly from the RAMPART study [45–47]. This double-blind, randomized, non-inferiority trial compared the efficacy of the intramuscular MDZ auto-injection with that of intravenous LZP for children and adults with epilepsy [46]. This study demonstrated that pre-hospital treatment with intramuscular MDZ was at least as effective as intravenous LZP with the advantage that intramuscular treatments can be given more quickly and reliably than intravenous treatments. A recent study showed similar figures in the paediatric population [47] but more that on the safety of the device and head-to-head comparisons are needed.

6. Unconventional routes

Historically, drug delivery has been an important research topic for clinical pharmacologists. Non-oral routes of administrations, apart from those already discussed, would include the skin and air ways (**Table 4**). It seems rather evident that transcutaneous administration is not particularly indicated in an emergency setting as the absorption is usually slow and unreliable. The implant of a device releasing BDZs subcutaneously may represent an interesting option but there is no data about such a technique.

A few delivery methods for BDZ though an inhalation route were developed many years ago, the first one through an aerosol [48] and a second one through a dry powder for pulmonary absorption [49]. However, no further studies are available on these two methods. A single-blind study from China investigated the effect of an aerosol of DZP and a mixture of Chinese herbs on epileptic auras showing a 90% response rate [50] but neither pharmacokinetic parameters were provided nor the concentration of DZP administered. This study was not subsequently replicated and did not lead to further controlled trials or the development of specific technologies.

Another potential route of administration would be the direct delivery in the central nervous system (CNS). A number of possible methods have been theorised (**Table 4**) and some of them are already available for some compounds other than BDZ [51]. For example, intrathecal baclofen is very well-known for the treatment of spasticity [52] but this route may not be ideal for antiepileptic drugs as the brain distribution is usually very limited. Local perfusion via an implanted catheter attached to a pump programmed to infuse medications after detection of a seizure may represent an interesting option and a proof-of-principal of this approach was already presented in an animal model of epilepsy 20 years ago [53]. However, this method is burdened by a number of potential limitations, such as the high risk of respiratory depression and infections. Drug wafers are another potential route for direct CNS delivery. They are made of a polymer matrix with interwoven drug, releasing the medication over a prolonged period of time from weeks to years. Although this approach may have a rational for chemotherapy in brain tumors [54], it is definitely not indicated for the delivery of BDZ in the acute management of seizures.

7. Conclusions

BDZs represent the first line treatment for the acute management of epileptic seizures. Rectal DZP and buccal MDZ are the only currently licensed formulations for BDZ apart from the usual oral and parental routes but both of them have disadvantages mainly related to unpredictable absorption. Data from the RAMPART study have clearly demonstrated the efficacy and safety of non-intravenous formulations of BDZ in the acute management of seizures and intramuscular MDZ showed to be as effective as intravenous DZP. A number of alternative methods are currently under investigation and results are promising for the intranasal delivery and the intramuscular auto-injection device. Pre-hospital rescue plans should be individualised on the basis of patient's needs, age, comorbidities potentially affecting absorption and distribution. Further studies are needed in order to establish efficacy and safety of these methods and to develop new potential delivery methods for BDZ in epilepsy.

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8.2 Conflicts of interest

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Table 1. Pharmacokinetics of diazepam, lorazepam and midazolam (data derived from[5,6][11][10][37]**).**

	Diazepam	**Lorazepam**	**Midazolam**
Volume distribution	0.8-1.4 L/Kg	0.8-1.3 L/Kg	4.2-6.6 L/kg
Elimination half-life	40-60 h	8-20 h	1.5-2.5 h
Clearance	0.5 mL/min/kg	0.7-1.2 mL/min/Kg	4-9 mL/min/kg
Protein binding	99%	90%	98%
Bioavailability	Intramuscular=100% Intranasal=70%-90% Rectal=80%-100%	Intramuscular=100% Intranasal=77% Sublingual=94%	Intramuscular = 91% Intranasal = 78%# Buccal = 74.5%
T max after single dose	Intramuscular=60min Intranasal=60-90 min Rectal = 30-75 min*	Intramuscular=80min Intranasal=30 min Sublingual=erratic (up to 120 min)	Intramuscular=20min Intranasal=10-15min Buccal=15-90min
Active metabolite	N-desmethyldiazepam, oxazepam	None	Alpha/hydroxy/midazolam

*absorption is faster in children and effective serum levels are reached in 5-10 min.

83% with spray; 50% with injection solution

Table 2. Advantages and disadvantages of non-intravenous delivery methods for benzodiazepines.

Delivery method	Advantages	Disadvantages
Intranasal	Ease to use Painless Avoid first pass metabolism Better bioavailability than rectal Socially acceptable	Need for a high concentration to achieve ideal dosing volumes Mucosal health impacts on absorption Need to an ad hoc technology (i.e. atomizer)
Buccal	Ease to use Painless Avoid first pass metabolism Better bioavailability than oral No ad hoc technology needed	Limited medications can be delivered in this fashion If swallowed convert to oral
Sublingual	Painless Ease to use	Extremely easy to swallow Compliance is needed
Intramuscular	Traditinal and well-known method Many medications available for this delivery method	Painfull Require training Variable onset of action and bioavailability Infection risk
Rectal	Minimal pain	Variable bioavailability Slow onset of action (sometimes erratic) Socially unacceptable Limited medications available for this delivery method

Table 3. Summary of clinical studies on alternative non-intravenous delivery methods for benzodiazepines in the acute treatment of epileptic seizures.

Route	Drug	Comparator	Endpoint	Pop	N pts	Results	Adverse events	Ref
Intranasal	LZP	IM-PAR	C	C	160	=IM-PAR	=IM-PAR	[24]
		IV-LZP	C	C	141	=IV-LZP	=IV-LZP	[23]
	MDZ	IV-DZP	TC	C	47	>IV-DZP	=IV-DZP	[21]
		R-DZP	C	C	45	>R-DZP	>R-DZP	[16]
		IV-DZP	TC	C	51	=IV-DZP	=IV-DZP	[20]
		R-DZP	TC	C	358	=R-DZP	=IV-DZP	[22]
		IV-DZP	TC	C	125	>IV-DZP	=IV-DZP	[19]
		R-DZP	TC	C	46	>R-DZP	<R-DZP	[13]
		IV-DZP	TC	C	70	<IV-DZP	=IV-DZP	[18]
		R-DZP	TC	A	21	=R-DZP	=R-DZP	[14]
		R-DZP	TC	C	124	=R-DZP	<R-DZP	[15]
Buccal	MDZ	R-DZP	TC	C	7	>R-DZP	=R-DZP	[30]
		R-DZP	TC	C	98	=R-DZP	=R-DZP	[31]
		R-DZP	TC	C	43	=R-DZP	=R-DZP	[32]
		R-DZP	C	C	177	>R-DZP	=R-DZP	[33]
		R-DZP	C	C	42	=R-DZP	=R-DZP	[26]
		IV-DZP	C	C	120	=IV-DZP	=IV-DZP	[29]
Sublingual	LZP	R-DZP	TC	C	436	<R-DZP	=R-DZP	[38]
Intramuscular auto-injection	DZP	Placebo	C*	C	234	>Placebo	=Placebo	[41]
	MDZ	IV-LZP	C	C-A	448	=IV-LZP[#]	=IV-LZP[#]	[46]

MDZ = midazolam; DZP = diazepam; LZP = lorazepam; PAR=paraldehyde; R = rectal; IV = intravenous; IN= intranasal; B= buccal; SL=sublingual; IM=intramuscular; TC=time to cessation; C (in Endpoint) =cessation; Pop=population; Pts = patients; C (in Pop) = children; A = adults; > superior than; < inferior than; = equal to; *Delaying the next seizure or rescue; [#]Non-inferiority trial

Table 4. Potential unconventional drug delivery methods for benzodiazepines.

Skin	Transcutaneous (patches) Subcutaneous (implants)
Inhalers	Aerosol Pulmonary inhalation
Direct CNS delivery	Intrathecal Local perfusion via implanted catheter Drug wafers

CNS = central nervous system