Overcoming the challenges of developing an intranasal diazepam rescue therapy for the treatment of seizure clusters

Narrator: [0:00] This podcast is presented and supported by Neurelis, Inc. It is provided for informational purposes only and is not intended to replace a discussion with a healthcare provider. All decisions regarding patient care must be made with a healthcare provider and consider the unique characteristics of each patient. This podcast discusses Valtoco® (diazepam nasal spray). Valtoco is indicated for the acute treatment of intermittent or stereotypic episodes of frequent seizure activity, also known as seizure clusters or acute repetitive seizures, that are distinct from a patient's usual seizure pattern in patients with epilepsy 6 years of age and older.

Here is some important safety information for Valtoco.

Warning: Risks from Concomitant Use with Opioids; Abuse, Misuse, and Addiction, and Dependence and Withdrawal reactions. Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs for patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.

The use of benzodiazepines, including Valtoco, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse of benzodiazepines commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes. Before prescribing Valtoco and throughout treatment, assess each patient's risk for abuse, misuse, and addiction.

The continued use of benzodiazepines may lead to clinically significant physical dependence. The risks of dependence and withdrawal increase with longer treatment duration and higher daily dose. Although Valtoco is indicated only for intermittent use, if used more frequently than recommended, abrupt discontinuation or rapid dosage reduction of Valtoco may precipitate acute withdrawal reactions, which can be life-threatening. For patients using Valtoco more frequently than recommended, to reduce the risk of withdrawal reactions, use a gradual taper to discontinue Valtoco.

Please listen to additional important safety information for Valtoco presented at the end of this podcast.

Welcome to the Neurelis Medical Affairs podcast series. These podcasts offer an opportunity to hear directly from the authors about recently published articles discussing strategies for the treatment of seizure clusters in patients with epilepsy. The series can be accessed at neurelismedicalaffairs.com or through a Neurelis Medical Science Liaison.

[2:40] In this episode, we hear from Dr. James Cloyd from the University of Minnesota, College of Pharmacy in Minneapolis. Dr. Cloyd recounts the challenges and successes of efforts to develop a diazepam nasal spray as a rescue therapy for frequent seizure activity among patients with epilepsy. Today's discussion is based on a critical review and invited commentary by Dr. Cloyd and colleagues published in the journal *Epilepsia* in 2021. The paper is entitled, “Overcoming the Challenges of Developing an Intranasal Diazepam Rescue Therapy for the Treatment of Seizure Clusters.”

[3:15] Welcome, Dr. Cloyd, and thank you for joining us today. Let's jump into this discussion with some background. Benzodiazepines are the foundation of rescue therapy in seizure clusters due to their rapid onset of action, high efficacy, and good tolerability.

Intravenous *[IV]* delivery of rescue therapy is frequently used for the administration of seizure rescue therapy in a hospital setting, but it must be given by trained medical personnel. However, seizure clusters most often occur outside the hospital setting. Dr. Cloyd, perhaps you can first provide some context for the clinical research efforts taken to create rescue therapies for use in the community.

Cloyd: [3:52] As you mentioned, intravenous delivery of benzodiazepine rescue therapy is the route of choice when and where it's possible. But this mode of therapy faces obstacles, including the impracticality of non-medical personnel providing this therapy, and that there can be a delay in starting drug administration due to difficulties in establishing an IV line, setting up IV tubing, and the recommended infusion time of several minutes required for the benzodiazepines used for rescue therapy. As a consequence, over the past three decades, formulations for other delivery routes had been developed that had been designed to overcome the challenges associated with IV therapy.

These alternatives include rectal diazepam, which has been available in the US as a rescue therapy for 25 years. Other formulations include two approved intranasal *[IN]* formulations for seizure clusters, and an intramuscular *[IM]* formulation of midazolam to treat status epilepticus. Additionally, off-label intranasal administration of injectable formulations or buccal administration of oral liquid formulations have been used. More recently, buccal and intrapulmonary formulations are under development. A systematic review and meta-analysis show that some benzodiazepine rescue therapies, using certain routes of administration, have a faster time to administer the drug, faster or similar time to seizure control—it is largely related to the fact that it does take some time to initiate IV therapy—and similar rates of adverse effects when compared to IV administration. These factors all indicate that alternative routes of administration hold promise as safe and effective treatments for seizure clusters.

Narrator: [5:46] That's very interesting. Dr. Cloyd, before we discuss different approaches taken to develop new modes of administration of benzodiazepines for rescue therapy, perhaps we can first explore the features of an ideal rescue therapy for use outside of the hospital setting.

Cloyd: [6:01] The ideal features of a rescue therapy include administration needs to be quick, because you need to interrupt the seizure cluster as fast as possible; it needs to be easy so that non-medical personnel can administer the therapy; and there should be little, if any, discomfort to the patient. It should be possible for the patient, his or herself, a family member, or a caregiver, care partner, school nurse, or emergency medical personnel to administer the formulation. And the route and formulation should offer rapid and consistent absorption and high consistent bioavailability. Now, this is crucial because what you want to do is get the same response time after time within a patient and across patients.

The therapy product should have very good efficacy, and because several of the routes have limited volume capacity, the product needs to have high potency. In other words, a small dose and a small volume is needed to produce the effect. The product should have a wide therapeutic index and a sufficient duration of action. And by that, I mean the action should be long enough to prevent recurrence, but short enough so that patients can return to activities of daily living without the risk of seizure occurrence. The formulation should have a good safety profile and the ideal product needs to have information for pediatric and adult dosing and have appropriate dosage strengths to accommodate young and older patients.

Narrator: [7:33] Thank you, Dr. Cloyd, for providing that context. Perhaps you can tell us more about the other routes of administration for benzodiazepine rescue therapy you mentioned earlier.

Cloyd: [7:43] Although the approval in 1997 of a rectal diazepam gel was met with considerable enthusiasm, the reality is it has limited social acceptability, especially among adults and older children. The net result of that is that some individuals would actually decline the therapy, even though it would have benefited them. For this reason, and soon after the approval of diazepam rectal gel, researchers, including our group, initiated work on the development of intranasal formulations. This work eventually led to FDA approval of two intranasal formulations. In 2019, intranasal midazolam was approved for the acute treatment of intermittent stereotypical episodes of frequent seizure activity that are different from the patient's usual pattern; in short, seizure clusters. And this was approved in patients with epilepsy age 12 years of age and older.

A year later, in 2020, diazepam nasal spray was approved with a similar indication, but allowed for patients as young as six years of age to get the medication. Intramuscular midazolam has been approved for use in adults with status epilepticus. However, it must be administered by a trained healthcare professional. Hence, it has limited use at home, work, or a school. Several benzodiazepine oral formulations, such as solutions and disintegrating tablets—administered in the oral cavity—are used off-label as rescue therapies. And currently, a buccal diazepam film and an intrapulmonary alprazolam formulation are in development. Each of these routes has advantages and disadvantages. And for this part of our interview, I wanted to focus on some of the limitations.

Depending upon the benzodiazepine and the route, the formulation may result in relatively slow absorption or poor or inconsistent bioavailability. For example, when

using diazepam rectal gel, there's wide interpatient variability in the absorption of the drug. In fact, in some of our studies we found that no drug was absorbed in certain circumstances. Also, there can be relatively slow absorption with buccal, IM, and IN lorazepam due to its physical chemical properties. And there's intermediate bioavailability with intranasal midazolam. Another limitation with some of these routes is pain or discomfort during administration. For example, there is pain associated with IM administration; the risk of a biting injury with buccal administration of a therapy; and disagreeable taste, which can occur when drug is administered intranasally and swallowed.

Also, for some of these routes of administration, there is a need for patient participation, but such participation can be compromised because of the seizure cluster. So for example, when getting a buccal treatment, one should not swallow the solution; rather, it should be allowed to be absorbed into the buccal tissue. And also, with the intrapulmonary delivery system under development, the patient needs to create a seal around the inhalation device, and this often can be difficult for a person with seizure clusters.

Narrator: [11:09] Let's focus on intranasal formulations. Dr. Cloyd, how does the nasal spray formulation align with the criteria of an ideal rescue therapy?

Cloyd: [11:18] Among the options I've just discussed, nasal drug delivery has the potential to meet most, if not all, of the requirements of an ideal rescue therapy. These include the fact that it's noninvasive and it is easy to access the site of administration. Intranasal drug delivery can offer rapid, high, and consistent absorption, allowing for the possibility of a rapid onset of action. It avoids first-pass metabolism. And by that, I mean that by

bypassing the intestinal tract and the liver, a much higher fraction of the dose can be absorbed.

Nasal drug delivery does not require patient cooperation and it is socially acceptable. However, the development of intranasal benzodiazepine formulations must consider the anatomy and physiology of the nose, as well as the physical, chemical, and pharmacokinetic properties of benzodiazepines.

Narrator: [12:12] We've talked about intranasal formulations. What about the site of delivery in the body, the nose, and nasal cavity? What are the features of the nasal cavity that are advantages, but also specific challenges for intranasal delivery of benzodiazepines?

Cloyd: [12:28] Some of the advantages include the fact that, although the nasal cavity itself is relatively small, it has a relatively large, wide absorptive surface area because of the microvilli, which are small, finger-like protrusions on the surface of the epithelial tissue, and a rich vasculature that facilitates drug absorption. Further, the olfactory and trigeminal nerve pathways that connect the nasal cavity to specific areas of the brain can potentially permit direct nose-to-brain drug delivery.

However, there are some factors that limit the rate and extent of absorption. And these include the fact that there is limited volume capacity in the nasal cavity; that the mucociliary clearance that occurs because of the formation of mucus and ciliary movement of the nasal microvilli result in movement of the drug into the esophagus. Or it can leak out to the front of the nose. And lastly, there can be poor or slow diffusion across nasal membranes, which is particularly relevant in the case of lorazepam, which has relatively low lipid solubility.

Narrator: [13:40] Thank you. Intranasal delivery does offer several advantages. Now, let's turn our attention to the specific drug component of the therapy, that is, the benzodiazepine. What are the specific challenges related to delivering benzodiazepines as rescue therapy for seizure clusters through this route?

Cloyd: [13:57] When giving intranasal benzodiazepines, the product needs to be a liquid formulation, so as to support rapid absorption. The product must be highly potent, so as to deliver a therapeutic dose in a small volume. It's known that about 100 microliters per nostril is the ideal volume to avoid leakage or swallowing, thus a total of 200 microliters and no more should be administered when the drug is given. Hence, the solubility of the drug must be high enough to provide a therapeutic dose in a limited volume.

These considerations make it a challenge for benzodiazepines because, as a class, they are hydrophobic with poor water solubility. Strategies to address this include manipulation of pH and use of surfactants, polymers, or organic solvents, such as ethanol. Nasal irritation, however, can occur with some of these strategies, which can result in poor tolerability and reduce patient acceptance of the medication. Another challenge in designing an intranasal formulation is the need for consistent and high bioavailability so as to ensure reliable response with every treatment.

Narrator: [15:11] As was mentioned earlier, two intranasal benzodiazepine rescue therapies have been approved for use in the United States. Intranasal midazolam was approved in 2019. What was the history of the development of this formulation?

Cloyd: [15:25] Early efforts of finding an alternative to rectal diazepam employed off-label administration of intranasal midazolam. But this was poorly tolerated and required a large volume. The product that was typically used was the injectable formulation of midazolam

at a strength of 5 mg/mL, which had a pH of 3–3.6. It was off-label use and was done by drawing up the needed volume, typically, at least 1 mL, then attaching an atomizer to the syringe tip. And keep in mind, the ideal volume for an intranasal dose is far less than that, about 200 microliters.

Aside from the significant discomfort to the pH, there were lower rates of successful administration due to the high volume dispensed, which can result in portions of the dose being swallowed or dripping out and not being delivered into the systemic blood flow. The intranasal midazolam product eventually brought to market for patients 12 years and older is a highly concentrated aqueous solution using several organic solvents to increase solubility while maintaining a pH of 5–9. However, pharmacokinetic studies have shown it to be a moderate and variable absorption—the product label actually indicates about 44% of a dose is absorbed—and it has a half-life of 1–6 hours.

In the development of this intranasal midazolam formulation, two phase 3–type studies were carried out. Today, I'm going to briefly mention the larger of these two studies. It was a phase 3, randomized, double-blind, placebo-controlled study with 5 milligrams of a nasal spray used for seizure clusters. The enrollment was 201 individuals 12 years of age or older with a history of seizure clusters. After giving an open-label test dose, the patients entered the blinded component of the study. The primary endpoint of the study was seizure termination within 10 minutes with no recurrence from 10 minutes to 6 hours thereafter.

Treatment success in the primary study was 54% as compared to the placebo group of 34, and this was statistically significant. 13 of the midazolam patients discontinued because of treatment-related emergent adverse events. The safety profile for the patients in this study showed that about 27% of the treated group, and about 22% of the patients

receiving placebo, had a treatment-emergent adverse event. The most common were a report of nasal discomfort in about 12.5% of the patients; followed by somnolence at about 9%; and then headache at about 6%.

Narrator: [18:17] Thank you for that summary. Switching to the other FDA-approved product, diazepam nasal spray is the most recently approved intranasal rescue therapy. It used a different approach to formulation. Could you tell us about the unique composition of diazepam nasal spray and the early phase pharmacokinetic findings for the therapy?

Cloyd: [18:36] Yes. This formulation employs two approaches that are unique to the available rescue therapies. The first is the inclusion of a compound known as Intravail. Intravail works to enhance nasal absorption by transiently and reversibly loosening joint junctions between cells, allowing for greater diffusion of the drug molecules across the nasal epithelial tissue. It also includes vitamin E, which is used as a non-aqueous, non-toxic, non-irritating solvent. Vitamin E also protects against inflammation and damage to the sino-nasal mucosa.

Early phase studies compare diazepam nasal spray with IV diazepam, the rectal gel, and the oral tablet in healthy volunteers. These studies showed that the absolute bioavailability of diazepam nasal spray is 97%, which is essentially the highest among the rescue therapies. It has a comparable time to maximum concentration and less variable maximum concentration and area under the curve as compared with rectal gel. Lastly, in these healthy volunteer studies, there was a lower rate of treatment-emergent adverse events for the nasal spray, as compared with the other routes of administration, including rectal gel and oral diazepam.

Diazepam nasal spray was also studied in patients with epilepsy. The investigators found that seizure conditions, that is ictal, peri-ictal or interictal, did not have an impact on the drug's pharmacokinetics. Treatment-emergent adverse events were reported in approximately 30% of the patients, but notably, only 14% had a treatment-related adverse event.

Narrator: [20:26] Diazepam nasal spray was evaluated in a large, long-term, phase 3 safety study with final results published in 2021. We discuss study results in detail with Dr. James Wheless in another podcast that is available at neurelismedicalaffairs.com or through the Neurelis Medical Affairs team. For this discussion, Dr. Cloyd, can you provide a summary of the study findings for our listeners?

Cloyd: [20:48] Yes. The so-called 05 study was a phase 3, repeat-dose, open-label, long-term, safety study of diazepam nasal spray in patients with epilepsy who had seizure clusters despite use of a stable regimen of anti-seizure medications. Inclusion criteria for this study were broad: it involved patients as young as 6 up to age 65 years; those with a history of status epilepticus were permitted, as was concomitant use of benzodiazepines. Individuals with seasonal allergies were also permitted into the study. The study included a safety population of 163 patients. Among these, 45 were children aged 6 to 11; 33 were adolescents aged 12 to 17; and 85 were adults older than 18, which indicates that the enrollment had a good distribution of patients across all age groups.

In the final analysis, more than 80% had at least a year of exposure to diazepam nasal spray with a total of 3,853 seizure clusters treated over the course of the study. The results of this study showed that the most common treatment-related treatment-emergent adverse event was nasal discomfort, which occurred in only 6% of individuals and were considered mild or moderate and transient. Notably, there were no cases of respiratory

depression; there was no discontinuation of treatment due to treatment-related adverse events. And this, the investigators concluded, indicated a safety profile of diazepam nasal spray which was consistent with the established profile of rectal diazepam.

As an exploratory endpoint, a second dose, given within 24 hours, was used as a proxy for effectiveness. The second dose was administered in 13% of the 3,853 seizure cluster episodes, indicating that the initial dose was quite effective. The results of this study may be applicable to a broad patient population, including children as young as 6 years, people taking concomitant benzodiazepines, or those with a history of status epilepticus or seasonal allergies.

Narrator: [23:08] Thank you. Dr Cloyd. Before we end, do you have any final thoughts that you'd like to share with our listeners?

Cloyd: [23:15] Yes. The introduction of diazepam rectal gel formally launched out of hospital treatment of seizure emergencies, now known as rescue therapy. In the ensuing 25 years, remarkable advances have been made in the development of rescue therapies for seizure emergencies. This includes the approval of two new intranasal benzodiazepine formulations for the acute treatment of seizure clusters. These products offer opportunities in terms of patient acceptance, ease of administration by non-medical caregivers, early treatment, and the potential for rapid onset of response.

There are, however, differences between the products, including the composition of the formulations, bioavailability, half-life, pediatric indication, and available dosage strengths. Nasal administration of diazepam provides an important treatment option, which supports the goal of reducing seizure cluster episodes and emergency department visits while improving patient and family quality of life.

Narrator: [24:19] Thank you, Dr. Cloyd, for speaking with us today and sharing your expertise. We very much appreciate it. And thank you to our audience for joining this conversation. Before we conclude, here's some important safety information about VALTOCO.

Narrator: [24:31] Valtoco is contraindicated in patients with:

- Hypersensitivity to diazepam and
- Acute narrow-angle glaucoma

Benzodiazepines, including Valtoco, may produce Central Nervous System (CNS) depression. Caution patients against engaging in hazardous activities requiring mental alertness, such as operating machinery, driving a motor vehicle, or riding a bicycle, until the effects of the drug, such as drowsiness, have subsided, and as their medical condition permits.

The potential for a synergistic CNS-depressant effect when Valtoco is used with alcohol or other CNS depressants must be considered, and appropriate recommendations made to the patient and/or care partner.

Antiepileptic drugs (AEDs), including Valtoco, increase the risk of suicidal ideation and behavior. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or unusual changes in mood or behavior.

Benzodiazepines, including Valtoco, can increase intraocular pressure in patients with glaucoma. Valtoco may only be used in patients with open-angle glaucoma only if they are receiving appropriate therapy. Valtoco is contraindicated in patients with narrow-angle glaucoma.

Valtoco is not approved for use in neonates or infants. Serious and fatal adverse reactions, including “gasping syndrome”, can occur in neonates and low-birth-weight infants treated with benzyl alcohol-preserved drugs, including Valtoco. The “gasping syndrome” is characterized by central nervous system depression, metabolic acidosis, and gasping respirations. The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known.

The most common adverse reactions (at least 4%) were somnolence, headache, and nasal discomfort.

Diazepam, the active ingredient in Valtoco, is a Schedule IV controlled substance.

Please read full Prescribing Information, including Boxed Warning, for additional important safety information—available at www.valtoco.com .

Narrator: [16:29] To close, we would like to say thanks again, Dr. Cloyd. We would also like to say thank you to our audience for joining this conversation. For more information on this particular article, please contact your Neurelis Medical Science Liaison directly or the Neurelis Medical Affairs team at medinfo@neurelis.com.

This podcast is one of a series. To access the series, as well as other resources for your patients with seizure clusters, visit NeurelisMedicalAffairs.com.