Clinical Pharmacokinetics and Drug Safety of Valtoco - Review for Nasal Administration of Benzodiazepine and Safety Analysis as Treatment for Seizure Clusters

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Abstract: A seizure is defined as a "sudden, uncontrolled electrical disturbance in the brain." [1]. Often, seizures can cause changes in behavior, movement, feelings, and levels of consciousness. Seizures are more common than you think and in the United States there are over 3.4 million people with epilepsy with around 200000 new patients being diagnosed with epilepsy each year. Even though chronic, daily oral medications are available to control epilepsy, there remains a large amount of people (around 170000) at risk for episodes of frequent seizure activity known as cluster seizures. This population represents a significant unmet need for patients of the epilepsy community. Valtoco was recently FDA approved on January 10, 2020, and is a solution to this unmet need. It is a benzodiazepine nasal spray that is used as a short-term active treatment for intermittent, stereotypic episodes of frequency seizure activity also known as seizure clusters. The seizure pattern must be distinct from the patient's usual seizure pattern. The mechanism at which nasal benzodiazepines are currently unknown but it appears to function by enhancing receptor activity of gamma-aminobutyric acid which functions as the major inhibitory neurotransmitter of the central nervous system. This paper will analyze and go through the mechanism and functions of Valtoco specifically, analyze the safety and side effects of the drug.

1. Introduction

Seizures are often induced by a sudden burst of neural activity in which physical symptoms of a seizure will occur. In most scenarios, a seizure is the coupling of excitatory overload and the decreased inhibition of neuronal discharge. There are also scenarios where a seizure may be induced by infection, injury, substance use or hypoxia [2]. By understanding the mechanism behind a seizure, epileptic drugs can be developed for reducing intensity of symptoms.

Valtoco is a prescription medication used for short term relief of episodes of frequency seizure activity or seizure clusters for patients 6 years old and up. Seizure clusters are a bit different from classic seizures in that a patient will undergo increased seizure activity and suffer one or more seizures in the span of 24 hours. The fundamental mechanism behind seizure clusters is still somewhat unknown as seizures inherently have the capacity to induce more seizures. Traditionally, rectal diazepam gel has been the common medication for treating seizure clusters. Valtoco combines the already established diazepam treatment with a novel formulation of technology. It allows for a small and discreet nasal spray that can be applied from home without medical care partners and on a ready-to-use basis that does not have a daily dosing schedule. Clinical research is especially important as the drug contains federally controlled substances such as benzodiazepine that can lead to dependence or be abused. Three main clinical studies were conducted, one to investigate the

efficacy of diazepam treatment on seizures and two, to investigate the safety of Valtoco for the patient demographic.

The exact mechanism of diazepam is still not fully understood amongst the scientific community. However, some researchers believe that diazepam involves the potentiation of GABA neurotransmission resulting from the binding of benzodiazepine site of the GABA receptor (FDA). Some other researchers also presume that perhaps diazepam and other influence the central nervous system and allow for potentiation of the inhibitory effect of gamma-aminobutyric acid on neuronal transmission [3].

Valtoco presents a novel intranasal drug delivery device in which it uses a highly lipophilic molecule of diazepam that can easily cross the blood-brain barrier and also has significant half-life in which high levels can be sustained within the patient's plasma. In addition to diazepam, Intravail and Vitamin E are incorporated into the device. Intravail is non-toxic substance that is designed to increase reliability and bioavailability of nasal drug delivery. It increases drug absorption across the nasal mucosa by increase permeability of cell membranes and temporarily allows drug to pass through by loosening the tight junctions across the membrane. Vitamin E functions as the primary solvent that coats the nasal cavity [4] and allows a small volume of the liquid to contain adequate amounts of drug concentration.

2. Clinical Pharmacokinetics

2.1 DIAZ.001.01: A Three-Period, Three-Treatment, Six-Sequence Randomized Crossover Study of the Bioavailability and Pharmacokinetics of Diazepam After Intranasal and Intravenous Administration to Healthy Volunteers Under Fasted Conditions

To assess the bioavailability and pharmacokinetics (PK) of diazepam after intranasal administration of suspension and solution formulations compared to intravenous (IV) administration to healthy volunteers under fasted conditions, researchers conducted an open-label, randomized, three-treatment, three-period, six-sequence crossover study to evaluate the PK of diazepam after administration of an intranasal suspension (NRL-1.A), 10mg, or an intranasal solution (NRL-1.B), 10mg, compared to 5mg administered by IV [5].

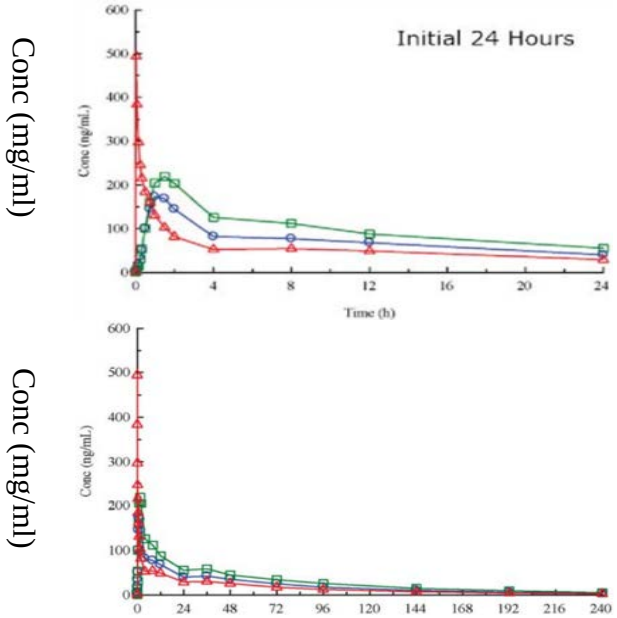


Figure 1. Arithmetic Mean Plasma Diazepam Concentrations (Initial 24 Hours)—Linear Axis

Diazepam was extensively absorbed after intranasal administration of non-aqueous solution (NRL-1.B) with an absolute bioavailability of 97%. The absolute bioavailability 67% from an aqueous suspension (NRL-1.A) and with an with a median Tmax of 1.5 hours and 1 hour respectively.

2.2 DIAZ.001.02: Pharmacokinetics, Dose Proportionality, and Comparison of One and Two Doses of Diazepam after Administration of NRL-1 to Healthy Volunteers

To assess the pharmacokinetics and dose proportionality of diazepam after single intranasal doses of NRL-1 to healthy volunteers under fasted conditions, to compare the pharmacokinetic parameters of diazepam after one and two dose treatments of NRL-1, and to assess the safety and tolerability of diazepam after intranasal administration, researchers conducted a study giving subjects single doses of 5, 10, and 20mg of NRL-1 in the first three treatment periods followed by two 10mg doses of NRL-1 4 hours apart, and analyze the diazepam plasma concentrations [5].

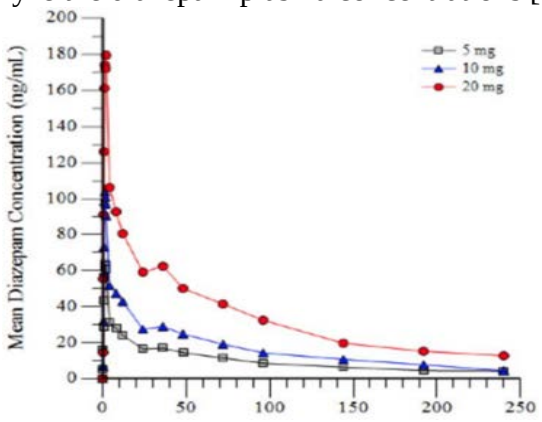


Figure 2. Mean Plasma Concentration-Time Profiles of Diazepam (Single Dose) Sorted by Dose: Linear Scale

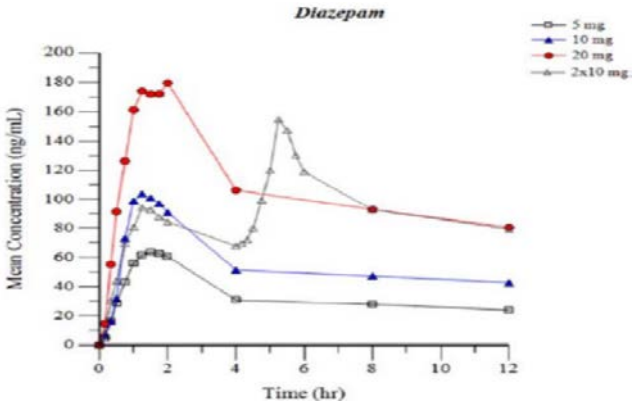


Figure 3. Diazepam Plasma Concentration versus Time Curves Initial Part

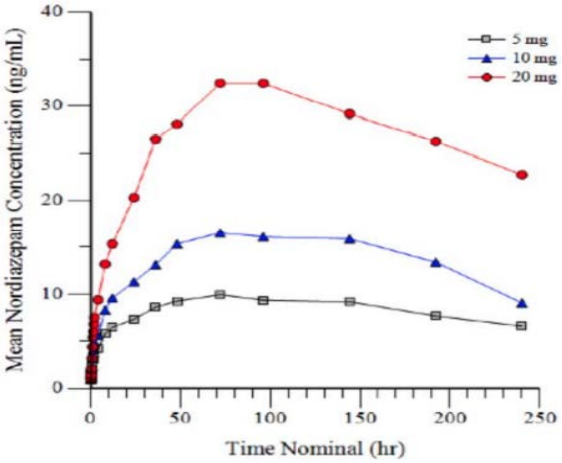


Figure 4. Mean Plasma Concentration-Time Profiles of Nordiazepam (Single Dose) Sorted by Dose

Diazepam and nordiazepam exposure increased proportionally with the increase of diazepam nasal spray dose from 5mg, 10mg, to 20mg

2.3 DIAZ.001.03: A Three-Period, Three-Treatment, Six-Sequence Randomized Crossover Study of the Bioavailability and Pharmacokinetics of Diazepam After Administration of NRL-1, Diastat®, and Oral Valium to Healthy Volunteers (DIAZ.001.03)

The researchers conducted a study to assess the comparative bioavailability of diazepam after intranasal and oral administration in healthy volunteers, they dosed subjects 51 to 75kg of weight 15mg of diazepam and 76 to 111kg of weight 20mg of diazepam. Then they collected their blood samples for 240 hours after dosing [5].

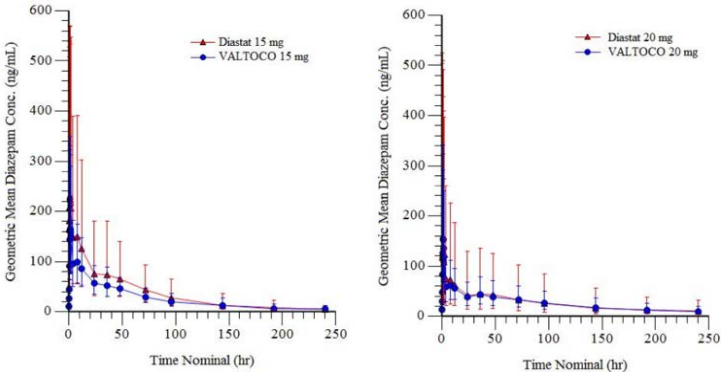


Figure 5. Mean Plasma Concentration-Time Profiles of Diazepam, 15 and 20mg VALTOCO Nasal Spray and 15 and 20mg Diazepam Rectal Gel (Geometric Mean with Upper and Lower 1 Geometric Deviation)

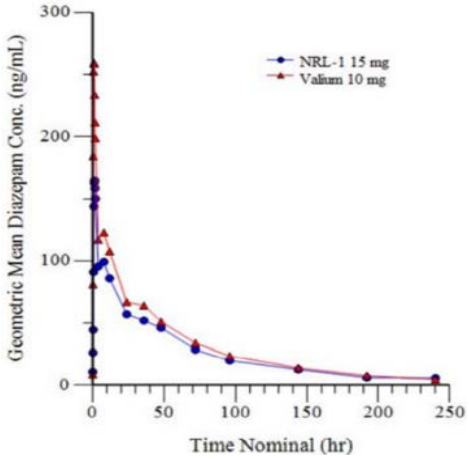


Figure 6. Mean Plasma Concentration-Time Profiles of Diazepam, 15mg NRL-1 and 10mg Valium (Geometric Mean): Linear Scale

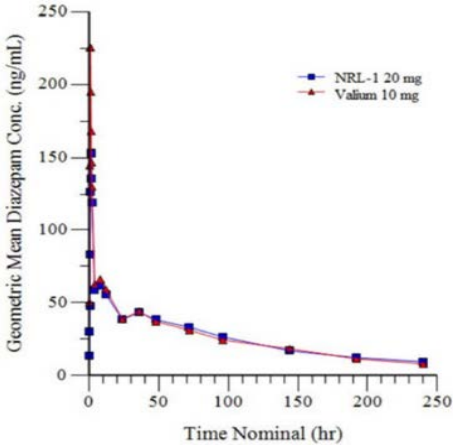


Figure 7. Mean Plasma Concentration-Time Profiles of Diazepam, 20mg NRL-1 and 10mg Valium (Geometric Mean): Linear Scale

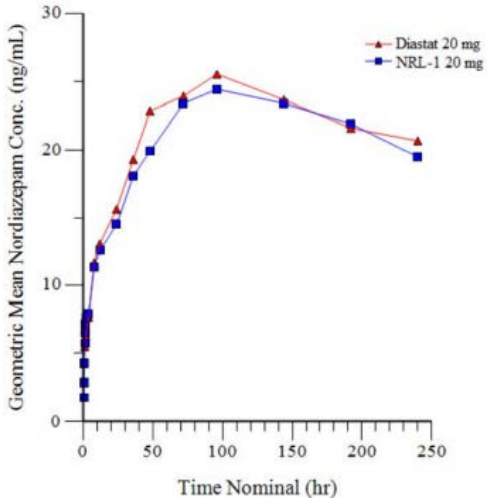
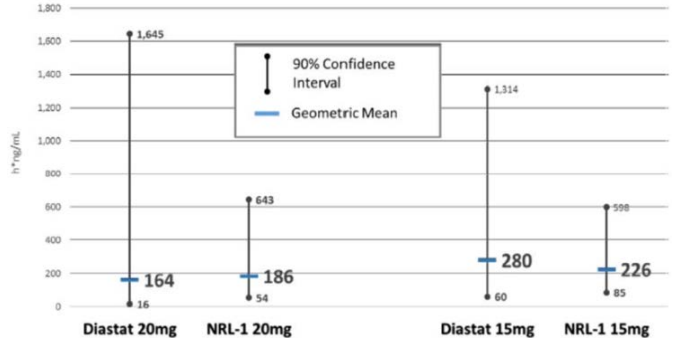
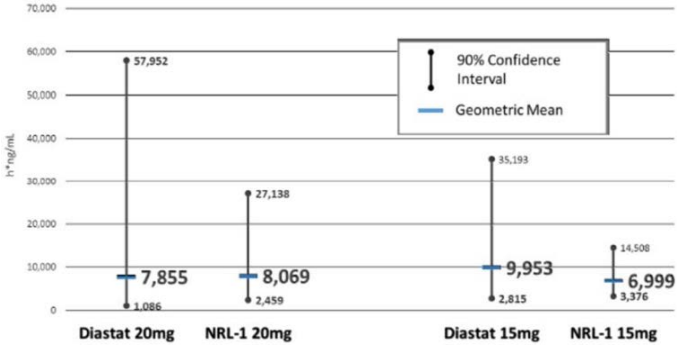


Figure 8. Mean Plasma Concentration-Time Profiles of Nordiazepam, 20mg NRL-1 and 20mg Diastat (Geometric Mean): Linear Scale



Plot 1. Diazepam Cmax Versus Treatment/Dose



Plot 2. Diazepam AUC0–∞ Versus Treatment/Dose

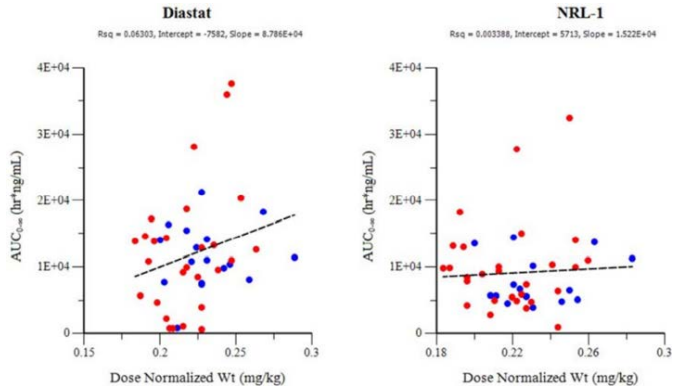


Figure 9. AUC0–∞ versus Diazepam Dose-Normalized by Body Weight: Diastat versus NRL-1

Comparing Valtoco with other diazepam products, the PK parameters for Valtoco were less variable and within the range of those seen with Distat. Distat showed the greatest variability

2.4 DIAZ.001.04: An Open-Label, Repeat Dose Pharmacokinetics Study of VALTOCO® (diazepam nasal spray) in Epilepsy Subjects under Seizure and Normal Conditions (DIAZ 001.04)

The researchers conducted a final study to assess the pharmacokinetics (PK) of diazepam after single intranasal doses of VALTOCO® (diazepam nasal spray) administered to Epilepsy subjects during the ictal or peri-ictal period (defined as either during or immediately following a seizure) [5], where the seizure involved motor activity or alteration of awareness. The primary PK variables to determine absorption were the maximum plasma concentration (Cmax) and the area under the curve through 6 hours (AUC (0- 6)).

Other objectives include: To compare the diazepam Cmax, time to peak concentration (tmax) and AUC (0-6) after single administration of VALTOCO (nasal spray) in Epilepsy subjects during the ictal or periictal period to that after administration of VALTOCO (nasal spray) to the same subjects under normal conditions; to compare the diazepam Cmax, tmax, and AUC (0-6) after single administration of VALTOCO (nasal spray) between Epilepsy subjects ages 6 to 11 and those greater than 12 years of age; to compare the diazepam Cmax, tmax, and AUC (0-6) after single administration of VALTOCO (nasal spray) in Epilepsy subjects during the ictal or peri-ictal period and that of healthy normal subjects from PK data obtained in the DIAZ.001.02 and DIAZ.001.03 studies; to assess the safety and tolerability of diazepam after intranasal administration of VALTOCO [5] (nasal spray).

Researchers impose two doses of intranasal VALTOCO at either 5mg, 10mg, 15mg, or 20mg based on the subject's body weight and measured their plasma concentrations of plasma diazepam and its active metabolite nordiazepam concentrations.

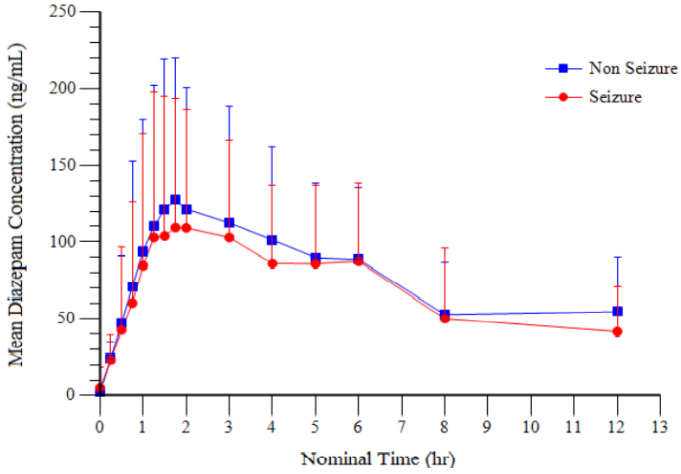


Figure 10. Mean Plots of the VALTOCO Nasal Spray Plasma Concentration versus Time Curves: Separated by condition

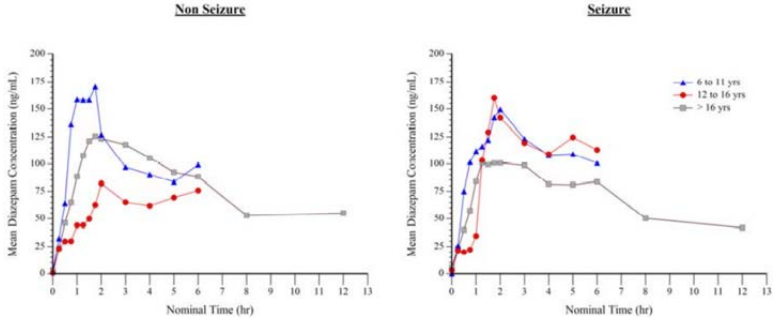


Figure 11. Mean Plasma Concentration versus Time Profiles of Diazepam by Age Group, Sorted by Condition

The mean PK profiles appeared similar with a large overlap following IN administration of Valtoco in patients during seizure (ictal or periictal) or non-seizure (normal state).

3. Safety Evaluation

Almost all people that use VALTOCO nasal sprays do not have serious side effects. However, for some people, the following side effects persist. Physiologically, you may feel drowsy, dizzy and diarrhea, nosebleeds, nasal discomfort, uncontrolled movement (such as tremors), and feeling slow or shallow. In terms of sleep, people that use VALTOCO may feel abnormally drowsy or difficult to wake up [6]. The use of VALTOCO may increase intraocular pressure in patients with glaucoma, which can only be used in patients with open-angle glaucoma that receive appropriate treatment but is taboo in patients with narrow-angle glaucoma. In terms of mental health, your mood, mind, or behavior may suddenly change. Signs of depression, suicidal thoughts or suicide attempts, thoughts about hurting yourself, and other psychological problems. Few people have a very severe allergic reaction to this drug. However, few people are allergic to it, and the symptoms of severe allergic reactions are rash, severe dizziness, difficulty breathing, itching or swelling with the skin or organs, especially an itchy or swollen face, tongue, and throat area more frequently. This drug can sometimes lead to addiction. This risk may be higher if the person has a drug disorder, such as overuse or addiction to drugs or alcohol.

Valtoco nasal spray and Nayzilam are both benzodiazepines used in acute treatment and acute repetitive seizures. The side effects are both can let people feel drowsiness, headache, and nasal discomfort. But still have some differences between VALTOCO, VALTOCO nasal spray also can make people feel diarrhea, lose coordination, dizziness, euphoria, rash, and asthma. NAYZILAM also can make people feel throat irritation and runny nose.

VALTOCO safety is also supported by a double-blind placebo-controlled trial using a tranquil rectal gel, using the same dose strategy 1,7 The most common adverse reactions (at least 4%) are depression, headache, and nasal discomfort. 1+clinical studies in adults and children 6 years and older. The study was designed for a 12-month treatment period, the most common treatment-related TEE, defined as occurring in ≥2 subjects, was nasal discomfort (5.3%), Headache (3%), epilepsy (2.3%), cough (1.5%), eye irritation (1.5%), pimping increase (1.5%), nasal pain (1.5%) and depression (1.5%). High subject retention rate, no treatment-related drug discontinuation, no serious adverse events are considered treatment-related. In the trial, 177 people with epilepsy were between the ages of 6 and 65. You can see the percentage of seizures of a single dose of VALTOCO within 24 hours, and you can see that the effect of control in the short term is the best to reach 96 percent, and by 24 hours its effect has not decreased much is still effective.

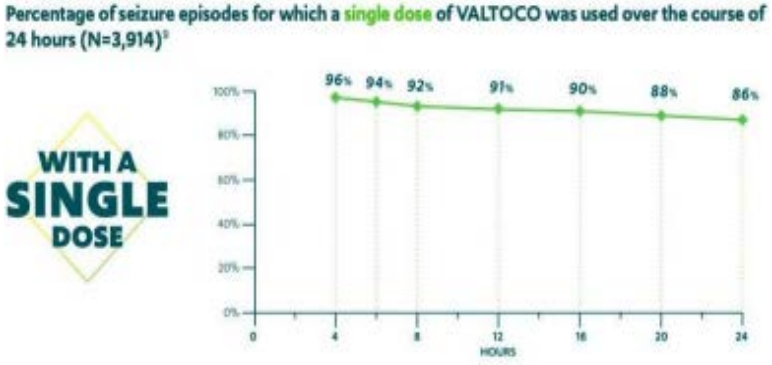


Figure 12. Single dose used for vast majority of episodes

A total of 39 sudden and severe adverse events (SAEs) were reported in the patient safety database of 24 patients (14.6 percent). It occurred mainly in patients in study 05 (23/24.96 percent). Most of these events occur to study 05 (n-36), while study 04 (n-2). As shown in Table 2, seizures are the most common SAE, occurring in 13 patients (7.9 percent). The only other SAE that occurred in more than 1 patient was pneumonia, which occurred in 2 patients (1.2 percent). The rest of SAES

occurs to only one patient per person. A small number of patients in the 5mg treatment arm complicate the estimation of dose effects. There was no significant dose effect on SAES. SAES was not reported on study 001.01, 001.02, or 001.03 [7]. The SAES incidence was the highest in the 6-11 age group (23.1 percent), while the incidence was the highest in patients (13.6 percent) and adults (12.9 percent) aged 12- 17.

From the data, 94/164 (57.3%) patients and 28% and 49% of patients in studies 04 and 05 had treatable adverse events (TEAEs) respectively. The table above provides a summary of the percentage of participants that have TEAEs in at least 2% of patients. The most-reported TAA is the systemic organ class (SOC) for neurological diseases, infections and intrusions, and respiratory diseases, all of which are commonto the patient population. The most common TEA in studies 04 and 05 were seizures (any) and respiratory infections, which occurred in 11% and 6.1% of patients, respectively [7]. In the aggregate data set for studies 04 and 05, at least 5% of patients with TEA were suffering from seizures, depression/calmness/fatigue/drowsiness, nasal discomfort, headaches (including migraines), and upper respiratory tract infections.

Table.1. Incidence of treatment emergent SAES (primary safety data set)

SAE (serious adverse events)	Total (n=164)	5mg (n=3)	10mg (n=38)	15mg (n=52)	20mg (n=72)
	N%	N%	N%	N%	N%
Any SAE	**24 (14.6%)**	**1 (33.3%)**	**7 (18.4%)**	**10 (19.2%)**	**6 (8.3%)**
Seizure (incl Status Epilepticus)	13 (7.9%)	0	5 (13.2%)	5 (9.6%)	3 (4.2%)
Pneumonia	2 (1.2%)	0	2 (5.3%)	0	0
Anterograde Amnesia	1 (0.6%)	0	0	1 (1.9%)	0
Anxiety	1 (0.6%)	0	0	0	1 (1.4%)
Asthma	1 (0.6%)	0	1 (2.6%)	0	0
Chest Pain	1 (0.6%)	0	0	0	1 (1.4%)
Chronic Myeloid Leukemia	1 (0.6%)	0	0	1 (1.9%)	0
Colorectal Adenocarcinoma	1 (0.6%)	0	0	1 (1.9%)	0
Dehydration	1 (0.6%)	0	0	1 (1.9%)	0
Dyspnea	1 (0.6%)	0	0	0	
Encephalopathy	1 (0.6%)	0	0	0	
Hip Arthroplasty	1 (0.6%)	0	1 (2.6%)	0	0
Hip Fracture	1 (0.6%)	0	0	0	

Table.2. TEAEs in ≥2% of patients by treatment arm (primary safety dataset)

TEAE (treatment emergent adverse events)	DZP NS Total (n=164)	DZP NS 5mg (n=3)	DZP NS 10mg (n=38)	DZP NS 15mg (n=52)	DZP NS 20mg (n=72)
	N%	N%	N%	N%	N%
Any adverse event	**94 (57.3%)**	**2**	**22**	**32**	**38 (52.8%)**
Any Local Nasal Symptoms (incl infections)	23 (14.0%)	1 (33.3%)	3 (7.9%)	11 (21.2%)	8 (11.1%)
Nasal Discomfort	10 (6.1%)	0	0	5 (9.6%)	5 (6.9%)
Nasal Congestion	5 (3.0%)	0	1 (2.6%)	3 (5.8%)	1 (1.4%)
Epistaxis	5 (3.0%)	0	3 (7.9%)	2 (3.8%)	0
Rhinorrhea	3 (1.8%)	1 (33.3%)	0	1 (1.9%)	1 (1.4%)
Nasal Pruritus	1 (0.6%)	0	0	0	1 (1.4%)
Nasal Ulcer	1 (0.6%)	0	0	0	1 (1.4%)
Seizure (Any)	18 (11.0%)	0	**7 (18.4)**	8 (15.4%)	3 (0.4%)
Status Epilepticus	3 (1.8%)	0	2 (5.3%)	1 (1.9%)	0
Somnolence/Sedation/Fatigue/Lethargy	10 (6.1%)	1 (33.3%)	2 (5.3)	5 (9.6%)	2 (2.8%)
Headache (incl Migraine)	10 (6.1%)	0	0	4 (7.7%)	6 (8.3%)
Upper Respiratory Tract Infection (incl Viral)	10 (6.1%)	0	2 (5.3%)	3 (5.8%)	5 (6.9%)
Nasopharyngitis	8 (4.9%)	0	3 (7.9%)	1 (1.9%)	3 (4.2%)
Nausea/Vomitting	7 (4.3%)	0	2 (5.3%)	3 (5.8%)	2 (2.8%)
Dizziness	6 (3.7%)	0	0	2 (3.8%)	4 (5.6%)
Pyrexia	6 (3.7%)	1 (33.3%)	4 (10.5%)	0	1 (1.4%)
Influenza	5 (3.0%)	0	1 (2.6%)	3 (5.8%)	1 (1.4%)
Ataxia/Gait Disturbance/Balance Disorder	5 (3.0%)	0	0	0	5 (6.9%)
Gastroenteritis	5 (3.0%)	1 (33.3%)	3 (7.9%)	1 (1.9%)	0
Confusion	4 (2.4%)	0	0	3 (5.8%)	1 (1.4%)
Dysgeusia	4 (2.4%)	0	0	3 (5.8%)	1 (1.4%)
Fall	4 (2.4%)	0	2 (5.3%)	1 (1.9%)	1 (1.4%)
Pneumonia	4 (2.4%)	0	3 (7.9%)	0	1 (1.4%)
Urinary Tract Infection	4 (2.4%)	0	2 (5.3%)	2 (3.8%)	0
Depression	4 (2.4%)	0	0	2 (3.8%)	2 (2.8%)

4. Discussion

From the analyzed data, it can be concluded that Valtoco is generally safe and well tolerated and presents a more efficient administration of benzodiazepine. As seizure clusters patients represents a significant underrepresented population in the scientific community, Valtoco functions as a solution to provide seizure cluster patients with a more accessible and single dose solution in treating their seizure clusters. Of note from the safety data, it seems that there exists an optimal dosage within the range of 5mg to 20mg that presents a reasonable risk to benefit ratio in regard to side effects. More

experimentation should be conducted to find the optimal dosage. Additionally, Valtoco represents a new innovative technique in which it addresses a significant limitation for traditional intranasal drug delivery. Where other intranasal drug delivery devices may lack, Valtoco boasts a 97% complete absorption of the drug [8]. This is due to the diazepam being a highly lipophilic molecule used in the device that allows for easy crossover through the blood-brain barrier. It also has a significantly increased half-life in which levels of the drug can be sustained for 24 hours within the patient's plasma. In the end, Valtoco presents comparable levels in bioavailability to rectal administration of diazepam, an established application of diazepam approved by the FDA in 1997, which reflects a more efficient and comfortable method of administration for patients. Compared to rectal diazepam, Valtoco also has a predictable PK of 2 to 4 fold less variable than rectal gel regardless of the patient's body weight.

5. Conclusion

In conclusion, Valtoco is a safe and well tolerated nasal benzodiazepine drug that is safe for treating cluster seizures. Based on the pharmacokinetics data, it is comparable to the most common administration (anal) of benzodiazepine. Valtoco addresses a crucial niche in the underrepresented population in the seizure community allowing better access, efficiency and a one-dose solution.

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