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Pharmacokinetics, pharmacodynamics, and tolerability of USL261, midazolam nasal spray: Randomized study in healthy geriatric and non-geriatric adults

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ABSTRACT

Aim: Characterize pharmacokinetics, pharmacodynamics, and safety/tolerability of USL261 in geriatric adults to inform its potential for treating bouts of increased seizure activity.
Methods: Phase 1, randomized, double-blind, 2-way crossover study in healthy geriatric (≥65 years; n = 18) and non-geriatric (18–40 years; n = 12) adults evaluated single USL261 doses (2.5 and 5.0 mg) administered intranasally. Pharmacokinetic parameters were estimated for midazolam and 1-hydroxymidazolam (active metabolite), including area under the plasma concentration-time curve (AUC), maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), and half-life ($t_{1/2}$). Stanford Sleepiness Scale and Observer's Assessment of Alertness/Sedation assessed sedation; Digit-Symbol Substitution Test assessed psychomotor performance.
Results: Midazolam exposure and plasma concentrations were higher in geriatric versus non-geriatric adults (geometric mean $AUC_{0-\infty}$ [ng*h/mL] 2.5 mg: 70 vs 54, respectively; 5.0 mg: 157 vs 110; C_{max} [ng/mL] 2.5 mg: 27.1 vs 22.5; 5.0 mg: 55.8 vs 46.1). USL261 was rapidly absorbed, with no differences in median T_{max} (14.5–17.3 min); mean $t_{1/2}$ was longer in geriatric subjects. Similar age-related trends were observed for 1-hydroxymidazolam. Mean maximum observed pharmacodynamic effects were not significantly different between age groups, though were more pronounced following 5.0 versus 2.5 mg ($P < .05$); return to baseline was generally achieved within 4 h. USL261 was generally well tolerated, with similar adverse event rates between age groups.
Conclusions: Despite increased midazolam exposure in geriatric subjects, there were no differences between age groups in pharmacodynamic effects or adverse event rates. USL261 was rapidly absorbed and pharmacodynamic effects returned to baseline within ~4 h, regardless of age. Dose-dependent pharmacokinetic and maximum pharmacodynamic effects were observed. Overall, pharmacokinetic findings for USL261 were similar to studies evaluating intravenous midazolam, whereas pharmacodynamic effects were less pronounced in the elderly than previously reported.

1. Introduction

Seizure clusters and prolonged seizures may result in brain injury, and are associated with increased morbidity, mortality, and risk of status epilepticus [1,2]; interventions that can quickly interrupt seizure progression are essential. Benzodiazepines—central nervous system depressants that modulate $GABA_A$ receptor activity [3]—are often administered intravenously (IV) for rapid cessation of acute seizures [4,5]. Intravenous administration requires skilled personnel, so treatment may not always be possible; therefore, benzodiazepines that can be administered at home fill an unmet patient need.

Rectal diazepam (DZP) is approved by the United States (U.S.) Food and Drug Administration as outpatient treatment for patients with bouts of increased seizure activity [6]. Although the rectum an effective delivery route, caregivers express desires for alternative, more socially satisfactory treatment options [7–11]. Buccal midazolam (MDZ) is approved in the European Union for the treatment of prolonged, acute, convulsive seizures in pediatric patients aged 3 months to <18 years [12]. In the U.S., MDZ is indicated for many non-seizure–related uses, including IV and oral administration during procedural sedation and anesthesia induction. Though not approved in the US as rescue treatment for seizures, several studies have found MDZ to be efficacious for the cessation of seizures in both children and adults [1,13–16]. A common route of administration studied has been intranasal (IN), which includes use of a mucosal atomization device [10,17] or needleless syringe to drip MDZ IV solution into nostrils [7,9,11,18,19]. However, IV MDZ is not

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optimized for IN use, and may necessitate large administration volumes [20,21].

Intranasal delivery of MDZ results in rapid absorption and largely avoids first-pass metabolism by cytochrome P450 (CYP) 3A in the liver [22] and small intestine [23]. This results in decreased production of the main metabolite 1-hydroxymidazolam (1-OH-MDZ), similar to that seen with IV administration [24–27]. Though 1-OH-MDZ is pharmacologically active and equipotent to MDZ [28,29], it is rapidly inactivated through glucuronidation [30]. In contrast, oral MDZ is subject to first-pass metabolism, decreasing its absolute bioavailability to 40–50% [14,31].

USL261, a single-dose nasal spray formulation of MDZ optimized with an appropriate volume for IN delivery, is being investigated as a treatment for patients who require control of intermittent bouts of increased seizure activity. A phase 1 study in healthy adults comparing pharmacokinetics (PK) and pharmacodynamics (PD) of a pilot formulation of USL261 to the IV MDZ formulation administered IV or IN showed that USL261 provided rapid delivery of MDZ, with increased absorption compared with IN administration of IV solution [32]. A phase 1 PK/PD study of USL261 2.5, 5.0, and 7.5 mg in patients with epilepsy showed MDZ exposure increased with ascending doses and PD effects returned to near baseline values within 4 h [33,34]. Both studies showed USL261 was well tolerated up to 7.5 mg. A third phase 1 study found USL261 was well tolerated up to 20 mg [35]. Three Phase 3 clinical trials evaluating efficacy and safety of USL261 in patients with epilepsy are ongoing (clinicaltrials.gov: NCT01390220, NCT01529034, NCT01999777).

As drug metabolism and drug sensitivity generally change with increasing age [36,37], it is necessary to evaluate drug pharmacology in the elderly to ensure safe and effective use [38]. However, PK and PD findings of non-nasal MDZ formulations have been inconsistent across studies. For example, while some studies have shown PK and PD differences between elderly and young adults [39–43], others have shown no differences [44–46]. Possible explanations for these conflicting results include variability in routes of administration and techniques, dosage, comorbidities, and normal age-related physiological processes related to absorption, distribution, metabolism, and excretion [36,37].

The purpose of this study was to evaluate the PK, PD, and safety/tolerability of two clinically relevant doses of USL261 in healthy geriatric and non-geriatric subjects.

2. Methods

2.1. Study design

A randomized, double-blind, single-dose, single-center, phase 1 crossover study was conducted to evaluate the effects of 2.5 mg and 5.0 mg USL261 administered intranasally in healthy geriatric and non-geriatric adults. Treatment periods were separated with a 4- to 10-day washout. For each study period, subjects were housed at the clinical research unit from ~10 h before dosing until after the 24-h blood draw.

The study was performed in accordance with the ethical principles set forth in the Declaration of Helsinki. All pertinent study documents were reviewed by the Chesapeake Research Review, Inc. Institutional Review Board prior to study initiation (reference number Pro00009179). Subjects provided written informed consent prior to study procedures.

2.2. Subjects

Eligible patients were healthy male and female adults aged 18–40 years of age, inclusive (non-geriatric), or ≥65 years (geriatric) with a body mass index of 18–32 kg/m^2. Subjects with MDZ allergies, acute or chronic nasal symptoms, nasal polyps, deviated septum, intolerance to intranasal administration or other nasal physical abnormalities were excluded. Additional reasons for exclusion included clinically significant medical conditions, alcohol/psychoactive substance use disorder in past 2 years, cardiac conduction defects, or neurological disorders. Subjects who used medications, vaccines, or supplements that might affect MDZ metabolism or nasal physiology within 14 days prior to study-drug administration were also excluded.

2.3. Pharmacokinetic (PK) measures

Blood samples were collected pre-dose and at 5, 10, 15, 20, 25, 30, 45, 60, 90 min, and 2, 4, 6, 8, 12, 16, and 24 h post-dose. Plasma concentrations of MDZ and 1-OH-MDZ were determined using a validated liquid chromatography tandem mass spectrometry method with a bias of 2.9% and precision of 8.5% at the lower limit of quantitation of 0.1 ng/mL for both analytes. No assay interference was observed with paracetamol, acetylsalicylic acid, caffeine, dextromethorphan, dimenhydrinate, diphenhydramine, ibuprofen, nicotine, pseudoephedrine, cotinine, ethinyl estradiol, levonorgestrel or salicylic acid.

2.4. Pharmacodynamic (PD) evaluations

Sedation was assessed using 2 validated instruments: the self-reported Stanford Sleepiness Scale (SSS) [47] and the clinician-rated Observer's Assessment of Alertness/Sedation Scale (OAA/S) [48]. The SSS is a 1-item test used to evaluate sleepiness at specific moments in time. Subjects select 1 of 7 statements best representing their sleepiness level, with higher values for increasing levels of sedation (1 = wide awake; 7 = sleep onset soon). For sleeping subjects, "7" was assigned. The OAA/S utilizes a qualitative categorical measure to rate sedation. Lower scores signify increasing sedation for all four categories: responsiveness, speech, facial expression, and eyes. OAA/S can be assessed using either Composite Score (lowest score in any of the 4 categories [range 1–5]) or Sum Score (sum of scores in all 4 categories). For Sum Score, responsiveness values ranged from 1 to 5, speech from 2 to 5, and facial expression and eyes from 3 to 5. The SSS and OAA/S measures were taken pre-dose and at 5, 10, 15, 30, 45, 60, 90 min, and 2, 3, 4, 6, 8, 10, and 12 h post-dose.

Psychomotor impairment was assessed using the paper-based Digit-Symbol Substitution Test (DSST), which measures associative ability and performance based on a digit-symbol code (each of 9 digits is paired with a different symbol) [49]. The DSST Completion Rate = number of trials attempted/90 s; DSST percent correct score = number of correct trials in 90 s/number trials attempted * 100. The DSST assessments were performed at initial screening, check-in, pre-dose and at 10, 20, 30, 45, 60, 90 min, and 2, 3, 4, 6, 8, and 12 h post-dose. To account for learning effects, different digit/symbol combinations were used at each time point. The DSST scores were baseline-adjusted due to the lower values for geriatric subjects, which is consistent with age-normative data for the DSST [50].

2.5. Safety and tolerability assessments

Treatment-emergent adverse events (TEAEs) were coded with the Medical Dictionary for Regulatory Activities (MedDRA®), Version 16.1 and summarized by dose, severity, and relationship to treatment for each age group. Safety was assessed through laboratory values (serum chemistry, hematology, and urinalysis), vital signs (including blood pressure, heart rate, and respiration), continuous pulse oximetry monitoring, electrocardiogram, examinations (physical, neurological, nasal), and the Columbia Suicidality Severity Rating Scale.

2.6. Study populations and statistical analyses

Assuming a between-subject coefficient of variation of 35% and 50% for non-geriatric and geriatric subjects, respectively, and a maximum dropout rate of 25%, a target population of 12 non-geriatric and 18 geriatric patients was selected to provide sufficient precision in the estimates of clearance and volume of distribution [51].