A Comparative, Randomized, Single-Dose, 2-Way Crossover Bioavailability Study of a Clonazepam Oral Solution Versus Tablets in Healthy Adult Volunteers

Nadia Cardillo Marricco[1], Marie-Chantal Bonhomme[1], Mike Di Spirito[1], Elliot M. Offman[1] and M. Kevan Cassidy[2]
[1]Celerion, Montreal, Canada; [2]Rosemont Pharmaceuticals Ltd, Leeds, UK.

BACKGROUND

Clonazepam is used, either alone or as an adjunct, for epileptic and seizure disorder in infants, children and adults, especially in the treatment of the Lennox-Gastaut syndrome (petit mal variant), akinetic and myoclonic seizures. It is also useful in patients with absence seizures (petit mal). Clonazepam is a benzodiazepine derivative with anticonvulsant properties. The site and mechanism of action are unknown. However, clonazepam does act with the benzodiazepine receptors to increase the efficiency of GABA binding which, at the limbic and subcortical levels of the CNS, help produce clonazepam's anticonvulsant and sedative effects.

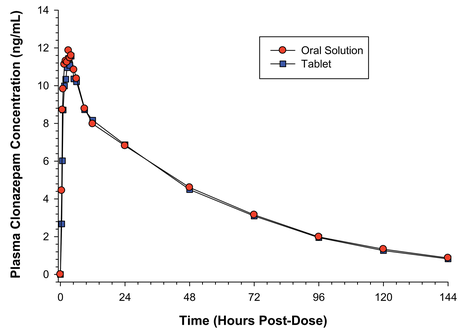
Treatment should be started with low doses. The dose may be increased progressively until the maintenance dose suited to the individual patient is established. The usual initial daily dose is 1 mg. The normal maintenance dose in adults is 4-8 mg daily, administered in 3 divided doses. The maximum daily dose should not exceed 20 mg.

An oral solution was developed with the intention of improving treatment compliance in patients who struggle swallowing solid oral dosage forms. In addition, the oral solution allows for individualized dosing, benefitting the patient population.

OBJECTIVE

The primary objective of this study was to assess the single-dose relative bioavailability of a test 2 mg/ 5 mL clonazepam oral solution and a marketed reference 2 mg clonazepam tablet, under fasting conditions.

Figure 1 Arithmetic Mean Plasma Clonazepam Concentrations versus Time



METHODS

- This was an open-label, randomized, 2-way crossover, 2-sequence, single-dose comparative bioavailability study.
- A total of 26 healthy adult subjects (11 males and 15 females) were enrolled in the study and were randomized to study treatments.
- In each study period, subjects received a single 2 mg oral dose of one of the following treatments following an overnight fast:
  - Test: 2 mg/ 5 mL clonazepam oral solution
  - Reference: marketed 2 mg clonazepam tablet
- Study periods were separated by a washout phase of 21 days.
- Serial blood samples drawn from predose through 144 hours postdose were quantified for plasma clonazepam using a validated LC-MS/MS method with a lower limit of quantification of 0.100 ng/mL.
- A noncompartmental analysis was performed on the plasma clonazepam concentrations to derive the pharmacokinetic (PK) parameters of interest (maximum plasma concentration [C_{max}], area under the curve from time 0 to 72 hours post-dose [AUC_{0-72}], area under the curve from time 0 to the last measureable concentration [AUC_{0-t}], area under the curve from time 0 to infinity [$AUC_{0-\infty}$], time to reach C_{max} [t_{max}], apparent elimination rate constant [kel], apparent terminal elimination half-life [$t_{1/2}$]), using PhAST 2.3-001 (Celerion, Lincoln, Nebraska).
- Analyses of variance were performed on the ln-transformed C_{max}, AUC_{0-72}, AUC_{0-t} and $AUC_{0-\infty}$ using the GLM procedure (SAS® version 6.12, SAS Institute, Cary, North Carolina).
- Since clonazepam has a long elimination half-life, an AUC truncated at 72 hours (AUC_{0-72}) was used instead of AUC_{0-t} for assessment of bioequivalence.
- The following standards were used to determine bioequivalence in this comparative bioavailability study:
  - The 90% confidence interval of the ratios of least-squares means of C_{max} and AUC_{0-72} of the oral solution to the tablet formulation should be within 80 – 125%. (The AUC_{0-t} and $AUC_{0-\infty}$ PK parameters were calculated for supportive information purposes.)
- A non-parametric analysis was performed on t_{max} using SAS® version 9.1.3 (SAS Institute, Cary, North Carolina).
- Safety assessments included vital signs, clinical laboratory evaluations and adverse event monitoring.

RESULTS

- Data from 24 subjects who completed the study were included in the PK and statistical analyses. All 26 subjects dosed were included in the safety assessment. Two subjects were withdrawn due to adverse events.
- One subject was discontinued from the study due to adverse events experienced following marketed 2 mg tablet dosing. From these events the SAE of "Appendicitis" was deemed severe and led to the hospitalization of the subject, however was judged unrelated to the study drug.
- A second subject was discontinued from the study due to adverse events experienced following 2 mg/ 5 mL oral solution dosing. The adverse events reported by this subject included upper body itchiness and redness with raised skin patches, and were deemed mild or moderate in severity, not serious, and likely related to the study drug.
- The arithmetic mean plasma clonazepam concentrations versus time plots following the administration of a single 2 mg oral dose of the clonazepam oral solution and tablet, under fasting conditions, are presented in Figure 1.
- A summary of plasma clonazepam PK parameters following the administration of a single 2 mg oral dose of the clonazepam oral solution and tablet, under fasting conditions, is presented in Table 1.
- Results from the ANOVA bioequivalence assessment are presented in Table 2.
- Peak and total exposure to clonazepam were comparable between the oral solution and tablet. The 90% confidence intervals of the ratios of least-square means for C_{max}, AUC_{0-72}, AUC_{0-t}, and $AUC_{0-\infty}$ were within the 80 – 125% acceptance range.
- The clonazepam intrasubject variability was low for the AUCs (< 10%) and slightly higher for C_{max} (16.7%).
- The $t_{1/2}$ and t_{max} values of clonazepam were comparable between the oral solution and tablet. The t_{max} median difference (formulation effect, oral solution - tablet) and 90% confidence interval was -0.5 [-1.13; 0.25].
- All vital sign and clinical laboratory results were judged by the Investigator as normal or not clinically significant.
- Overall, 23 subjects (92% of the study population receiving the oral solution) and 24 subjects (96% of the study population receiving the tablet) experienced adverse events likely related to clonazepam, consisting mainly of reported sleepiness, dizziness and weakness.

CONCLUSIONS

The oral solution is bioequivalent to the marketed reference tablet under fasting conditions. Both the oral solution and the tablet products were equally well tolerated by all subjects. No serious or severe adverse events related to the study drug were observed.

Table 1 Summary of Plasma Pharmacokinetic Parameters for Clonazepam Following a Single 2 mg Dose of Clonazepam

Pharmacokinetic Parameters	Statistics	Oral Solution N= 24	Tablet N= 24
C_{max} (ng/mL)	Arithmetic Mean (± SD) Geometric Mean	14.1 (2.3) 14.0	12.8 (3.3) 12.4
AUC_{0-72} (ng·hr/mL)	Arithmetic Mean (± SD) Geometric Mean	432 (80) 425	429 (87) 420
AUC_{0-t} (ng·hr/mL)	Arithmetic Mean (± SD) Geometric Mean	561 (116) 549	553 (122) 540
$AUC_{0-\infty}$ (ng·hr/mL)	Arithmetic Mean (± SD) Geometric Mean	612 (137) 597	600 (141) 584
t_{max} (hr)	Arithmetic Mean (± SD) Median (Min-Max)	2.59 (1.6) 2.75 (0.75, 6.00)	3.10 (1.4) 3.25 (0.75, 6.00)
$t_{1/2}$ (hr)	Arithmetic Mean (± SD)	38.7 (6.5)	37.9 (6.2)
k_{el} (1/hr)	Arithmetic Mean (± SD)	0.0184 (0.003)	0.0188 (0.003)

Table 2 Summary of the Statistical Comparison of Plasma Clonazepam Pharmacokinetic Parameters: Test (2 mg/ 5 mL Oral Solution) Versus Reference (Marketed 2 mg Tablet)

Clonazepam PK Parameter	Mean Ratio [90% Confidence Interval]	Intrasubject CV (%)
C_{max} (ng/mL)	112.4% [103.5-122.0%]	16.7
AUC_{0-72} (ng·h/mL)	101.3% [98.6-104.2%]	5.6
AUC_{0-t} (ng·h/mL)	101.8% [99.2-104.4%]	5.2
$AUC_{0-\infty}$ (ng·h/mL)	102.3% [99.7-104.9%]	5.1