A Single-Dose, Three-Period, Six-Sequence Crossover Study Comparing the Bioavailability of Solution, Suspension, and Enteric-Coated Tablets of Magnesium Valproate in Healthy Mexican Volunteers Under Fasting Conditions

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ABSTRACT

Background: Valproic acid has been associated with a highly variable intersubject absorptive phase; therefore, magnesium salt (magnesium valproate [MgV]) was developed to diminish variation during enteric absorption.

Objectives: The aims of this study were to assess the pharmacokinetics of single oral doses of MgV 500-mg solution, suspension, and enteric-coated tablets in a healthy Mexican population, and to compare formulation-related differences.

Methods: This was a randomized, single-dose, 3-period, 6-sequence crossover study in healthy Mexican volunteers aged 18 to 45 years. In each period, subjects received single oral doses of 500-mg MgV solution, suspension, and enteric-coated tablet formulations, with a 7-day washout period between each dosing period. Serial blood samples were collected at 0 hour (prior to MgV administration) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 9, 12, 24, 48, and 72 hours after dosing. Valproate was measured by a new method of ultraperformance liquid chromatography coupled with mass spectrometry. Pharmacokinetic parameters of interest were C_{max}, T_{max}, AUC_{0-72}, $AUC_{0-\infty}$, $t_{1/2}$, V_d/F, CL/F, and mean residence time (MRT). Formulation-related differences were assayed in accordance with the Mexican regulatory bioequivalence criteria. Log-transformed values of C_{max} and AUC were used to construct a classic 90% CI. Bioequivalence was established if the 90% CI for the mean test:reference ratio of log-transformed C_{max} and AUC were within the range of 0.80 to 1.25. Tolerability was assessed based on subject interview, vital sign monitoring, and clinical assessment.

Results: A total of 24 healthy volunteers (12 women and 12 men; mean [SD] age, 28.79 [6.5] years; height, 164 [9.8] cm; weight, 65.42 [8.95] kg; and body mass index, 24.28 [2.11] kg/m^2) were included. For the MgV solution, the mean (SD) pharmacokinetic parameters of C_{max}, T_{max}, AUC_{0-72}, $AUC_{0-\infty}$, $t_{1/2}$, V_d/F, CL/F, and MRT were 59.75 (8.24) μg/mL, 0.542 (0.14) hours, 1099.67 (241.70) μg · h/mL, 1156.30 (264.01) μg · h/mL, 16.19 (2.36) hours, 9633.68 (1892.70) mL, 418.35 (92.01) mL/h, and 18.36 (1.44) hours, respectively. For the MgV suspension, the mean (SD) pharmacokinetic parameters of C_{max}, T_{max}, AUC_{0-72}, $AUC_{0-\infty}$, $t_{1/2}$, V_d/F, CL/F, and MRT were 55.04 (7.72) μg/mL, 0.773 (0.51) hour, 1057.76 (223.37) μg · h/mL, 1111.09 (245.07) μg · h/mL, 16.32 (2.20) hours, 1069.05 (1775.64) mL, 435.43 (99.59) mL/h, and 18.41 (1.43) hours, respectively. For the MgV enteric-coated tablets, the mean (SD) pharmacokinetic parameters of C_{max}, T_{max}, AUC_{0-72}, $AUC_{0-\infty}$, $t_{1/2}$, V_d/F, CL/F, and MRT were 54.88 (6.73) μg/mL, 2.79 (0.89) hours, 1100.79 (216.70) μg · h/mL, 1163.61 (238.36) μg · h/mL, 16.48 (2.10) hours, 9675.15 (1659.36) mL, 412.36 (85.24) mL/h, and 19.95 (1.53) hours, respectively. The 90% CIs for the tablets:solution ratio were 82.15 to 95.44, 94.60 to 105.39, and 95.43 to 105.95 for C_{max}, AUC_{0-72}, and $AUC_{0-\infty}$, respectively. The 90% CIs for the suspension:solution ratio were 84.79 to 98.50, 88.89 to 99.02, and 89.15 to 98.97, respectively. The 90% CIs for the tablets:suspension ratio were 89.90 to 104.43, 100.84 to 112.34, and 101.60 to 112.80, respectively.

Conclusion: This single-dose study found that the 3 formulations (solution, suspension, and enteric-

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