Comparative Bioavailability of 2 Tablet Formulations of Levodopa/Benserazide in Healthy, Fasting Volunteers: A Single-Dose, Randomized-Sequence, Open-Label Crossover Study

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ABSTRACT

Background: Currently, levodopa administered with decarboxylase inhibitors is the gold standard for the management of the motor symptoms of Parkinson's disease, a neurodegenerative disorder characterized by the degeneration of dopaminergic neurons in the substantia nigra pars compacta. In Argentina, only 1 commercial product is available with such composition; this study was contracted by the manufacturer to comply with new generic product regulations.

Objective: The aim of this study was to evaluate the fasting bioavailability of a new generic formulation of levodopa 200 mg/benserazide 50 mg tablets (test) and compare this generic formulation with the branded formulation (reference) to meet regulatory criteria for marketing the test product in Argentina.

Methods: A randomized-sequence, open-label, 2-period, crossover study was conducted between August and October 2009 in healthy Caucasian volunteers (n = 24; 18 males, aged 21 to 42 years, with a body mass index ranging from 19.7 to 26.0 kg/m^2) in the fasted state. A single oral dose of the test or reference formulation was administered, and after a 7-day washout period, the other formulation was given. Blood samples were collected at baseline and at 10, 20, 30, 40, 50, 60, 70, 80, 90, and 105 minutes and 2, 2.5, 3, 3.5, 4, and 6 hours after dosing. Levodopa plasma concentrations were measured by high-performance liquid chromatography with electrochemical detection, without stereo-specificity assessment. The formulations were considered bioequivalent if the 90% CI of the geometric mean ratios (test/reference) for the C_{max} and AUC_{0-t} of levodopa were within the 0.8 to 1.25 range. Adverse events were monitored throughout the study, based on clinical parameters and patient reports.

Results: The geometric means (90% CI) of the C_{max} for the test and reference formulations were 2462.02 (2312.06–3492.40) and 2542.85 (2394.49–3231.29) ng/mL, respectively; the AUC_{0-t} was 3878.04 (3623.88–5393.09) and 3972.10 (3765.88–5393.02) ng/mL/h, respectively; and the $AUC_{0-\infty}$was 4610.37 (4315.71–6315.70) and 4728.96 (4502.17–6828.26) ng/mL/h, respectively. There were no significant differences in pharmacokinetic parameters between the 2 formulations. The test:reference ratios for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 96.82% (90% CI, 83.87–111.77), 97.63% (90% CI, 85.95–110.91), and 97.49% (90% CI, 84.09–113.02), respectively. No clinically significant adverse events were reported; this finding is probably the result of subjects not believing that their side effects were severe enough to be reported and not because of a genuine and absolute lack of predictable side effects.

Conclusions: In this single-dose study, the test formulation of levodopa/benserazide tablets met the Argentinean criterion for bioequivalence to the reference formulation. (www.clinicaltrials.gov: NCT01327261). (*Clin Ther.* 2011;33:500–510)

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Key words: benserazide, bioequivalence, levodopa, Parkinson's disease, pharmacokinetics.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease associated with trembling of the arms and legs, stiffness and rigidity of the muscles, and slowness of movement (bradykinesia) that affects 0.3% of the general population and 1% to 2% of people >60 years.[1,2]

Motor impairments in PD arise from selective loss of pigmented midbrain neurons in the substantia nigra pars compacta.[3] These neurons project to the striatal nuclei putamen and caudate, where they release dopamine (DA). Parkinsonian features emerge when more than half of the dopaminergic terminals in the striatum are lost.[4] Since 1967, when Cotzias et al confirmed improvements in patients with PD treated with levodopa, this drug has remained the gold standard of PD pharmacotherapy.[5–8] Levodopa provides rapid and effective symptomatic control of motor symptoms in virtually all PD patients,[9,10] and since its introduction, it has improved dramatically survival and quality of life for people with PD.[11,12]

Levodopa (3,4-dihydroxy-L-phenylalanine), a naturally occurring amino acid, is an intermediate in DA synthesis. After oral ingestion, levodopa is actively transported from the upper small intestine into the circulation by a carrier specific for large, neutral L-amino acids.[13,14]

Levodopa is also metabolized rapidly to DA by aromatic amino-acid decarboxylase (AADC) and to 3-*O*-methyldopa (3-OMD) by catechol-*O*-methyltransferase (COMT). The plasma half-life of levodopa elimination is, therefore, approximately 90 minutes.[15] The active metabolite of levodopa, DA, is responsible for the control of PD symptoms; however, DA does not cross the blood–brain barrier.[16,17] Because levodopa crosses the blood–brain barrier, it acts as a prodrug for brain DA. However, levodopa is also rapidly decarboxylated to DA in peripheral tissues, especially in the gastrointestinal tract, following oral administration; therefore, only a small portion (~1%) of a levodopa dose is transported across the blood–brain barrier to the central nervous system.[18]

For this reason, in the last 40 years, levodopa has been combined with a peripheral inhibitor of AADC (either carbidopa or benserazide), which results in a 3-fold increase in the amount of oral levodopa reaching the systemic circulation and the striatum.[19] This increases the bioavailability of levodopa without changing its half-life.[17,20]

Peripheral AADC inhibitors, such as benserazide and carbidopa, do not enter the central nervous system in significant amounts. As a result, these inhibitors prevent the formation of peripheral DA and the associated dose-dependent undesirable effects, such as nausea, vomiting, and orthostatic hypotension. The increase in bioavailability achieved by AADC inhibitors reduces the levodopa dose by ≥80%.[21] After crossing the blood–brain barrier, levodopa is taken up by living striatal aminergic terminals of the CNS and converted to DA, which is then released by synaptic terminals.[22]

A new generic formulation containing 200 mg levodopa and 50 mg benserazide (test) has been developed in tablet form.* To comply with Argentine regulations for marketing approval, this study was conducted to investigate whether the relative bioavailability of the test formulation met the regulatory criterion for bioequivalence to the branded formulation† (reference). The criterion was established in dispositions 3185/1999, 5040/2006, and 1746/2007 of the Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT),[23] of the Argentinean drug regulatory agency.

PATIENTS AND METHODS

Patients

Healthy Caucasian Argentinean male and female volunteers, aged 21 to 50 years, with a body mass index ranging from 19 to 26 kg/m^2 were enrolled in this study. All volunteers provided written informed consent before study initiation. Exclusion criteria were a history of cardiovascular, hepatic, renal, psychiatric, neurologic, hematologic, or metabolic disease; drug or alcohol abuse within 2 years before the start of the study; smoking; HIV, hepatitis B virus, or hepatitis C virus infection; consumption of any prescribed or over-the-counter drug within 2 weeks before the start of the study; or participation in a similar study within the past 6 months. Female subjects were not pregnant, planning to become pregnant, or breastfeeding at the time of the study and were required to use an effective method of contraception (intrauterine device or hormonal method) throughout the study.

*Trademark: Evoser® (Laboratorios Phoenix S.A.I.C. y F., Buenos Aires, Argentina).

†Trademark: Madopar® (Roche Pharma, Switzerland).