Pharmacokinetics and Tolerability of Etamicastat Following Single and Repeated Administration in Elderly Versus Young Healthy Male Subjects: An Open-Label, Single-Center, Parallel-Group Study

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ABSTRACT

Background: Etamicastat is a new dopamine-β-hydroxylase (DβH) inhibitor currently in clinical development for the treatment of hypertension and heart failure.

Objectives: To evaluate the pharmacokinetics and tolerability of etamicastat after single and repeated administration in elderly subjects (aged ≥65 years) relative to young adult healthy controls (aged 18–45 years).

Methods: This was a single-center, open-label, parallel-group study in young male adults (n = 13; mean [SD] age 32.6 [16.4] years; range, 18–44 years; weight 79.0 [16.4] kg; systolic blood pressure 117 [12] mm Hg and diastolic blood pressure 61 [7] mm Hg) and 12 elderly male volunteers (n = 12; age 69.3 [3.3] years; weight 69.2 [9.5] kg; systolic blood pressure 115 [13] mm Hg and diastolic blood pressure 64 [4] mm Hg), conducted in 2 consecutive periods. All subjects were white, except for 1 black elderly subject. In Phase A, subjects received a single dose of 100 mg etamicastat. In Phase B, subjects received 100 mg/d etamicastat for 7 days. The pharmacokinetic parameters of etamicastat and its acetylated metabolite BIA 5-961 were calculated after the single dose of Phase A and the last dose of Phase B. Subjects' *N*-acetyltransferase type 1 (NAT1) and type 2 (NAT2) genotyping was performed and acetylator status inferred.

Results: After a single dose of etamicastat 100 mg, mean (SD) plasma C_{max} and plasma $AUC_{0-\infty}$ were, respectively, 1.3 (0.5) ng/mL/kg and 12.4 (7.8) ng × h/mL/kg in elderly subjects, and 1.3 (0.4) ng/mL/kg and 10.0 (6.6) ng × h/mL/kg in young subjects. At steady-state, C_{max} and AUC_{0-24} were 1.8 (0.5) ng/mL/kg and 15.0 (6.4) ng × h/mL/kg in elderly subjects, and 1.5 (0.7) ng/mL/kg and 12.5 (6.5) ng × h/mL/kg in young subjects. Elderly/young geometric mean ratios and 90% CIs were, respectively, 0.944 (0.788–1.131) and 1.164 (0.730–1.855) for etamicastat C_{max} and $AUC_{0-\infty}$ after a single dose, and 1.225 (0.960–1.563) and 1.171 (0.850–1.612) for etamicastat C_{max} and AUC_{0-24} at steady state. Etamicastat steady-state plasma concentrations were reached after 3 to 4 days of dosing. The mean etamicastat accumulation ratio was 1.7 in both age groups. Following etamicastat single dose, mean (SD) BIA 5-961 C_{max} and $AUC_{0-\infty}$ were, respectively, 3.5 (2.1) ng/mL/kg and 28.4 (14.7) ng × h/mL/kg in elderly subjects, and 2.5 (1.5) ng/mL/kg and 16.5 (9.7) in young subjects. At steady state, BIA 5-961, C_{max}, and AUC_{0-24} were 4.3 (2.6) ng/mL/kg and 34.6 (17.6) ng × h/mL/kg in elderly subjects, and 3.1 (2.0) ng/mL/kg and 22.2 (11.8) ng × h/mL/kg in young subjects. Large interindividual variability dependent on the NAT2 acetylator status was found in the pharmacokinetic parameters of etamicastat and BIA 5-961. Systemic exposure to etamicastat was higher and systemic exposure to BIA 5-961 was lower in NAT2 poor metabolizers compared with rapid metabolizers. No effect on heart rate and blood pressure was found in the young group. In the elderly, a decrease of supine blood pressure was observed. Postural changes in blood pressure were unaffected. Four

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adverse events (AEs) were reported by each group: nasopharyngeal pain, sciatica, asthenia, and back pain the elderly group, and headache (2 cases), insomnia, and myopericarditis by the young group. Myopericarditis led to study discontinuation for this subject and was considered to be of probable viral etiology. All other AEs were mild to moderate in intensity.

Conclusion: The pharmacokinetic profile of etamicastat was not significantly different in these small groups of healthy young versus elderly adult male volunteers. (*Clin Ther.* 2011;33:776–791) © 2011 Published by Elsevier HS Journals, Inc.

Key words: age effect, dopamine-β-hydroxylase, dopamine-β-hydroxylase inhibition, etamicastat, heart failure, hypertension, pharmacokinetics.

INTRODUCTION

Activation of the sympathetic nervous system is an important feature in hypertension and congestive heart failure.[1–6] This sympathetic activation, in addition to causing blood pressure elevation, most likely also contributes to left ventricular hypertrophy and to the commonly associated metabolic abnormalities of insulin resistance and dyslipidemia.[1] Inhibition of sympathetic nerve function with adrenoceptor antagonists is a rational approach, but some patients do not tolerate the immediate hemodynamic deterioration that accompanies adrenoceptor blockade, particularly heart failure patients.[7]

An alternative strategy for directly modulating sympathetic nerve function is to reduce the biosynthesis of noradrenaline via inhibition of dopamine-β-hydroxylase (DβH),[8] the enzyme that catalyzes the conversion of dopamine into noradrenaline in the catecholamine biosynthetic pathway. The inhibition of DβH has several putative advantages over adrenoceptor blockade, such as gradual sympathetic modulation as opposed to abrupt inhibition of the sympathetic system observed with β-blockers.[9] In addition, inhibition of DβH increases the release of dopamine,[10,11] which can promote renal vasodilation, diuresis, and natriuresis.[9,12,13] Therefore, it may be hypothesized that DβH inhibitors could be advantageous over conventional pure β-blockers or mixed α,β-blockers.

Several DβH inhibitors have been described. The early first and second generation DβH inhibitors, such as disulfiram,[14] diethyldithiocarbamate[15] or fusaric acid,[16] and aromatic or alkyl thioureas,[17] were devoid of selectivity for DβH and presented a nonsatisfactory tolerability profile. A third generation DβH inhibitor, nepicastat (RS-25560-197, Roche Bioscience, Palo Alto, California),[8] was a selective and potent DβH inhibitor that was developed in early clinical trials.[18] Although devoid of some of the problems associated with the earlier DβH inhibitors, nepicastat development in congestive heart failure did not progress. Because nepicastat is able to cross the blood–brain barrier and is a central nervous system active DβH inhibitor, its clinical development is in progress for the indication of cocaine addiction (NCT00656357 at www.clinicaltrials.gov) and post-traumatic stress disorder(NCT00641511andNCT00659230atwww.clinicaltrials.gov). Therefore, there yet remains an unmet clinical need for a potent, safe, and peripherally selective DβH inhibitor.

Etamicastat (development code BIA 5-453) is a potent and reversible inhibitor of peripheral DβH currently under clinical development for the treatment of hypertension and heart failure. Etamicastat is a reversible DβH inhibitor, displaying mixed (noncompetitive) type inhibition with respect to dopamine with a low nanomolar inhibition constant (Ki) value,[19] which prevents the conversion of dopamine to noradrenaline in peripheral sympathetically innervated tissues and slows down the drive of the sympathetic nervous system.[20] In contrast to that found in peripheral tissues, etamicastat does not affect dopamine and noradrenaline tissue levels in the brain.[20]

Etamicastat was tested in animal models predictive of efficacy in cardiovascular disorders.[21–23] Etamicastat reduced systolic (SBP) and diastolic blood pressure (DBP) in spontaneously hypertensive rats with no changes in normotensive Wistar-Kyoto rats.[21,22] Etamicastat did not affect heart rate (HR) in both spontaneously hypertensive rats and Wistar-Kyoto (WKY) rats. Etamicastat increased survival rates in male cardiomyopathic hamsters (Bio TO-2 dilated strain) with advanced congestive heart failure.[23]

The metabolism of etamicastat is species dependent.[24] In the rat, *N*-acetylation is the major metabolic pathway leading to the formation of BIA 5-961. All other metabolites occur in minor amounts and correspond to oxidative deaminated (BIA 5-965), C-oxidated (BIA 5-998), and N-oxidated (BIA 5-1016) derivatives of etamicastat.[25] Entry-into-man studies in healthy subjects administered a single oral doses of etamicastat (range, 2–1200 mg) and multiple doses (range, 25–600 mg/d) showed approximately dose-

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