Comparative Pharmacokinetic Analysis of Thiamine and Its Phosphorylated Metabolites Administered as Multivitamin Preparations

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ABSTRACT

Purpose: Fursultiamine and benfotiamine are lipophilic thiamine derivatives used as oral sources of thiamine. Although there are many publications on the pharmacokinetic (PK) properties of thiamine-containing products, no direct comparisons between these agents . We aimed to compare the PK profiles of these lipophilic thiamine derivatives and to compare the extent of the increase in bioavailability to that of naïve thiamine.

Methods: Two randomized, single-dose, 2-way crossover, full PK studies were conducted in healthy Korean male subjects (n = 24 per group). Among the test compounds, fursultiamine was compared with benfotiamine (reference A in study A) and thiamine nitrate (reference B in study B). All formulations were multivitamin preparations containing the test or reference formulation as the major thiamine source. In study A, the plasma and hemolysate concentrations of thiamine and its metabolites were measured, while only the plasma thiamine concentration was assayed in study B.

Findings: The systemic thiamine exposure of the test compound was slightly greater than that of reference A, based on the geometric mean ratio (%) of the AUC_{last} value for plasma (116.6%) and hemolysate (137.5%). The thiamine diphosphate (TDP) distribution between plasma and hemolysate showed clear differences according to the formulations, in that more TDP was present in the hemolysate when thiamine was given as the test formulation. The AUC_{last} value of plasma thiamine showed a >300% increase when thiamine was given as the test formulation in study B. The summed total exposure to thiamine (thiamine + TDP in both plasma and hemolysate) observed as a point estimate after the administration of fursultiamine was slightly greater than that with benfotiamine; however, the 90% CI was within the conventional bioequivalence range.

Implications: These findings support clear benefits of lipophilic thiamine derivatives in the absorption of thiamine in healthy volunteers. Clinical Research Information Service identifiers: KCT0001419 (study A), KCT0001628 (study B). (*Clin Ther.* 2016;38:2277–2285) © 2016 Elsevier HS Journals, Inc. All rights reserved.

Key words: multivitamin, pharmacokinetics, phosphorylated, thiamine.

INTRODUCTION

Thiamine, also known as vitamin B_1, plays a fundamental role in energy metabolism.[1] It is not synthesized in the human body; thus, it needs to be ingested via the diet or as a nutritional supplement to maintain homeostasis.[2] Thiamine has several phosphorylated metabolites: thiamine monophosphate (TMP), thiamine diphosphate (TDP), and thiamine triphosphate. TDP is biologically active and acts as a cofactor for several enzymes, such as pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, and transketolase, whereas it remains unknown as to whether there is a specific biological role for TMP in humans.[1,3]

The absorption of thiamine occurs primarily in the jujunum and ileum, with lesser amounts absorbed in the duodenum. Free thiamine is transported in the proximal

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small intestine by a saturable transport system that is thought to limit the absorption of thiamine after oral administration.[4] To increase the bioavailability of thiamine, various lipophilic thiamine derivatives, such as fursultiamine (thiamine tetrahydrofurfuryl disulfide) and benfotiamine (*S*-benzoylthiamine *O*-monophosphate), have been developed and have been associated with significant improvements in bioavailability compared with water-soluble thiamine.[3,5–8] Few pharmacokinetic (PK) data in humans exist in the literature, and those available are inconsistent among studies. For example, benfotiamine was reported to have greater systemic exposure compared with fursultiamine after the administration of 50 mg in healthy subjects,[9] whereas a greater systemic exposure and faster absorption of fursultiamine, as compared to those from the previous study,[9] were published.[10] Moreover, those PK studies were conducted using single-substance preparations, while most lipophilic thiamine derivatives are typically used in multivitamin preparations. Thus, a PK study using a multivitamin complex is desirable to reflect the interactions among such substances in the preparations. In this study, we aimed to compare the PK profile and relative bioavailability of fursultiamine to those of benfotiamine and thiamine nitrate.

SUBJECTS AND METHODS

Study Design and Ethical Considerations

Two separate studies (A and B) were designed as open-labeled, randomized, single-dose, 2-way crossover trials in Korea involving healthy male subjects. Each study period was separated by a 7-day washout period. Subjects enrolled in each study were assigned randomly to a sequence group for the 2 treatments by computer-generated randomization. In each study, sequence group 1 received the reference formulation in period 1 and the test formulation in period 2 and vice versa in sequence group 2. Subjects received a single, oral, 50-mg dose of fursultiamine or benfotiamine in study A and 100 mg of fursultiamine or thiamine nitrate in study B.

The protocols were approved by the institutional review board at Seoul St. Mary's Hospital (Seoul, Republic of Korea). All study-related procedures were conducted in accordance with the Declaration of Helsinki, as revised in 2008 (final revision, Seoul, Republic of Korea), and the Korean Good Clinical Practice guidelines, as revised in 2013. The studies were registered with the Clinical Research Information Service (KCT0001419 [study A]; KCT0001628 [study B]).

Investigational Products

The test product was Aronamin Gold®,* which contains 50 mg of fursultiamine (a thiamine derivative) with riboflavin tetrabutyrate 2.5 mg, pyridoxal-5-phosphate 2.5 mg, hydroxocobalamin acetate 5.22 μg, and ascorbic acid 72.2 mg. The reference formulations used in studies A and B were Impactamin Power®† (reference A) and VitaB-100®‡ (reference B), respectively. Reference A contains benfotiamine (a thiamine derivative) 50 mg, riboflavin 50 mg, niacinamide 50 mg, calcium D-pantothenate 50 mg, pyridoxine hydrochloride 50 mg, biotin 0.05 mg, inositol 50 mg, folic acid 0.2 mg, cyanocobalamin 0.05 mg, coated ascorbic acid 31.25 mg, choline bitartrate 50 mg, and zinc oxide 18.7 mg. Reference B contains thiamine nitrate 100 mg, riboflavin 100 mg, nicotinamide 100 mg, calcium pantothenate 100 mg, pyridoxine hydrochloride 100 mg, biotin 0.1 mg, folic acid 0.4 mg, cyanocobalamin 0.01 mg, and ursodeoxycholic acid 30 mg.

Subjects

Healthy Korean male volunteers, aged 20 to 45 years, were eligible for inclusion in the study if they weighed >50 kg and were within ± 20% of their ideal body weight. Their medical histories were recorded, and physical examinations, laboratory tests (hematology; clinical chemistry; urinalysis; and serology including hepatitis B virus surface antigen, anti–hepatitis C virus, and anti-HIV antibodies), and 12-lead ECG were performed for screening.

Exclusion criteria included diseases or abnormal diet that could have influenced the absorption, disposition, metabolism, or excretion of thiamine and its metabolites; a history of alcohol or drug abuse; participation in another clinical trial within 60 days prior to the start of the study; smoking >10 cigarettes per day; consumption of >5 glasses of beverages containing xanthine derivatives; and the use, within 7

*Trademark of Ildong Pharmaceutical Co Ltd (Seoul, Republic of Korea).

†Trademark of Daewoong Pharmaceutical Co Ltd (Seoul, Republic of Korea).

‡Trademark of Yuhan Corporation (Seoul, Republic of Korea).

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