Brief Report

Investigation of Potential Pharmacodynamic and Pharmacokinetic Interactions Between Selexipag and Warfarin in Healthy Male Subjects

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ABSTRACT

Purpose: Selexipag is a new orally available nonprostanoid prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension. Warfarin is commonly used in patients with pulmonary arterial hypertension. Possible pharmacodynamic and pharmacokinetic interactions between selexipag and warfarin in healthy individuals were investigated.

Methods: This was a double-blind, 2-way, 2-treatment crossover, Phase I study. Nineteen healthy men received a single dose of selexipag 400 μg or placebo on day 1, followed by selexipag 400 μg or placebo BID on days 2 to 12. A concomitant single dose of warfarin 20 mg was administered in the morning of day 8.

Findings: Both treatments were well tolerated. The most frequently reported adverse event was headache in both treatments. Geometric mean ratios and 90% CIs of the maximum international normalized ratio (geometric mean ratio = 0.96; 90% CI, 0.90–1.03) and international normalized ratio AUC_{0-144h} (geometric mean ratio = 0.98; 90% CI, 0.96–1.00)] during treatment with warfarin and selexipag versus treatment with only warfarin were inside the reference limits of 0.80 to 1.25. The 90% CIs of the geometric mean ratios of AUC and C_{max} for R- and S-warfarin during treatment with warfarin and selexipag versus treatment with warfarin alone were inside the reference range of 0.80 to 1.25. After repeated-dose administration of 400 μg selexipag, the AUC of selexipag and its active metabolite, ACT-333679, at steady state were not affected by a single dose of 20 mg warfarin.

Implications: Steady-state levels of selexipag and ACT-333679 after repeated doses of 400 μg selexipag had no influence on the warfarin pharmacodynamic variables. There was no pharmacokinetic interaction between selexipag and warfarin. (*Clin Ther*. 2016;38: 1228–1236)

Key words: drug-drug interaction, pharmacodynamics, pharmacokinetics, selexipag, warfarin.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a disease of the pulmonary arterioles characterized by progressive increases in pulmonary artery pressure and pulmonary vascular resistance.[1] Prostacyclin (PGI_2) is a potent vasodilator, inhibitor of platelet aggregation, and inhibitor of smooth muscle cell proliferation.[2–4] These effects are mediated via the PGI_2 receptor (IP receptor). The binding of prostacyclin to the IP receptor, a G-protein coupled receptor on the surface of vascular smooth muscle cells, triggers an increase of intracellular cyclic adenosine monophosphate (cAMP), which in turn mediates the cellular effects of PGI_2.[5] The predominant cardiovascular actions of PGI_2 are vasodilation and inhibition of smooth muscle cell proliferation and of profibrotic pathways in fibroblasts.[3,6] Thus, prostacyclin contributes to the maintenance of vascular homeostasis, and its decrease leads to vasoconstriction and proliferation of vascular smooth muscle cells. Because PAH is associated with vasoconstriction, proliferation, and

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thrombosis, restoration of IP receptor signaling using IP receptor agonists is an effective strategy in the treatment of the disease.[7,8]

Selexipag (ACT-293987) is an orally bioavailable, nonprostanoid IP receptor agonist, which is rapidly absorbed after oral administration and hydrolyzed to the pharmacologically more active metabolite ACT-333679 through hepatic carboxylesterase 1.[9–13] Cytochrome P450 (CYP) 2C8 and CYP3A4 are also involved in the metabolism of both selexipag and ACT-333679, whereas the UDP-glucuronosyltransferase (UGT) enzymes UGT1A3 and UGT2B7 are involved only in the metabolism of ACT-333679. Biliary elimination accounts for approximately 90% of the excretion of selexipag and its metabolites in animals and humans.[13] Selexipag and ACT-333679 are both highly selective for the human IP receptor. Selexipag recently was granted approval by the US Food and Drug Administration and Health Canada and received a positive opinion of the Committee for Medicinal Products for Human Use in Europe for the treatment of PAH. In the event-driven, phase III, randomized, double-blind Prostacyclin (PGI2) Receptor agonist In Pulmonary arterial HypertensiON (GRIPHON) study, the efficacy and safety of selexipag among patients (n = 1156) with PAH were investigated. Selexipag reduced the risk of the composite primary end point of morbidity or mortality events up to the end of treatment by 40% (log rank $p < 0.0001$) in patients treated with selexipag versus placebo.[14]

Warfarin is an anticoagulant with a narrow therapeutic index that is used for prevention of systemic embolization. The degree of anticoagulation induced by warfarin should be carefully monitored during treatment by measuring the international normalized ratio (INR) and the dose adjusted accordingly.[15] Warfarin is a racemic mixture of the R and S enantiomers. S-warfarin is 3 to 5 times more potent than R-warfarin as an inhibitor of the vitamin K epoxide reductase complex. Enantiomers of warfarin are metabolized by different CYP enzymes. R-warfarin is metabolized primarily by CYP1A2 and CYP3A4. S-warfarin is metabolized primarily by CYP2C9. The efficacy of warfarin is affected in particular when the metabolism of S-warfarin is altered.[16,17] Drugs that compete as substrates for these enzymes or inhibit their activity may increase warfarin plasma concentrations and INR, potentially increasing the risk of bleeding. There is no known inhibitory or inductive effect of warfarin on the enzymes involved in the metabolism of selexipag and ACT-333679.[16,18,19] Previous studies have found that concomitant treatment with multiple-dose lopinavir/ritonavir, a strong inhibitor of CYP3A4, and selexipag did not result in a clinically meaningful change in the pharmacokinetic (PK) of ACT-333679.[13] It is, therefore, unlikely that warfarin would affect the PK of selexipag by competing for CYP3A4, which is involved in the metabolism of both drugs.

On the basis of in vitro studies, it is not expected that selexipag and its active metabolite ACT-333679 have an inhibitory effect on the CYP enzymes involved in the metabolism of warfarin (Actelion Pharmaceuticals Ltd, data on file). Anticoagulants, particularly warfarin, are often used in patients with PAH who are eligible to receive PAH-targeted therapy, such as selexipag.[20] The objective of this study was, therefore, to examine the lack of interaction between selexipag and warfarin in healthy individuals.

METHODS

Study Population

Eighteen healthy men, aged 18 to 45 years, with a body mass index of 19 to 30 kg/m^2, were to be enrolled in the study. Men with no history or clinical evidence of any disease and/or existence of any surgical or medical condition that might interfere with the PK properties of the drug or that might predispose them to an increased risk of bleeding were eligible for the study. Men were included in the study if during screening no clinically relevant findings in physical examination, vital signs, laboratory values, and 12-lead ECG results were obtained. Tests for drugs of abuse and alcohol were performed at screening and admission. The CYP2C9 genotype was determined at screening. Men who had used other investigational drugs, smoked, or donated blood within 3 months before the first dosing were excluded from the study.

Before any study procedure, written informed consent was obtained from each participant after adequate explanation of the objectives, methods, and potential hazards of the study. The protocol was approved by the Research Ethics Committee at St Thomas' Hospital (London, United Kingdom). The study was conducted in full compliance with the principles of the Declaration of Helsinki and with laws and regulations of the United Kingdom, where the research study was conducted. Before any activities were started, the Medicines and