Population Pharmacokinetic Analysis of the Major Metabolites of Capecitabine

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Capecitabine has been developed as an orally administered tumor selective fluoropyrimidine for use in the treatment of breast and colorectal cancer. The metabolic pathway for capecitabine includes 5′-deoxy-5-fluorocytidine (5′-DFCR) and 5′-deoxy-5-fluorouridine (5′-DFUR), which is then converted to the pharmacologically active agent 5-fluorouracil (5-FU). A previous analysis showed that systemic exposure to 5′-DFUR and α-fluoro-β-alanine (FBAL), a catabolite of 5-FU, was predictive of dose limiting toxicities. Therefore, a multi-response population pharmacokinetic (PK) model for the description of plasma concentrations of 5′-DFUR, 5-FU and FBAL following oral administration of capecitabine was developed using NONMEM. PK data from a bioequivalence study in 24 patients with various solid tumors were used to develop the PK structural part of the population PK model. The 5′-DFUR, 5-FU and FBAL plasma concentrations were described by a linear disposition PK model with first order absorption and lag time. Sparse plasma concentration data from 54 Phase II breast cancer patients were added to the bioequivalence data and the influence of covariates on the apparent oral clearances of 5′-DFUR, 5-FU and FBAL and on the apparent volume of distribution of FBAL was investigated. This was conducted by including all significant (p<0.05) single covariate-PK parameter pairs in the full PK model, followed by one by one deletion (p<0.001) from the population model. Statistically significant effects were found for the influence of gender, body surface area and total bilirubin on 5′-DFUR clearance and the influence of creatinine clearance on FBAL clearance. However, none of these effects were considered to have clinical relevance.

KEY WORDS: capecitabine, 5-FU, population pharmacokinetics, NONMEM.

INTRODUCTION

Capecitabine is a newly developed orally administered tumor selective fluoropyrimidine for use in the treatment of colorectal and breast cancer. After oral administration, capecitabine is well absorbed and metabolized

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primarily in the liver by the 60kDa carboxylesterase to 5′-deoxy-5-fluorocytidine (5′-DFCR), which is then converted to 5′-deoxy-5-fluorouridine (5′-DFUR) by cytidine deaminase, principally located in the liver and tumor tissues (1). Further metabolism of 5′-DFUR to 5-fluorouracil (5-FU) occurs throughout the body including the site of the tumor by pyrimidine nucleoside phosphorylase (PyNPase), which is present at considerably higher concentrations in tumor tissues compared to normal tissues. Known catabolites of 5-FU are 5,6-dihydro-5-fluorouracil (FUH₂), α-fluoro-β-ureido propionic acid (FUPA) and α-fluoro-β-alanine (FBAL).

The relationship between exposure to capecitabine and its metabolites and the occurrence of adverse effects has been previously reported (2). Pharmacokinetic and safety data from two Phase I studies (using either a continuous or an intermittent two-weeks on/one-week off schedule) were combined and logistic regression was used to quantify the exposure-effect relationships. Cmax and AUC for 5′-DFUR and FBAL were found to be predictive of Dose Limiting Toxicities (DLT), whereas systemic exposure to 5-FU was poorly predictive, and exposure to intact drug or 5′-DFCR was not predictive. These results suggested that the pharmacokinetics of 5′-DFUR, FBAL, and 5-FU (as the intermediate metabolite and active moiety after administration of capecitabine) should be further investigated because of their potential relationship to adverse events.

The objective of this investigation was to develop a population multi-response pharmacokinetic model for capecitabine’s main metabolites (5′-DFUR, 5-FU, FBAL) following oral administration of capecitabine. This included investigating the influence of covariates (e.g., patient characteristics, type of cancer) on the pharmacokinetic parameters of 5′-DFUR, 5-FU and FBAL. A preliminary structural pharmacokinetic model for 5′-DFUR, 5-FU and FBAL was developed using the data from a bioequivalence study performed in patients with various solid tumors. A more comprehensive population pharmacokinetic model was subsequently developed using the data from both a Phase II breast cancer study and the bioequivalence study.

METHODS

Patients

A total of 78 patients from two studies were included in the present analysis: 24 adult patients with solid tumors from a bioequivalence study (3) and 54 adult patients with breast cancer from a Phase II study (4).