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Quantifying Induction/Inhibition Effects on Fuzuloparib Using a Physiologically Based Pharmaco-Kinetic (PBPK) model

Jingxi Li[1], Keheng Wu[2], Xue Li[2], Sihui Long[1], Zhou Zhou[2] Youni Zhao[2], Ranran Jia[2], Pingping Song[3], Jack Liu[2] and Bo Liu[1*]

Abstract

The model was verified using the clinical study of fuzuloparib with moderate inhibitor fluconazole and strong inducer rifampicin. After validation, the model was used to predict the effects of the mild inhibitor fluvoxamine and moderate

of efavirenz or fluvoxamine on fuzuloparib. The model predicted that the AUC
the efavirenz and fluvoxamine were 0.71 and 1.14 times of the original, respectively. It is suggested that efavirenz significantly affects fuzuloparib exposure and should be avoided when used together with fuzuloparib. Fluvoxamine 50 mg has no significant effect on fuzuloparib exposure. Higher doses of fluvoxamine increase the risk and should
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Keywords: CYP3A; Inhibi o ; Ind ce ; F lo a ib; Pha ma-co ine ic/Pha macod na mic model; D g-d g in e ac ion

Introduction

F lo a ib i a PARP inhibi o inde enden ly de elo ed by Jiang Heng i Medicine Co. L d fo ea ing o a ian cance and o he olid cance in a ien i h ge mline BRCA m a ion ho ha e nde gone econd-line o abo e che mo he a y. P eclinical ha macological e l ho ed ha f lo a ib co ld ignifi can ly inhibi PARP ac i i y and mo g o h in vivo and in vitro, and ha e ignifi can an i- mo e ec [1-6]. In he do e-e calae do aile 9 0 0 9 0 0 e38h o ha ma321 y deo7 T TTJ0.10321 Td[(e(e)-5 (d ig)-4.9 (nA)53 (UCo)7 ( )-4 5.2471 ( ) o mach o 6 h a e a meal, hile he e ec on e o e o AUC

0- and C ma e e in ignifi can [7]. In vitro d y of f lo a ib i h h man li e mic o o me c ochrome P450 en y me (CYP450) indica ed ha CY3A4/5 i he ima y CYP i ofo m in ol ed in he me aboli m of f lo a ib [6]. I i nece a y o d y he D g-D g In e ac ion (DDI) be een d g me aboli ed by CYP3A4/5 and f lo a ib. Fo e am le, en y me ind c ion by d g and o he enobio ic chemical e e di co e ed mo e han 30 y ea ago. The ind c ion co ld inc ea e he me aboli m and clea ance of a ha macologicall y ac i e d g, leading o a ed c ion in ha macological ac i i y [8].

Th i d y aim o edic he e ec of mild me aboli m-inhibi o fl o amine and mode a e me aboli m-ind ce efa i en on f lo a ib e o e. The PBPK model cce f lly edic ed he im ac of fl cona ole (a mode a e inhibi o) on d g by a e me aboli ed ima ily by CYP2C9 and CYP3A [9]. I i he fi ime o e hi model o edic he ind c ion e ec of an ind ce on a b a e li e f lo a ib. Do ing g idance a al o o ided fo llo ing he modelling die . In hi d y, he PBPK model a e abli hed ba ed on he mechani m of DDI and he in ence of li e blood-

d g concen a ion of inhibi o /ind ce on en y me ac i i y. Blood

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$$CL_{int,h,ind} = CL_{int,h} \cdot \left(1 + E_{max} \cdot \frac{\frac{f_u \cdot I_h}{K_{liver}}}{EC_{50} + \frac{f_u \cdot I_h}{K_{liver}}}\right)$$

$CL_{int,h}$ is the hepatic clearance rate. E_{max} is the maximum induction ratio. I_h is the hepatic concentration. f_u is the unbound fraction of the drug in the liver. K_{liver} is the ratio of liver to plasma concentration. EC_{50} is the concentration of the inducer at half maximum induction.

The PBPK model was established and validated using clinical data on the observed effects of food, and then validated using the moderate inhibitor fluconazole and the strong inducer rifampicin, respectively. The maximum dose and dosage form of the clinical trial studies were used in the fluzoparib PBPK model. To ensure the feasibility of detection and minimize impact on the healthy subjects, the dose of fluzoparib in the study was selected as 50 mg/day [6].

In vitro and *in vivo* parameters were used during modelling. *In vitro* data described the physicochemical properties and metabolism of the drug. The drug's absorption, distribution, and elimination parameters, such as K_a, V_1, K_{12}, K_{21}, and [illegible], were derived from *in vivo* data. K_a is the absorption rate. V_1 is the central compartment volume. K_{12}/K_{21} is the absorption and elimination rate of the two-compartment in the two-compartment model, and [illegible] is the delay time. When K_{12}/K_{21}=0, a one-compartment model was used in the simulation.

Simulations of DDIs

No clinical studies have been published on the effects of the moderate inducer efavirenz or the mild inhibitor fluvoxamine on fluzoparib. Based on the dose information published by Jiangsu Hengrui Medicine Co. LTD [4], efavirenz was orally taken 600 mg/day until the plasma concentration reached a steady state, and then fluzoparib 50 mg was orally taken in combination. For inhibitor, fluvoxamine was orally taken 50 mg/day until the plasma concentration reached a steady state, and then fluzoparib 20 mg was orally taken in combination. Fifty healthy men were simulated in both studies.

PBPK modelling software

This study used a web-based platform B_2O simulator to simulate drug exposure in the presence of DDI. Ratios between exposure with and without DDI perpetrators (inducer or inhibitor) were calculated and compared with clinical studies (if available). With the lower and upper CI% (confidence interval) limit of 2.5%-97.5%, the geometric mean of all C_{max} and AUC_{0-} were calculated. Changes that were 2 fold were considered significant.

Results

Parameters used in the PBPK model

Parameters were used to simulate single drug plasma concentrations to evaluate the model's performance at the beginning of modelling. The parameters were adjusted to the single drug model best, and the results are shown in Table 1. The drug is assumed

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