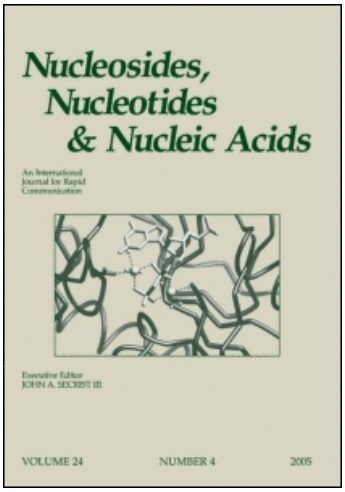

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PHARMACOKINETIC MODELLING OF [2-^{13}C]URACIL METABOLISM IN NORMAL AND DPD-DEFICIENT DOGS

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□ *A physiologically based pharmacokinetic (PBPK) model to simulate the plasma concentration and $^{13}CO_2$ exhalation after [2-^{13}C]uracil administration to DPD-suppressed dogs was developed. Simulation using this PBPK model should be useful in clinical situations where DPD-deficient patients at risk are to be detected with [2-^{13}C]uracil as an in vivo probe.*

Keywords ^{13}C; uracil; Breath test; Physiologically based pharmacokinetic model

INRODUCTION

Dihydropyrimidine dehydrogenase (DPD), the first enzyme in the sequential metabolism of pyrimidines, regulates blood concentrations of 5-fluorouracil, and is implicated in its toxicity. [2-^{13}C]Uracil (^{13}C-uracil) is metabolized by pyrimidine-metabolizing enzymes and finally expired as $^{13}CO_2$. To understand the pharamacokinetics of pyrimidine catabolism, ^{13}C-uracil was orally administered to DPD normal dogs or DPD suppressed dogs prepared by pretreatment with 5-(*trans*-2-bromovinyl)uracil (BVU).[1] The concentrations of drug in the blood and $^{13}CO_2$ in breath were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) and gas chromatograph isotope ratio mass spectrometry (IRMS), respectively. We

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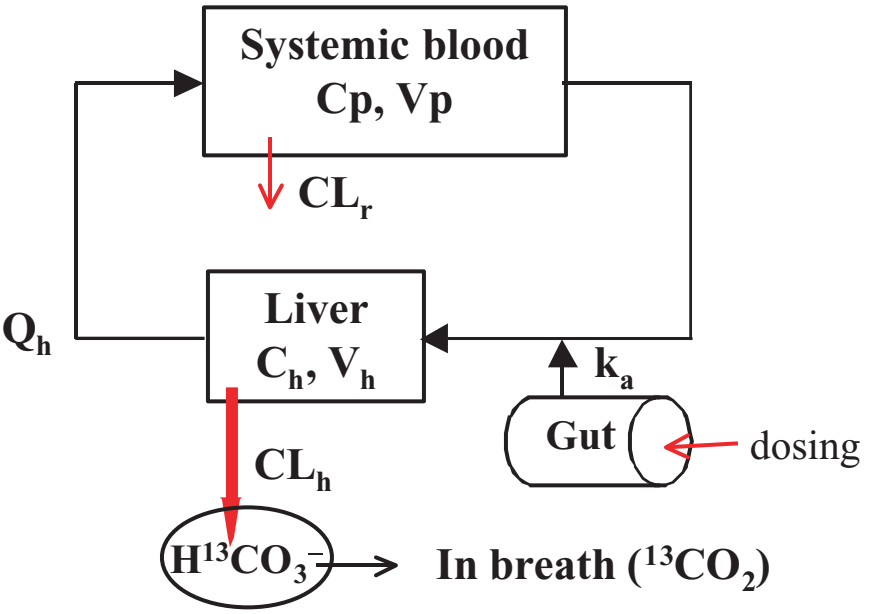

FIGURE 1 A physiologically-based pharmacokinetic model for breath output of ^{13}C-uracil.

speculate that the DPD-deficient dog model is a good surrogate model for DPD deficient patients.

METHODS

A PBPK model (Figure 1) was constructed to describe the time course of plasma concentrations of ^{13}C-uracil and $^{13}CO_2$ in expired air. This model incorporates Michaelis-Menten catabolic and first-order degradation processes. The differential equations for the PBPK model were expressed as follows:

1. $V_p \times (dC_p/dt) = Q_h \times C_h/K_p - Q_h \times C_p - C_p \times CL_r$
2. $V_h \times (dC_h/dt) = k_a \times F_a \times \text{Dose} \times e^{-kat} - f_p \times C_h \times CL_{int}/K_p - Q_h \times C_h/K_p + Q_h \times C_p$
3. $d\Delta/dt = fp \times C_h \times CL_{int}/K_p \times (at + b)$

$CL_{int} = V_{max}/(K_m + f_p \times C_h/K_p)$, K_p, f_p and F_a were set at 1.0 according to our preliminary experiments. Where V_h is the volume of the liver; V_p is the volume of distribution in rapidly equilibrating tissues, including the systemic plasma compartment of ^{13}C-uracil; C_h is the concentration of ^{13}C-uracil in liver; C_p is the plasma concentrations of ^{13}C-uracil; Q_h is the hepatic blood flow rate; K_p is the liver-to-blood concentration ratio of ^{13}C-uracil; CL_r is the renal clearance of ^{13}C-uracil; CL_{int} is intrinsic metabolic

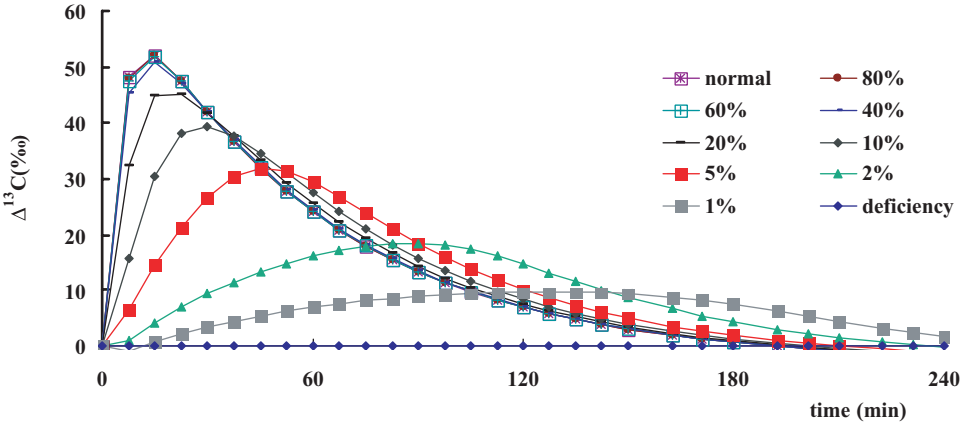

FIGURE 2 Simulation of exhalated $^{13}CO_2$ after oral administration of [2-^{13}C]uracil at dose of 20 μmol/kg in dogs.

clearance; V_{max} and K_m are the maximum rate of ^{13}C-uracil metabolism and the Michaelis-Menten constant, respectively; f_p is the unbound fraction of ^{13}C-uracil in plasma; and a and b are constants. The pharmacokinetic software SAAM II (SAAM Institute Inc., Seattle, WA, USA) was used for nonlinear least squares analysis.

RESULTS

The pharmacokinetic parameters estimated by nonlinear least squares regression were followed: $K_m = 0.416$ μg/mL, $V_{max} = 9030$ μg/min, $V_p = 2.22$ L and $k_a = 0.221$ min^{-1}. We simulated the plasma concentration after intravenous administration of ^{13}C-uracil (Figure 2) and $^{13}CO_2$ exhalation after oral administration of ^{13}C-uracil (Figure 3) by changing the V_{max} value by use of computer. The breath response after oral administration changed drastically, when the residual DPD activity was less than 10%. The blood concentration of ^{13}C-uracil after intravenous administration changed, when the residual DPD activity was less than 10%.

DISCUSSION

Diagnostic methods able to predict and prevent adverse drug reactions to 5-FU in patients with pyrimidine metabolism disorders have been actively desired. Although several methods are now available, including quantification of urinary pyrimidine,[2,3] measurement of DPD activity in peripheral monocytes[4,5] and evaluation of DPD genotype,[6,7] none are considered highly reliable for carrier detection. The breath response

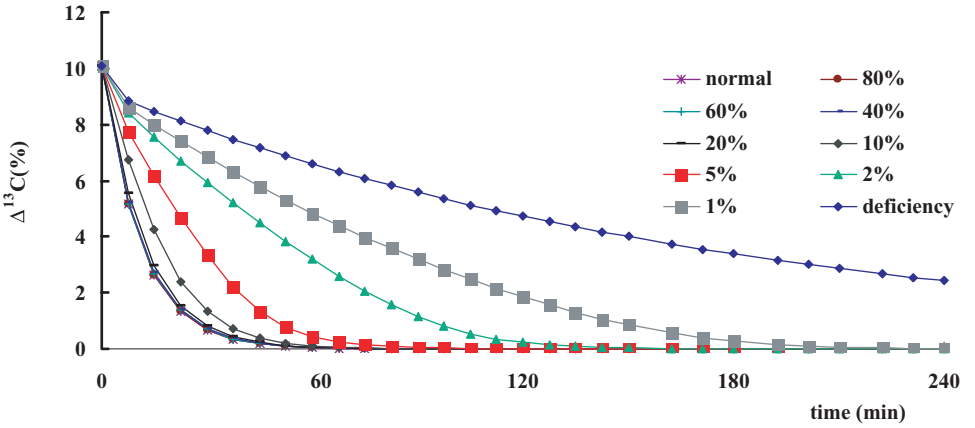

FIGURE 3 Simulation of plasma concentration of [2-^{13}C] uracil after intravenous administration at dose of 20 μmol/kg in dogs.

($^{13}CO_2$) after ^{13}C-uracil administartion to dogs reflected the degree of DPD activity in the liver. We strongly speculate that ^{13}C-uracil breath test facilitates the identification of patients at risk of a severe adverse response to chemotherapeutic treatment with 5-FU. Our PBPK model could predict the breath response and the plasma concentration of ^{13}C-uracil in various DPD suppressed conditions. Our PBPK mode was validated by the breath data by Mattison et al.[8] who administrated ^{13}C-uracil to the DPD deficient patients across wide range activity. We believe that this model may be useful for the preliminary assessment of inter-individual variability in 5-FU pharmacokinetics and toxicity caused by genotype-dependent DPD deficiency in humans.

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