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TRANSLATABILITY OF HUMAN PK PROFILE FROM ANIMAL DATA BY A NEW CONCEPT EXPLORATORY PPK ANALYSIS USING NONMEM(E-PPK)

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[Purpose] We had recently proposed a new concept that might be applied on drug discovery process for predicting human pk profile based on the NONMEM analysis1), which was named as exploratory population pharmacokinetics (e-ppk). The aim of this analysis is to compare the predictability of human clearance and half life by e-ppk analysis with those calculated by PBPK analysis, because the availability has not been assured yet.

[Methods] Eleven clinically tested compounds were selected for the comparison analysis. The two-compartment pharmacokinetics models were adopted to all compounds on this analysis. The predicted human pk parameters were quoted from previous report. The commonly used analysis such as in vitro – in vivo extrapolation and physiological based pharmacokinetics models were chosen for the competitors, and the hepatic clearances and pk profiles were also estimated.

[Results and Discussion] The predictability of pk parameters obtained from e-ppk was almost comparable to those from common methods, suggesting the availability of the e-ppk methodology. To understand well the pkpd relationship of new chemical entity in human before entering phase 1 study, this kinds of prediction might become a key point. Once getting time-course of both pk and pd marker, we can provide the more reliable information to scientific discussion related to the estimation of pharmacologically relevant dosage regimen.

[Conclusions] This results insured the adequacy of the new concept and e-ppk should be a promising tool for the translational research in pharmaceutical industry.


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DISPOSITION OF A NEW TAMIBAROTENE PRODRUG IN MICE

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[Purpose] Recently, a new compound IT-M-07000 was designed as a prodrug of tamibarotene, one of the therapeutic agents for acute promyelocytic leukemia. In the present study, IT-M-07000 was administered to mice to investigate whether it is actually metabolized to tamibarotene. Its metabolic pathway and the utility as a tamibarotene prodrug were also evaluated.

[Methods] IT-M-07000 (3.3 mg/kg) or tamibarotene (3.3 mg/kg) was administered orally to ddY mice. Blood was collected at 0.25, 0.5, 1, 2, 3, 6, and 12 h after administration, and the compounds in plasma were identified by LC/MS and quantified by HPLC.

[Results and Discussion] IT-M-07000, tamibarotene and two compounds that were supposed to be metabolic intermediates in a β-oxidation pathway of IT-M-07000 to tamibarotene were detected in mouse plasma after oral administration of IT-M-07000. It was thus shown that IT-M-07000 is probably β-oxidized to tamibarotene in mice. Comparison of tamibarotene concentration profiles after oral administration of IT-M-07000 or tamibarotene showed that the plasma tamibarotene concentration increased slower and was retained stable, and the AUC of tamibarotene was larger in mice administered IT-M-07000 than tamibarotene.

[Conclusions] IT-M-07000 is possibly useful as a prodrug of tamibarotene with reduced side effects and expected longer duration of pharmacological effects.

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