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徐放性製剤の *In Vitro-In Vivo* 相関 (IVIVC) の活用に関する基礎的検討
― IVIVC モデルによる予測性に及ぼす *In Vivo* データの個体間変動の影響―

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Applicability of *In Vitro-In Vivo* Correlation (IVIVC) Analysis to Extended Release Formulations
― Effects of Inter-Subject Variation on the Predictive Ability of IVIVC ―

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Summary

We evaluated the effect of inter-subject variation in pharmacokinetic data on *in vitro-in vivo* correlation (IVIVC) analysis, in response to a question raised by the IVIVC Working Group, which is a collaboration between industry, government and academia. In this study, we created virtual data on metoprolol extended release tablet formulations by reference to the literature, and used them to investigate the relationship between inter-subject variation *in vivo* and the predictive ability of the IVIVC model.

Based on reference values, plasma concentrations of 12 individuals with 5 levels of inter-subject variation were generated for 3 formulations with different release rates. Pharmacokinetic parameters (C_{max}, AUC_{inf}) predicted by the IVIVC model constructed from the mean data were then compared with the values observed in the virtual subjects. Our results showed no significant difference between the observed and predicted values of C_{max} and AUC_{inf} at any inter-subject variation level (C_{max} ratio, 0.92–1.19; AUC_{inf} ratio, 1.00–1.07). Furthermore, this IVIVC model accurately predicted the inter-subject variability of C_{max} throughout the study. These observations suggest that inter-subject variability in pharmacokinetic data has no serious impact on IVIVC reliability. We consider that IVIVC models meeting the criteria for validation should also be effective for predicting the bioequivalence of extended release formulations. We anticipate that these results will accelerate discussions on the effective and practical use of IVIVC in Japan.

Key words

In vitro-in vivo correlation (IVIVC), Extended release formulation, Inter-subject variation, Predictive ability, Metoprolol tartrate, Biowaiver