Redefining normal variability of drug pharmacokinetics

Hesham S Al-Sallami\textsuperscript{1}, Song Lim Cheah\textsuperscript{1}, Shiou Yi Han\textsuperscript{1}, Joel Liew\textsuperscript{1}, Jin Lim\textsuperscript{1}, Mary Anne Ng\textsuperscript{1}, Hayneil Solanki\textsuperscript{1}, Run Jie Soo\textsuperscript{1}, Victoria Tan\textsuperscript{1}, Stephen Duffull\textsuperscript{1}

\textsuperscript{1}School of Pharmacy, University of Otago, Dunedin, New Zealand

Objective: The pharmacokinetics of many drugs are said to be predictable. However, predictability requires both accuracy (lack of bias) and precision (reproducibility). In the context of pharmacokinetics, precision is proportional to the inverse of between-subject variance (BSV). In this setting, the greater the BSV in PK parameters the less precise/predictable drug concentration will be across the population. BSV is quantified by the coefficient of variation (CV%). The current convention is that BSV in PK parameters is considered “low” (CV% ≤ 10%), “moderate” (CV% ~ 25%), or “high” (CV% > 40%).\textsuperscript{[1]} The objective of this work is to explore the range of BSV values in population PK parameters.

Methods: A literature review of population PK studies from various data sources was conducted. Estimates of clearance (CL) and volume of distribution (V) and their corresponding CV% were recorded.

Results: A total of 181 studies involving 95 drugs were reviewed. The mean CV% in CL/F was 40.3% and in V/F was 51.3%. The mean CV% in CL/F in predominately renally cleared drugs was 31% and those predominately hepatically cleared was 47.4%. Age, sex, weight, and renal function were among the most significant covariates reported across the drug classes.

Conclusions: According to the current convention most drugs show “moderate” to “high” BSV. The current convention needs to be recalibrated to consider that a low BSV in CL is < 25%, 25 – 50% is normal, and > 50% is high. Clinically, this means that a normal level of variability in CL would result in a 5- to 6-fold variability in steady state average plasma concentrations and therefore for all drugs with a low therapeutic index, monitoring plasma concentration or response and dose-individualisation will be essential.