Dosing Strategies of Drugs with Narrow Therapeutic Windows: A Simple Approach to Determine Trade-off Between Efficacy and Toxicity

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OBJECTIVES
Dosing strategies of drugs with narrow therapeutic windows are difficult to develop and apply in clinical practice. Population pharmacokinetics offers the possibility of explaining the between subject variability (BSV) with patient-specific covariates. The objective of this work was to develop a quick method to determine trade-offs between efficacy and toxicity in order to design better dosing strategies given a BSV of a drug with narrow therapeutic window.

METHODS

The methodology will be illustrated using a Drug X with a predefined AUC therapeutic window of 220 and 360 mg.h/L. A previous population pharmacokinetics analysis showed that body surface area (BSA) is a significant covariate on clearance:

\[ CL = TVCL \cdot \frac{BSA^{1.2}}{1.1} \]

The unexplained BSV on AUC was:

\[ BSV(AUC) = 38\% \]

The original dosing regimen was:

- 0.8 mg/m² for patients with BSA < 1.2 m² and 1.0 mg/m² for patients with BSA > 1.2 m².

This dosing regimen resulted in a median AUC of 200 mg.h/L and a percentage of patients in the sub-therapeutic, therapeutic and toxic range of 53%, 41% and 6%, respectively. Two methods were used in order to optimize the dosing strategy of this drug.

METHODS (Continued)

- Method I:
  The method of Jonsson et al. 1 was used to estimate optimal cutoffs and doses that will maximize the attainment of the therapeutic target. Strategies with 2, 3, and 5 BSA cutoffs were estimated. The loss function was chosen to be quadratic, symmetrical and centered around the middle of the therapeutic window (i.e: 290 mg.h/L). Each estimated dosing strategy was then tested by simulation (n=200), incorporating parameter uncertainty, and the percentage of patients within sub-therapeutic, therapeutic and toxic ranges were computed.
  - Method II:
    - The area under the log-normal distribution of AUC was used. The dosing strategy was assumed to change the location parameter (translation on the x-axis) but not the variance. Percentage of the patient population within sub-therapeutic, therapeutic and toxic ranges were computed and plotted versus the targeted AUC. The optimal AUC was deduced graphically as a trade-off between the population of patients in therapeutic and toxic ranges.

RESULTS

- Method I identified the optimal cutoffs and doses. When tested by simulation, the percentages of subjects within the sub-therapeutic, therapeutic and toxic range were computed for dose levels 2 (46%, 48%, and 6%, respectively), dose level 3 (21%, 55%, 24%, respectively) and dose levels 5 (25%, 56%, 19%, respectively) (refer to Figure 1). As the number of cutoffs increased, the distribution of AUC was more centered on the targeted exposure (i.e: the middle of the therapeutic range). However, because of the large variability the percentage of toxic patients did not necessarily decrease.

- Method II calculated the percentages of patients within the sub-therapeutic, therapeutic and toxic range as a function of the target AUC (Figure 2). This approach helps to visualize the percentage of patients in the therapeutic and toxic range for any targeted AUC.

CONCLUSION

Method I and II are complementary. Before conducting Method I, we suggest to determine graphically the best targeted AUC in order to determine the trade-off between patients in therapeutic and toxic ranges. Once an optimal target AUC is determined, Method I can be used to estimate the optimal cutoffs and doses that will center the distribution of AUC over the optimal target.

REFERENCES