Title: 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 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 pre-defined AUC therapeutic window of 220 and 360 mg.h/L. Assuming that a population pharmacokinetics analyses showed that BSA is a significant covariate on clearance (Power model, CL=TVCL.(BSA/1.1)1.2), and that the unexplained BSV on AUC was 38%, an original dosing regimen of 0.8 and 1.0 mg/m^2 was developed for patients with BSA < 1.2 m^2 and > 1.2 m^2, respectively. 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. The first method (Method I) to estimate an optimal dosing strategy was previously described by Jonsson et al. Optimal cutoffs and doses to use were estimated with 2, 3, and 5 BSA cutoffs. The loss function was chosen to be quadratic, symmetrical and centered on 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. The second method (Method II) used the area under the log-normal distribution of AUC. 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: For Method I, optimal cutoffs for 2, 3, and 5 dose levels the percentages of patients within the sub-therapeutic, therapeutic and toxic ranges are presented in Figure 1. As the number of cutoffs increased, the distribution of AUC was more centered on the target (i.e., the middle of the therapeutic range). However, because of the large variability, the percentage of patients in the toxic range did not necessarily decrease.

![Figure 1](image-url)

**Figure 1:** Upper left, densities of AUC with the original dosing regimen. Upper right, densities of AUC with 5 dosing levels. Lower Left, barplot summarizing the results of the different regimens tested. Green areas display the therapeutic window or percentage of therapeutic patients. Blue and red areas display sub-therapeutic and toxic areas or patient populations within sub-therapeutic or toxic ranges, respectively.
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. Furthermore, this helps to optimize the targeted AUC according to pre-defined acceptable percentage of patients within the toxic range. Figure 2 shows that a target AUC of 290 mg.h/L would result in the highest percentage of patients within the therapeutics range while toxicity would increase to more than 20%. This is consistent with the results of Method 1. An alternative to Method II would be to conduct Method I with more complex loss function with a penalty if a patient falls within the toxic range.

Conclusions: 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: