Kinetic nomograms assist individualization of drug regimens

Poster III-19

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Introduction

- Therapeutic Drug Monitoring (TDM) aims to individualize drug dosages or schedules in order to maximize therapeutic outcomes and minimize toxicities, or both in a variety of clinical settings. Drug regimen is adjusted individually using either a priori or a posteriori approaches [1].
- Bayesian techniques have been successfully used to estimate the pharmacokinetic (PK) parameters of a drug in a given patient. Owing to its precision and to the amount of information provided, is the method of choice for predicting appropriate and correct dosage regimens to attain defined target concentrations.
- However, this cpmplex procedure necessitates well trained professionals and specialized software. Its implementation in clinical practice might add delay in the clinical decision making and its use has been restricted to large hospitals with their own TDM laboratories.

Objective

- First, develop kinetic nomograms (KN), a useful tool in achieving with few samples and in a short period of time individual drug blood levels within the therapeutic window.
- Second, evaluate by simulation their performances in adjusting doses and compare these performances with the Bayesian procedure.

Materials and Methods

A. Designing Kinetic Nomograms

- KN (Figure 1) are built as a collection of time-concentration curves following a fixed “identification protocol” witch divide the “time-concentration space” in several areas (decision regions) each of them corresponding to a given adjusted drug dose.
- To illustrate our proposal, individualization of dosage regimen of rapamycin (sirolimus®), an immunosuppressant drug widely used for the prophylaxis of renal allograft rejection, characterized by a wide inter- and intra-patient variability and a narrow therapeutic window, is presented.
- From already published population analyses [2], a large number of individual parameters are randomly drawn (building group) and the corresponding adjusted drug doses are calculated in order to achieve a given steady state target levels according to the physician’s requirements.
- The doses so obtained are classified according to their possible fractions. For example, since sirolimus is issued in 1 mg tablets, “decision regions”, correspond to 1, 2, 3 etc milligrams. The regions are separated by decision boundaries which in this case are 1.5, 2.5, 3.5 etc milligrams.
- The patterns of PK parameters that correspond to these boundaries were calculated. This is accomplished by averaging the individual parameters of patients leading to adjusted doses which are close to the decision boundaries, e.g., between 1.4 and 1.6 mg for the boundary of 1.5 mg.
- Using the patterns and the fixed identification protocol, one simulates the decision-boundary time-concentration curves.
- The key element to obtain these curves is using the statistical description of the inter-individual variability (prior information) provided by population PK study.

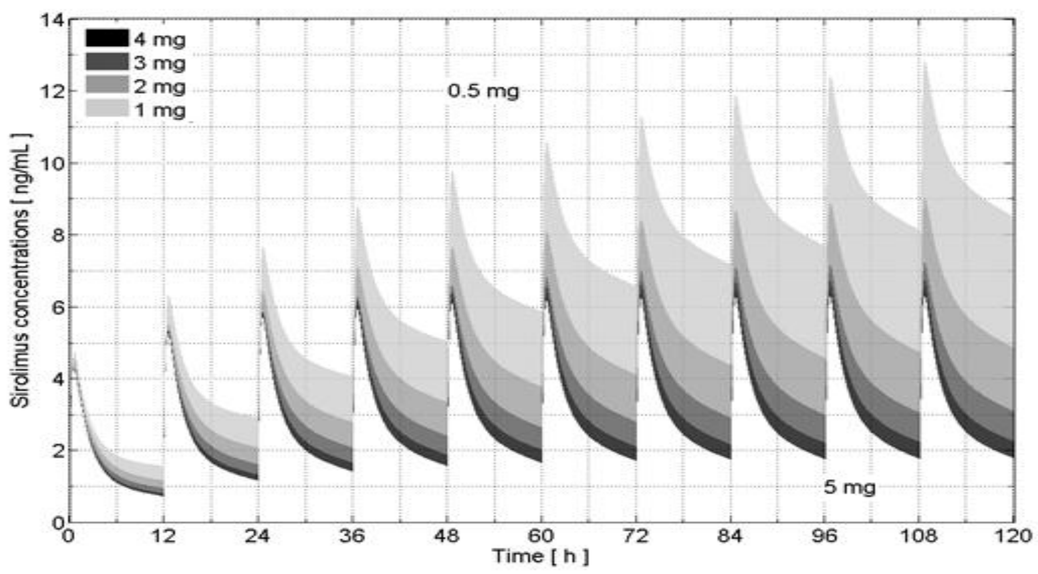

Figure 1: Kinetic nomogram obtained with identification dose of 1 mg q12h. and target minimum steady-state concentrations of 8 ng/mL when sirolimus is associated with mycophenolate mofetil.

- 71.6% of individuals underwent modification of the identification protocol in order to reach steady-state trough levels at 8 ng/mL. This confirmed the need for individual dosage adjustment.
- When regimens were adjusted by KN and Bayesian procedure, the trough steady-state concentrations of sirolimus showed low variability (CV of 23.4 and 24%, respectively) as compared to those obtained by standard protocols of 4 mg qd. (68.6%).

B. Using KN

- To use KN, one has only to locate the assayed drug concentration and then, read the dose corresponding to the area containing this location.
- A rough “salvage” adjustment is obtained with a first sample (e.g., 48 h after the start of the treatment). A second confirmatory trough sample (e.g., 96 h) allows for a possible dose update and a finer adjustment.
- Final dose adjustment will be held, with only two determinations in blood samples and before the end of the first treatment week.

C. Evaluation of performances

- In a simulation study, a large number of sample-patients (test group) were drawn again according to the sirolimus population study in [2]. For each individual the fixed identification protocol was administered.
- The drug levels were computed at two successive sampling times (48 and 96 h) and then corrupted by a measurement error. These data were used to adjust dosages.
- For the doses adjusted by KN, the doses obtained by Bayesian procedure, and for the standard recommended doses (4 mg qd), we simulated drug levels at steady state by using known individual parameters of the test group.
- Bayesian dosage adjustments was performed by using the APIS software [3]. All others calculations were performed with the MATLAB software [4]. The probability density functions were estimated using the Epanechnikov kernel.

Results

- Doses adjusted by KN and Bayesian procedure are linearly linked and highly correlated *(r = 0.96*).
- Both provided simultaneous control on minimum and maximum steady-state drug levels (63.9 and 68.7% of cases between 6 and 20 , respectively).

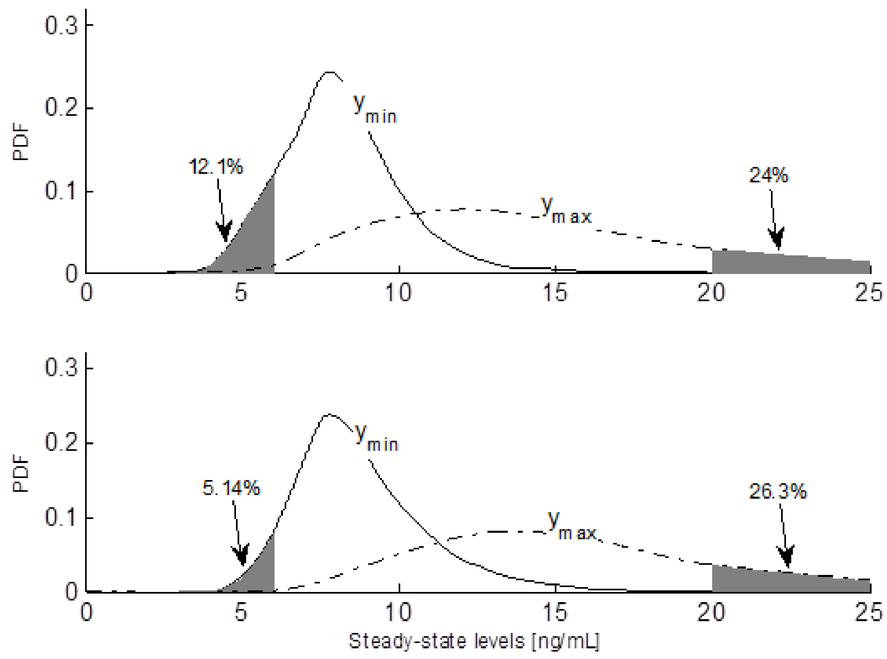

Figure 2: Probability density functions (PDF) of steady state y_{min} and y_{max} for dosages adjusted by KN (up) and Bayesian procedure (down). Dashed areas indicate regions outside the therapeutic window.

Conclusion

- KN allowing rapid dosage adjustment represent reliable alternatives to the cumbersome Bayesian procedure.
- KN provide dosage adjustment even for drugs exhibiting large intra-patient variability.
- They could be tailored for several clinical situations and different schedules and could assist population studies aiming at dose individualization.

References:

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