A Semiparametric Method for Describing Noisy Population Pharmacokinetic Data

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Received July 17, 1997—Final January 14, 1998

We propose a semiparametric method to estimate model-independent pharmacokinetic (PK) measures such as area under concentration-time, peak concentration and time to peak concentration ($T_{\text{peak}}$), for noisy population PK data from a sparsely sampled prospectively designed trial. The method is developed within the mixed-effect model framework, for the single-dose and steady-state case. We describe individual concentration vs. time using a longitudinal spline, consisting of a template spline, common to all individuals, and an individual-specific distortion spline accounting for individual differences. We impose a number of constraints on the longitudinal spline, including (i) it has a decreasing tail, (ii) its typical $T_{\text{peak}}$ is near the modal $T_{\text{peak}}$ observed in the population data, and (iii) its value is zero at time zero (single dose), or the same nonzero value at the beginning and end of a dosing interval (steady state). We test our method using simulated data and compare its performance to that of a parametric and a nonparametric method. An actual data example is also shown. The performance of the method is as good or better than that of a standard nonparametric method, and when the analysis model is misspecified, the method is superior to a standard parametric one. Since it is often not apparent that an analysis model is correct, we propose this approach as a general method for analysis.

KEY WORDS: semiparametric; population pharmacokinetics; mixed-effects model; random-effects; longitudinal spline; nonparametric.

INTRODUCTION

Figure 1 presents a data set from a pharmacokinetic (PK) study of 42 HIV-infected patients receiving the drug saquinavir, an HIV-1 protease inhibitor, in a clinical trial of its efficacy [see Collier et al. (1) for details].

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Individual data points are connected by thin solid lines. The purpose of collecting such data is to discover saquinavir's "population pharmacokinetics"; that is, the quantitative relationship of model-independent PK features, such as area under the curve (AUC), time of peak (T_peak) and height of peak (C_peak), to patient covariates such as age and weight so that dosage can be adjusted for these features to assure beneficial exposure for future patients (2-4).

The saquinavir data and design exhibit certain features that make analysis by traditional PK methods problematic. First, the data are "sparse," that is, each individual contributes few data points (here, about 7). Second, the data are noisy, so that the shape of the typical underlying PK curve is not at all obvious. The data are, however, balanced and well designed, in that all subjects are sampled at approximately the same set of times, and those times are chosen to reveal important features of the concentration-time curve.

Simple methods involving essentially data interpolation are traditionally used to estimate the PK features of individual profiles, from which relationship to covariates can be inferred. When the data are imprecise and/or sparse, as in Fig. 1, nonparametric approaches to individual curve analysis may yield estimates with unacceptably large variances (5). Use of parametric models to describe individual profiles largely avoids this problem for well-designed data, even if sparse, when the assumed models are correct, but may be seriously biased when they are not. A reasonable approach is to use semiparametric models that compromise between bias and variance.

A spline (6), or piecewise polynomial, is a potentially good choice for a semiparametric model. Spline functions have been used extensively in many different areas; interpolating splines were introduced for area calculations in pharmacokinetics (7). Splines are not limited to any fixed shape, and they can smooth the data. When data represent a group of individuals or population as in Fig. 1, a mixed-effect modeling approach is generally used to take into account individual random effects [see Yuh et al. (8) for a bibliography pertinent to pharmacokinetics]. The illustrative work that uses a spline to model population PK data within a mixed effect model framework is found elsewhere (9,10). Recently, a new class of spline models, called longitudinal splines, has been developed (11,12), tested (13,14), and used in pharmacokinetic/pharmacodynamic modeling (15). A subject-specific longitudinal spline is the "product" of a template spline, common to all individuals, and a distortion spline, representing the individual's differences from the template. To impose additional structure on the longitudinal splines, we impose several constraints that cause them to resemble standard parametric PK models. We call the resulting splines Constrained Longitudinal Splines (CLS). The heavy lines on Fig. 1 are the typical curves estimated by two variants of the CLS method to be presented here.