

Stochastic Models for Compliance Analysis Based on Dose Timing

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Abstract

Compliance is the extent to which a patient follows the prescribed regimen. The most common types of poor compliance are related to the excessive variations in dose timing. Good compliance is crucial for maintaining the drug concentration in the body, thus very important in both clinical trials and medical practice. Many different compliance indices have been proposed in the literature. However, few studies have been devoted to study the compliance process, and there is no published work on systematically studying the statistical properties of these compliance indices. We utilized the information-rich electronic event monitoring (EEM) data, built realistic stochastic models to describe them, and studied the statistical properties of several clinically meaningful compliance indices. (1) *The percentage of days with sufficient medication* is based on the binary data of whether enough doses were taken in each day. We used stationary Markov Chains to model the dependence structure, and empirical Bayes approach to account for the variations among patients. (2) *The delayed medication index (DMI)* is the proportion of time when there is a dose overdue. (3) *The premature medication index (PMI)* is the proportion of time when a dose is taken before it is due. (4) *The therapeutic coverage (TC)* is the proportion of time when the drug concentration in the body is within the therapeutic window. The last three compliance indices are based on the Markov-dependent mixture models proposed to model the inter-dosing times. To study the most biologically meaningful index of compliance – the therapeutic coverage – we applied the pharmacokinetic (PK) model of the drug to transform the dose-timing data into approximated drug concentrations. We also constructed hypothesis tests to compare the compliance levels of patients or different groups of patients. As an illustration, we analyzed the data from an AIDS clinical trial.