Using seconds-resolved pharmacokinetic datasets to assess pharmacokinetic models encompassing time-varying physiology

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Abstract

Aim Pharmacokinetics have historically been assessed using drug concentration data obtained via blood draws and bench-top analysis. The cumbersome nature of these typically constrains studies to at most a dozen concentration measurements per dosing event. This, in turn, limits our statistical power in the detection of hours-scale, time-varying physiological processes. Given recent advent of in-vivo electrochemical aptamer-based (EAB) sensors, however, we can now obtain hundreds of concentration measurements per administration. Our aim in this paper is to assess the ability of these time-dense datasets to describe time-varying pharmacokinetic models with good statistical significance. Methods Here we use seconds-resolved measurements of plasma tobramycin concentrations in rats to statistically compare traditional one- and two-compartmental pharmacokinetic models to new models in which the proportional relationship between a drug's plasma concentration and its elimination rate varies in response to changing kidney function. Results We find that a modified one-compartment model in which the proportionality between the plasma concentration of tobramycin and its elimination rate falls reciprocally with time either meets or is preferred over the standard two-compartment pharmacokinetic model for half of the datasets characterized. When we reduce the impact of the drug's rapid distribution phase on the model, this one-compartment, time-varying model is statistically preferred over or tied with the standard two-compartment model for 80% of our datasets. Conclusions Our results highlight both the impact that simple physiological changes (such as varying kidney function) can have on drug pharmacokinetics and the ability of high-time-resolution EAB sensor measurements to identify such impacts.

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