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Sensitivity Analysis of a Pharmacokinetic Model of Vaginal Anti-HIV Microbicide Drug Delivery

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ABSTRACT

Uncertainties in parameter values in microbicide pharmacokinetics (PK) models confound the models' use in understanding the determinants of drug delivery and in designing and interpreting dosing and sampling in PK studies. A global sensitivity analysis (Sobol' indices) was performed for a compartmental model of the pharmacokinetics of gel delivery of tenofovir to the vaginal mucosa. The model's parameter space was explored to quantify model output sensitivities to parameters characterizing properties for the gel–drug product (volume, drug transport, initial loading) and host environment (thicknesses of the mucosal epithelium and stroma and the role of ambient vaginal fluid in diluting gel). Greatest sensitivities overall were to the initial drug concentration in gel, gel–epithelium partition coefficient for drug, and rate constant for gel dilution by vaginal fluid. Sensitivities for 3 PK measures of drug concentration values were somewhat different than those for the kinetic PK measure. Sensitivities in the stromal compartment (where tenofovir acts against host cells) and a simulated biopsy also depended on thicknesses of epithelium and stroma. This methodology and results here contribute an approach to help interpret uncertainties in measures of vaginal microbicide gel properties and their host environment. In turn, this will inform rational gel design and optimization.

Introduction

Microbicide drugs, that act locally to prevent infection by HIV, are being developed as an alternative to vaccines in the fight to combat HIV/AIDS.[1,2] Recent evidence indicates that diligent, continuous oral administration of microbicide drugs can reduce the likelihood of sexual HIV transmission.[3,4] Alternative microbicide delivery techniques, for example, gels and intravaginal rings, have been in development for some time.[5-8] These diversify the need to administer the drugs, either in on-demand products (e.g., gels, films, dissolving tablets, or suppositories) or in ones that require infrequent administration (e.g., intravaginal rings, subdermal implants, and injections). Gels were the original vaginal dosage form developed for microbicides and have been evaluated for multiple drugs in multiple clinical trials,[9-11] but no gel–drug dosage regimen combination has been proved efficacious in multiple trials. A leading microbicide drug, tenofovir, has been evaluated in 3 phase 3 clinical trials. The first trial demonstrated a significant reduction in sexual transmission of HIV, but the second and third trials did not.[9,12] However, results of the second and third trials were confounded by the very poor adherence of users to the specified gel application regimens.[10] Furthermore, recent post hoc analyses of data for the second trial (Vaginal and Oral Interventions to Control the Epidemic; VOICE) coupled to analysis of the first successful trial (CAPRISA 004), show that if women did apply gel, as instructed, there was a significant reduction in the rate of HIV transmission and that greater adherence to designated administration reduced the rate of transmission.[13] Thus, there remains significant motivation to include gels in the set of dosage forms and products being developed for vaginal microbicide use worldwide. The microbicide field is addressing lessons learned from the gel studies to date, including gaps in the methodologies that are applied in product design and performance evaluation. The hope is to design future products, and their dosage regimens, that foster both pharmacologic success in preventing HIV transmission and behavioral success in willingness to use. The present study is intended to help fill some of those gaps.

Microbicide products function by delivering drugs that prevent HIV virions from infecting host cells through several different mechanisms. Some drugs, termed entry inhibitors, target the processes that enable viral binding and entry into host cells. Vehicles

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for these drugs (e.g., gels) are intended to deliver some (e.g., cyanovirin, Griffithsin, which target glycoproteins on the viral envelope) to the fluids of the vaginal canal and others (e.g., maraviroc, a CCR5 receptor antagonist) to the host cells in the mucosa, as well. Other antiretroviral drugs act exclusively within the mucosa, on the virion–host cell interaction, by multiple mechanisms including reverse transcriptase inhibition (e.g., tenofovir, dapivirine) and post-transcription integrase inhibition (e.g., raltegravir, cabotegravir). A number of these drugs are already used in oral therapy for previously infected individuals. Delivery of such drugs in sufficient concentrations to target sites at times of exposure to infectious HIV is paramount in the functioning of microbicide products. Such delivery, that is, microbicide pharmacokinetics (PK), has been studied primarily by experiments—for example, studies in which humans or animals are dosed with candidate products, after which tissues and fluids from the lower reproductive tract and blood are collected and evaluated for drug concentrations.[14-17]

There has been a small but increasing amount of theory-based computational work related to microbicides—including deterministic models of vaginal deployment of microbicide gels and films and of drug transport per se as released by gels, films, and intravaginal rings.[18-25] Predictions from recent models of the delivery of the drug tenofovir via a gel to the epithelial and stromal layers of the vaginal mucosa were in good agreement with experimental data in women.[23] The models have parameters characterizing properties of the products: drugs and their delivery vehicles (e.g., diffusion and partition coefficients) and the host environment (e.g., dimensions of the vaginal canal, thicknesses of the epithelial and stromal layers of the vaginal mucosa).

Understanding how the outcomes or predictions of the models depend on variations in values of parameters is of great value when developing, analyzing, and using mathematical modeling in conjunction with experimental studies. For example, this can be used in product design, namely in choosing product properties that optimize drug delivery performance over variations in properties of the host environment. One of the most useful methods for quantifying and describing how an outcome depends on inputs (or parameters) is referred to as sensitivity analysis (SA). This can help us (1) understand how natural biologic variations in product users (i.e., properties of the host environment) affect drug distribution and, thus, help interpret and control for "population variability" in data from experimental PK studies and (2) delineate the roles that different product-based parameters play in drug delivery, informing the design of products in which those parameters are manipulated to optimize such delivery. The goal of the present work was to implement a formal parameter SA to address such questions. We worked with a recent model of tenofovir delivery by a vaginal gel,[23] focusing on parameters that characterize both the gel product and its host environment.

Sensitivity Analysis

SA often has been used to check for robustness of a model, but classifying parameters as sensitive and nonsensitive also helps with 3 additional challenges to model application:

- identifying parameters that most require estimation,
- identifying experimental targets for model application, and
- reducing uncertainty in model results.

Sensitive parameters must be estimated with care due to the fact that small changes in their values lead to large changes in the measured output; a model can only make robust predictions if there is some level of certainty for sensitive parameters' values. Additionally, sensitive parameters can be identified as targets for possible experimental interest because they require the least alterations to have significant impact on the physical system. Furthermore, there may be highly uncertain parameters to which the model is not sensitive and, therefore, have little effect on the predictions—reducing uncertainty in the results. These may reflect biologic processes that need not to be fully explored to understand the behavior of the system to a reasonable degree. There is no clear way to determine which of these 3 aspects of SA are the most important—primarily because "importance" depends on the target audience. Our view is typically that the most useful aspects for biomedical applications are the identification of both sensitive and nonsensitive parameters for the purpose of exposing useful targets and potential dead-ends, respectively.

Another application of SA results is in model reduction. In contrast to classical model reduction, where we use asymptotic arguments to neglect certain terms and reduce the number of state variables, here we refer to the size of the parameter space that must be explored. Model results can depend heavily on particular parameters, but other parameters may be essentially irrelevant to the overall results. Identifying and "freezing" these parameters can reveal simpler models for the same complex biologic system. This reduces the computational demands when dealing with stochastic processes. Also, this reduces the number of "fudge factors" that may need to be introduced.[26,27]

One of the major difficulties that arise when trying to understand the effects of variations in parameters is ranking them in terms of their effects on model predictions. There are many approaches used to quantify such parameter effects—such as differential SA, statistical measures, and different sampling methods.[27,28] Broadly, SA methods can be separated into local SA and global SA methods. Local SA only investigates single parameters at a time, where the impact on the output due to changes in a particular input variable is calculated, whereas the other inputs are kept constant at their given values. Global SA considers variations of all input variables simultaneously, covering the entire parameter space. As a result, global SA methods are less likely fail to identify a significant parameter (i.e., type II errors).[29]

Sobol'[30] sensitivity measures are among the most widely used global SA methods. Their use employs the ANOVA decomposition of the model outputs, and a normalized measure of variance is defined, called the global sensitivity index. There are many methods for quantifying sensitivity, including partial rank correlation coefficient and extended Fourier amplitude sensitivity test,[31] a statistical measure and a variance-based measure, respectively. However, the Sobol' method has several strengths compared with other methods. It is quite flexible and is capable of handling essentially any relationships between inputs and outputs. It is well established in the literature, which means that there are a host of options for algorithms that optimize both efficiency and accuracy of these sensitivity calculations. Finally, the method can provide 3-fold information about the model parameters.

As a variance-based measure, the Sobol' method exploits the recursive construction and orthogonality of the functions given by the ANOVA decomposition in calculating sensitivity indices. These can be obtained for all parameters investigated for every model output.[29,30,32] The importance of the each input can be split into 2 types of effects: main effects and total effects. Total effects are the importance of the input parameter with respect to individual outputs along with any secondary effects from other parameters. Main effects only consist of the effects of the input parameter alone (most other sensitivity methods only give main effects measures). The additional effects, coming from the difference of the total and main effects, can identify parameter interactions that often imply subtle interactions between components of the model that might not be deduced from intuition or heuristics. However, such interactions are premature in the present work, and we have