Drug Forgiveness and Interpatient Pharmacokinetic Variability in Tuberculosis

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(See the article by Srivastava et al, on pages 1951–9.)

An important—but sometimes difficult to quantify—characteristic of a drug is “forgiveness.” Forgiveness (F) is defined as the difference between the medication’s postdose duration of beneficial action (D) and the prescribed dosing interval (I): F = D − I [1]. In plain words, it directly relates to the number of doses that can be skipped without causing detectable disease relapse. Forgiveness arises by 2 major mechanisms: prolonged inhibitory effect of the drug on its target (pharmacodynamics [PD]) and/or prolonged half-life of the drug at the site of action (pharmacokinetics [PK]).

Drug forgiveness has been characterized in several disease areas in which rebound can be measured noninvasively with a readout that accurately reflects the pharmacological effect of the drug in real time. Examples are β blockers, antihypertension drugs, and anti–human immunodeficiency virus (HIV) agents. The emergence of drug-resistant bacteria is a special form of such rebound. When antimicrobial treatment is too short to achieve complete sterilization, but long enough to eradicate the more drug-sensitive microbes, it leaves the less sensitive ones able to multiply when treatment lapses. This phenomenon has been observed during drug holidays with an HIV protease inhibitor [2], and it is well accepted—although not formally proven—as a major factor in the emergence of multidrug-resistant tuberculosis [3–5].

Nonadherence to a recommended antituberculosis regimen is not a spotty phenomenon but an integral part of long-term pharmacotherapy with multiple agents, each having its own set of adverse effects. In an attempt to mitigate this issue, the World Health Organization implemented the Directly Observed Therapy program in the 1990s, to ensure adherence by integrating the supervision of antituberculosis drug administration by a healthcare worker, family, or community member, as 1 of 5 components to improve adherence by integrating the supervision of antituberculosis drug administration by a healthcare worker, family, or community member, as 1 of 5 components to improve disease control (http://www.health.state.mn.us/divs/ideph/diseases/tb/dot.html).

Measuring the impact of omitted doses on drug action classically requires blinded substitution of placebo for active drug, combined with frequent pharmacological measurements. Anti-tuberculosis drug forgiveness has not been explored for ethical, technical, and clinical reasons. Quantifying drug action is challenging because of the difficulty of measuring real-time bacterial regrowth or emergence of drug-resistant populations in pulmonary lesion types, and the lack of validated surrogate markers in circulating fluids. The problem is further compounded by the combinatorial nature of anti-tuberculosis therapy, the presence of multiple bacterial populations that are likely to be killed more or less effectively by any given drug [6], the slow and largely unknown regrowth rate of Mycobacterium tuberculosis in various lesion types, and the fact that disease severity is driven by the immune system in response to pathogen exposure (rather than by the bacterial load per se).

In this issue of the Journal, the group of Tawanda Gumbo (Srivastava et al) reports the surprising results of a study in which an elegant in vitro model was used to evaluate, for the first time, the forgiveness of a standard tuberculosis drug regimen (isoniazid, rifampicin, and pyrazinamide). The hollow fiber system is an in vitro PD model, in which M. tuberculosis is exposed to simulated serum concentration-time profiles that mimic those encountered in humans. In this case, daily administration of the 3-drug combination was simulated for 4–6 weeks. The objective was to determine whether poor adherence, in the form of simulated drug holidays, would lead to incomplete sterilization and/or emergence of drug resistance.

Interestingly, none of the nonadherence schemes mimicked in the hollow fiber system led to the development of resistance to any of the 3 study drugs, with resistance defined as >1% of the total bacterial population. Even more surprising, >60% of simulated nonadherence was required to observe incomplete...
sterilization, measured as positive culture present by day 28 or at the end of the experiment. Thus, the results put into question the common belief that resistance largely emerges as a consequence of non-adherence. At first glance, the report even seems to challenge the statement attributed to former US Surgeon General C. Everett Koop, “Drugs don’t work in patients who don’t take them” [6].

What are the implications of these observations in the context of tuberculosis control programs and chemotherapy guidelines? One has to consider that the tuberculosis pathology seen in humans is very diverse, affecting the efficacy of anti-tuberculosis therapy in 2 major ways. First, pulmonary tuberculosis presents with different forms of dynamic lesions, made of several compartments each harboring metabolically distinct bacterial subpopulations. These populations are believed to show differential drug susceptibility, including phenotypic drug resistance [7, 8]. Second, the distribution of anti-tuberculosis agents from blood to pulmonary granulomas and cavities is thought to be lesion- and drug-specific, with subtherapeutic concentrations likely present in some lesions. One aspect of the heterogeneity of the bacilli was reproduced in this study, with both replicating and semidormant bacilli being addressed in separate experiments, leading to similar outcomes. The patterns of drug exposure in specific lesion types remain largely unknown. Effective monotherapy might be encountered frequently in vivo, where suboptimal penetration of drugs in distinct lesion compartments adds to the relative insensitivity of some bacterial populations. Such conditions could be more prone to resistance emergence than those simulated in the hollow fiber model of M. tuberculosis infection, which integrates free-drug levels measured in plasma. Clearly, there are limitations to the simple extrapolation of in vitro data to the clinical situation. Nevertheless, Srivastava et al make an important point that should constitute the starting hypothesis for future studies in animal models of chronic cavitary tuberculosis.

In the second part of their work, Srinivasta and colleagues ask, “If not drug holidays, as suggested by the hollow fiber data, what is driving the emergence of drug resistance against [tuberculosis]?” To address this question, they resort to a form of Gedankenexperiment. They combine computer-aided clinical trial simulations with analyses of published PK and microbiology data to propose that inter-patient PK variability alone could account for the development of drug resistance. PK variability can be defined as the result of interindividual differences in the absorption, disposition, and elimination pathways of a drug. A given dose does not lead to identical concentration-time profiles in all patients, but rather it generates a distribution determined partly by patient physiology, alleles of genes encoding enzymes involved in drug metabolism, dietary considerations, concomitant drug administration, and comorbidities. This usually results in a Gaussian distribution of daily exposure where 10-fold interindividual differences are common. The population PK and interpatient variability of isoniazid, rifampicin, and pyrazinamide have been well described, mostly in South African populations [9–11], with rifampicin presenting the most unpredictable and widest range of exposure [12].

As recapitulated in their title, Srivastava et al dismiss nonadherence as a trigger for drug resistance development and propose, instead, PK variability as the culprit. Although both parts of the story are told separately, one cannot ignore the impact they have on one another. Because forgiveness is dose-dependent, it is likely that interindividual PK variability influences the impact of noncompliance. In other words, although a short drug holiday might have no consequence in a patient with canonical drug exposure (such as that simulated in the hollow fiber experiment), the same drug omission might result in disease rebound and resistance development in someone in the 5th percentile of low drug exposure.

Therapeutic drug monitoring (TDM) has been increasingly advocated to improve the clinical outcome of infections and to reduce the development of antimicrobial resistance [13, 14]. TDM is the measurement of medication levels in blood from a limited number of samplings after drug administration (classically at the anticipated peak of plasma drug levels and a few hours later, once absorption is thought to be complete). It is helpful in detecting abnormal PK and further adjusting drug dose to reach the target PK-PD ratio, particularly in the context of escalating drug resistance. What seems to emerge from Srivastava et al’s work is that monitoring patient PK could be at least as critical as monitoring patient compliance. Individualized dose regimens and adaptive control of drug therapy are likely to play important roles in preventing the emergence of drug resistance.

The work of Gumbo’s group nicely shows how thoughtful in vitro experiments and population PK simulations can generate working hypotheses to be tested in animal models and in the clinic. Predictive studies will require the validation of real-time markers of bacterial regrowth and creative readouts for detecting the emergence of drug resistance within pulmonary tuberculosis lesions.

Notes

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References


