The Rifamycins: Renewed Interest in an Old Drug Class

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Abstract

There is renewed interest in the rifamycins, primarily from evidence that higher doses than have been previously used may allow a markedly shortened treatment of active and latent tuberculosis (TB). We review recent studies of the pharmacokinetics, pharmacodynamics and pharmacogenomics of rifampicin, rifapentine and rifabutin. The rifamycins have complex metabolic pathways and, therefore, have wide interpatient variability in drug exposure (10-fold or greater). Some of the reasons for the broad range in rifamycin exposure are now being elucidated: body weight, disease state, ingestion with food and polymorphisms in genes for drug transporter proteins. Children require 2- to 3-fold higher doses of rifampicin and rifapentine than adults do. Greater rifamycin exposure is closely correlated with bactericidal and sterilizing activities in the mouse model of TB treatment. The use of high-dose rifampicin and daily rifapentine allows treatment to be shortened to 3 months in the mouse model, and clinical trials are under way to evaluate these regimens in humans. Little is known about the relationship between rifamycin dose and toxicity, when daily dosing is used. New ways of using an old drug class – the rifamycins – may markedly improve TB treatment yet again.

The HIV pandemic re-ignited the TB epidemic and brought renewed interest and funding to TB research. However, the rifamycin class seemed to be of little interest in this new era of TB drug development. Rising rates of rifampicin resistance were reported from a number of places in the world. Drug-drug interactions with key classes of antiretroviral agents highlighted one of rifampicin's faults – its remarkable potency as an inducer of drug-metabolizing enzymes, thereby decreasing the concentrations and efficacy of a broad spectrum of drugs. Rifabutin was developed as a form of prophylaxis for disseminated \textit{Mycobacterium avium} complex, but was soon supplanted by a more effective agent (azithromycin). Rifabutin was also shown to have problematic drug interactions, causing toxic concentrations of the drug (and its principal metabolite) when given with inhibitors of cytochrome P450-3A4 (CYP3A4). Finally, interest in rifapentine waned after regimens designed to take advantage of its long half-life did not perform as well as more frequently administered rifampicin-based regimens [1–3].

Ten years later, there has been a remarkable renaissance in interest in the rifamycins (table 1). Higher doses of rifampicin and higher and more frequently dosed rifapentine are being evaluated as interventions to shorten the treatment of drug-susceptible TB. Despite its problematic drug-drug interactions, rifabutin is being evaluated as a key element in the cotreatment of patients with HIV-related TB who have HIV strains resistant to the non-nucleoside reverse transcriptase inhibitors (NNRTIs). Several rifamycin-based regimens are being evaluated as ways to markedly decrease the duration of treatment of latent TB infection.
We review the basis for the renewed interest in the 3 rifamycins currently in clinical development – rifampicin, rifapentine and rifabutin – and then highlight areas in need of additional research. The pharmacokinetics of the rifamycins are being more carefully studied, including the pharmacogenomics of rifamycin metabolism. There is now greater understanding of the mechanisms of the many drug-drug interactions of the rifamycins. For the first time, the pharmacodynamics – the relationship between drug concentrations and treatment outcomes (efficacy and toxicity) – of the rifamycins is being rigorously evaluated.

### Updated Review of the Pharmacokinetics of the Rifamycins

Although rifamycins are one of the oldest classes of antimicrobials, many of the aspects of their complex pharmacokinetics have been elucidated only recently. Rifampicin and rifapentine are well absorbed from the gastrointestinal tract, whereas the bioavailability of rifabutin (approx. 20%) is substantially lower, perhaps due to the extent of metabolism in the gut wall [4]. Ingestion with food has relatively little effect on the absorption of rifampin and rifabutin, but a variety of types of food markedly increase the bioavailability of rifapentine and its principal, biologically active metabolite [5]. To enhance absorption, some clinical trials require that subjects take the study drug with food, but the magnitude of increase in oral bioavailability differs by food type, and it is not clear that this strategy will be feasible in the broad range of clinical settings in which tuberculosis treatment is given.

The hepatic metabolism of the rifamycins has been the focus of attention for many years. Rifampin and rifapentine are metabolized by esterases in hepatocytes to desacetyl derivatives, and both parent and metabolite are excreted into the bile and eliminated largely in the faeces. The metabolism of these two drugs is not mediated by cytochrome P450 enzymes, but their pharmacokinetics are complex, with drug metabolism and transport at the levels of the gut and liver each playing a role. The brush border membrane of enterocytes contains P-glycoprotein (PGP), an efflux transporter. Rifampicin both induces PGP activity and is a PGP substrate [6, 7]. Drug that escapes the PGP efflux pump and successfully enters the portal venous system may enter the hepatocyte via influx transporters, organic anionic transport proteins 1B1 and 1B3 (OATP1B1 and OATP1B3) located in the basolateral membrane [8]. Once in the hepatocyte, rifamycins can be metabolized and/or pumped out via PGP into the biliary tract to be eliminated (or reabsorbed). Interestingly, rifampicin is not only a substrate of OATP1B1 and OATP1B3, but it also inhibits the OATP1B1- and OATP1B3-mediated uptake of drugs into the liver [9]. In addition, once rifampicin enters the hepatocyte, it may then interact with pregnane X receptor (PXR) leading to upregulation of multiple metabolizing enzymes and transporters.

To enter the systemic circulation, a drug must be absorbed, enter the portal system and pass through the liver without being metabolized or excreted. Rifamycins
are subject to the ‘first-pass effect’ via the mechanisms described above, which reduce bioavailability. However, hepatic elimination of rifampicin, at least, is saturable, which results in non-linear increases in drug exposure with doses above 5–7.5 mg/kg. The use of rifampicin is further complicated by time-varying pharmacokinetics. After multiple oral or intravenous doses, there are substantial reductions in half-life regardless of the route of administration, suggesting auto-induction of hepatic metabolism and/or elimination [10]. Bioavailability of oral drug is diminished after multiple doses, pointing to induction of prehepatic metabolism or elimination. The mechanism by which rifampicin increases its own clearance after multiple doses is unclear, but may involve auto-induction of hepatic and gut metabolizing enzymes or PXR-mediated induction of PGP. Rifapentine may also induce its own elimination, leading to decreased parent drug and metabolite concentrations [11].

Given the complexity of rifamycin absorption, metabolism and elimination, it is not surprising that there are marked interpatient differences in drug exposure: 10-fold or greater differences in the maximal concentration and area under the curve (AUC) of rifampicin, rifapentine and rifabutin [12–14]. Rifampicin concentrations below recommended targets are common, with suboptimal levels seen in as many as 70–80% of TB patients in some populations [15, 16]. Factors associated with low rifamycin exposure include high or low body weight, unapproved formulation, HIV co-infection and male sex [12, 15]. Recent studies suggest that patients with active TB have lower rifampicin and rifapentine exposure than healthy controls [12, 17]. More work needs to be done to evaluate this association between disease state and rifamycin exposure. Possible explanations for lower exposure among patients with active TB include differences in absorption (perhaps related to the effects of companion drugs) or to effects of tuberculosis and/or related inflammation on rifamycin metabolism.

Pharmacogenomics may help explain the marked interpatient variability in rifamycin pharmacokinetics. Polymorphisms in the solute carrier organic anion transporter family, member 1B1 (SLCO1B1) gene that encodes the OATP1B1 transmembrane receptor affect rifampicin drug concentrations. Persons with the SLCO1B1 rs11045819 gene mutation at exon 4 (variant name c463C→A) had 42% lower AUC and 34% lower maximal concentration values than those without it [12], and an rs4149032 C→T polymorphism was associated with 20 and 28% reductions in rifampicin bioavailability in heterozygotes and homozygotes, respectively [18]. Age-dependent changes in organ function and body composition affect drug absorption, distribution, metabolism and excretion. However, children were nearly completely left out of the series of clinical trials that led to current tuberculosis treatment regimens [19], and with 1 exception, drug doses recommended by the World Health Organization for the treatment of TB in children are the same as those in adults [20]. Only in the last few years has rifamycin exposure been carefully evaluated among children. Children with and without HIV co-infection who were receiving the 10 mg/kg dose of rifampicin recommended by the World Health Organization had mean 2-hour plasma concentrations of 3.9 and 4.8 mg/l, respectively [21], far below the recommended value of 8 mg/l for adults [22]. Children also have a higher oral clearance of rifapentine and lower drug exposures than adults [23]. Doses of rifampicin and rifapentine for young children need to be 2- to 3-fold higher than adult doses [21, 24].

Due to the lack of child-friendly formulations of the rifamycins, clinics use extemporaneous formulations to administer these drugs to children who cannot swallow a whole tablet (e.g. crushed tablets in a vehicle such as applesauce). Initial work with rifapentine suggests that administration in such an extemporaneous preparation is associated with significantly lower drug exposure [24]. Therefore, it is critical that future clinical trials of the rifamycins include children and that pharmacokinetics be assessed, including the effects of differences in drug formulation and administration.

**Pharmacodynamics of the Rifamycins**

Given its use for over 30 years and in millions of TB patients, one would think that the standard dose of rifampicin (450 mg for weight ≤45 kg and 600 mg for weight >45 kg) was the result of careful dose comparisons. However, the standard rifampicin dose was based on the results of 2 relatively small clinical trials [25, 26]. Higher doses of rifampicin were evaluated, primarily in studies of highly intermittent dosing (once or twice weekly) and were abandoned because of increased risks of hypersensitivity (flu-like syndrome) [27]. Higher daily doses of rifampicin were used in small non-comparative studies, and appeared to be well tolerated and more efficacious than the standard dose [28]. Similarly, rifapentine was nearly abandoned when initial clinical trials showed insufficient efficacy of once weekly therapy dosing during the continuation phase of therapy of what may prove to be a low dose of the drug [1–3]. Much of the current interest in the rifamycins stems from a better understanding of