Why Do We Use 600 mg of Rifampicin in Tuberculosis Treatment?

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The 600-mg once daily dose of rifampicin plays a key role in tuberculosis treatment. The evidence underpinning this dose is scant. A review of the historical literature identified 3 strands of reasoning. The first is the pharmacokinetic argument: The 600-mg dose yields serum drug concentrations well above the minimum inhibitory concentration of rifampicin against Mycobacterium tuberculosis. The second is the argument that adverse events may be dose related. The third is the economic argument: Rifampicin was prohibitively expensive at the time of its introduction. Recent in vitro, animal, and early bactericidal activity studies suggest that the 600-mg once daily dose is at the lower end of the dose-response curve, refuting the pharmacokinetic argument. The reduced cost and the lack of evidence of toxicity at higher daily doses remove the other arguments. To optimize tuberculosis treatment, the clinical value of higher doses of rifampicin should be tested in clinical trials.

In 1957, Sensi and coworkers at Lepetit Laboratories discovered a new antibiotic which they named rifamycin. It was obtained from fermentation cultures of Amycolatopsis rifamycinica (designated Streptomyces mediterranei at the time) and later found to consist of 5 substances, then renamed rifamycin A–E. Absorption of all of these substances from the gastrointestinal tract was minimal; hence, they were first developed as parenteral agents. Rifamycin B proved most stable, least toxic, and active against a broad spectrum of bacteria, mainly gram-positive cocci and Mycobacterium tuberculosis [1, 2]. Of note, the name “rifamycin” refers to the popular 1955 French film noir movie Riffifi [2]. Although rifamycin B was sporadically used clinically in tuberculosis treatment, the search for an oral equivalent with good intestinal absorption continued. In 1965, rifampicin, a hydrazone of a rifamycin B derivative with N-amino-N'-methylpiperazine, proved to be well absorbed orally and retained its highly bactericidal action (Figure 1) [1–3]. Rifampicin was approved by the Food and Drug Administration (FDA) in 1971 [2].

By this time, a range of trials and case series were finalized or had been published that found efficacy for rifampicin-containing regimens in tuberculosis treatment [4–12]. Virtually all of these studies had used a single daily dose of 600 mg of rifampicin [5–11]. Why was this dose chosen? The reasoning for the 600-mg once daily dosing could not be extracted from any of the published trials. Given the critical role of rifampicin in short-course chemotherapy, we performed a review of the literature to try to understand the reasoning behind the choice of this dose.

SEARCH STRATEGY AND SELECTION CRITERIA

We performed a literature search using PubMed (National Center for Biotechnology Information; http://www.ncbi.nlm.nih.gov), applying the Medical Subject Heading (MeSH) terms “rifampin” with subheading “history” combined with the MeSH term “tuberculosis”; publications in English, German, French, and Italian were considered. The review focused on the first 2 decades after the development of rifampicin (1957–1977) and those
papers in which rifampicin was explored as an agent for tuberculosis treatment.

RESULTS

We found a total of 3137 publications; 1003 were from the period 1957–1977. Relevant papers were selected on the basis of the title and abstract, where available. From our review of the literature, we extracted 3 main arguments that ultimately led to the 600-mg daily dose of rifampicin, although this is, inevitably, a post hoc analysis: (1) the pharmacokinetic argument; (2) the toxicity argument; and (3) the cost argument.

Pharmacokinetics

Early pharmacokinetic studies established that a single daily dose of 600 mg of rifampicin yielded serum concentrations of 7.0 μg/mL 90 min after ingestion, or 8.80–12.0 μg/mL after 2 hours—that is, well above .2 μg/mL, the mean minimum inhibitory concentration (MIC) of M. tuberculosis [13–15]. Higher doses yielded significantly higher serum concentrations and half-life [14–17]; one study in France applied 900 mg of rifampicin once daily and found mean serum concentrations of 16.2 μg/mL 3 h after intake [18]. Since peak serum concentrations (C_max) are reached 2 h after intake [15, 16], the value of C_max was likely to be higher. One year later, Furesz and coworkers measured peak serum concentrations (after 2 h) of 20.87 ± 3.25 μg/mL after a single 750-mg dose and 27.70 ± 4.16 μg/mL after administration of 900 mg of rifampicin in healthy volunteers [14]. Still, they stressed that the 600-mg doses already ensured therapeutic (ie, equal to or above the MIC) blood levels for 24 h after administration [14].

Toxicity

A second argument underlying the 600-mg dose is based on a fear of hazardous adverse effects of higher doses. In the literature, there is little evidence that higher daily doses lead to increased toxicity. Very few studies used higher daily doses, and the few that have been performed report little or no safety and toxicity data [12, 16–19]. Thus, we are presented with a few anecdotal notes. Looking back at their use of 900 mg of rifampicin, Constans and coworkers said that this was “liable to induce slight disorders” but did not provide additional data [9]; Favez and coworkers drew similar conclusions [12]. In the United States Public Health Service (USPHS) study 19, drug-induced hepatitis frequency did not differ between patients who were given 450, 600, or 750 mg of rifampicin [20]. In contrast, intermittent therapy with high doses of rifampicin (once or twice weekly) has been associated with increased toxicity, but its nature is quite distinct from the hepatotoxicity that is most common in daily dosed rifampicin therapy [20, 21]. Intermittent high doses of rifampicin (1200 mg twice weekly with 900 mg of isoniazid) led to rifampicin sensitization and antibody formation; in one study, 11 (22%) of the 49 patients discontinued treatment after developing mostly fever, thrombocytopenia, or renal failure, which is designated as the “flu-like syndrome” [21]. This experience with high-dose intermittent rifampicin resulted in an end to clinical trials with high-dose rifampicin.

Cost

The third argument is economical in nature. All early publications on the use of rifampicin warned about its cost. At the time, rifampicin was expensive to produce and it was thought that, because of its semisynthetic nature, it would remain so [1, 8, 22, 23]. This cost pressure affected the pace of implementation of the drug we now know to be central to short-course chemotherapy. In the late 1960s and early 1970s, rifampicin was considered a second-line drug, at first to add to previously unsuccessful regimens [5] and later to be part of retreatment regimens [24]. Rifampicin long held its position as a second-line drug, since first-line triple therapy (streptomycin, isoniazid, and para-aminosalicylic acid) was already highly effective and
rifampicin was considered too expensive for extensive use [24, 25]; hospital prices were 2.5 p for 10 g of para-aminosalicylic acid, 22 p for 1 g of ethambutol, and 68 p for 600 mg of rifampicin (the latter comparable to £3.79 or $6.05 today; calculated at http://www.nationalarchives.gov.uk/currency/) [25]. For this same reason, the British Medical Research Council (BMRC) preferred isoniazid-pyrazinamide regimens over equally active isoniazid-rifampicin regimens as rifampicin cost more than £110 for 6 months, which was >4 times the cost of pyrazinamide. The benefit of their study was formulized giving “good prospects of developing practical short-course regimens which do not contain rifampicin” [8]. This view was contested by others based on the principle that shortening tuberculosis treatment would justify (and, in part, make up for) the expense [22]. In the second half of the 1970s, rifampicin became a first-line drug, at least for countries that could afford its extensive use [26, 27]. The evidence to support its use and introduce successful treatment with 6-month short-course regimens overruled the associated cost [20, 26, 27]. Still, use of this costly drug was at times met with vehement criticism [28].

DISCUSSION

This review of the literature reveals that pharmacokinetic, toxicity, and cost arguments ultimately led to the 600-mg daily dose of rifampicin that eventually made its way into tuberculosis treatment guidelines [26, 29, 30]. A more explicit comment came from Richard O’Brien and Andrew Vernon who, in their 1998 editorial [31], stated that determination of the optimal dose of rifampicin “was done by the USPHS Tuberculosis Study 19 which established 600 mg as the optimal dose for most adults.” That randomized trial evaluated daily dosages of 450 mg (7.5 mg/kg), 600 mg (10 mg/kg), and 750 mg (12.5 mg/kg) of rifampicin with a fixed dose of isoniazid and observed no significant difference in the rate of sputum conversion or the rate of relapse between those who received 600 mg and those who received 750 mg of rifampicin, with a lower rate of sputum conversion and a higher rate of treatment failure among those who received 450 mg of rifampicin [20]. Interestingly, the 600-mg dose had become standard practice even before FDA approval of rifampicin for tuberculosis treatment occurred in 1971 [4–12] and it is still recommended as the maximum daily dose for daily and intermittent treatment [30]. Deviations from the 600-mg dose in trials were either small (±150 mg in the USPHS study [20]) or part of regimens that diverged so far from common practice that it was difficult to single out the effect of rifampicin. An important example is the study by Kreis and coworkers, published in 1976, which tested two 3-month regimens of high-dose rifampicin (1,200 mg daily or every other day) combined with high daily doses of isoniazid and streptomycin [19]. These regimens yielded almost 100% sputum culture conversion, but 16% of patients relapsed after 12–24 months [19]. From today’s perspective, the most likely contributor to the high initial cure rate achieved is the high dose of rifampicin; addition of pyrazinamide to this regimen would likely have further increased its efficacy. This alone makes the entrenched maximum daily dose of 600 mg of rifampicin worth revisiting.

More importantly, what renders a dose optimal from today’s point of view? According to current standards, the optimal dose of rifampicin would be derived from relationships between dosing, drug exposure achieved, and desirable and undesirable responses in phase 1 and 2 studies with clearly differing doses of rifampicin, followed by pivotal phase 3 studies of regimens. We found no evidence of such a sequence of studies. The historical pharmacokinetic, toxicity, and cost arguments have largely been refuted by more recent scientific progress.

Pharmacokinetics

Although the pharmacokinetic argument is compelling, it was based on the assumption that rifampicin is active when serum concentrations exceed the MIC throughout the dosing interval, which means that the ratio of the trough concentration (Cmin) to the MIC is the relevant pharmacodynamic index (time-dependent inhibition) [1, 13, 14, 32]. Similar reasoning is illustrated by the statement by Constans that the 900-mg dose applied in a pilot of their trial was “unnecessarily high” [9].

In the following decades, in contrast, it was assumed that the efficacy of rifampicin is concentration-dependent, correlating with peak plasma concentration (Cmax) divided by the MIC [33]. This view was based on the intracellular target of rifampicin: other drugs with intracellular targets (eg, aminoglycosides and fluoroquinolones) were shown to have concentration-dependent activity, albeit against extracellular, fast-growing bacteria. Concentration-dependent activity and the associated postantibiotic effect also better explained the efficacy of intermittently administered rifampicin [33]. Recent studies have challenged this assumption and established that the activity of rifampicin is exposure-dependent; the area under the concentration-time curve (AUC) divided by the MIC correlates better with killing than the value of Cmax/MIC [34, 35]. Of note, the choice of medium (eg, solid or liquid medium) influences MIC measurements [32].

For a bacterium that resides in macrophages, especially in early phases of infection, rifampicin concentrations in alveolar macrophages and epithelial lining fluid (ELF) may be more relevant than those in plasma. Rifampicin concentrations in ELF and bronchial biopsy specimens are slightly below those in serum, whereas those in alveolar macrophages are >10 times higher [36, 37].
Consequently, AUC/MIC or Cmax/MIC ratios compatible with bacterial killing were generally achievable in serum and alveolar macrophages, but not in ELF [37]. The use of a 1,200-mg rifampicin dose significantly improved attainment of AUC/MIC or Cmax/MIC ratios compatible with bacterial killing [37]. If the 600-mg dose was applied, rifampicin concentrations attained at the site of infection were too low [36, 37]. Recently, Gumbo and coworkers demonstrated that exposure to higher concentrations of rifampicin led to a nonlinear increase in rifampicin concentrations inside the bacteria, a phenomenon possibly related to saturation of bacterial efflux pumps [35]. Whether raising these concentrations in the bacterium and at the site of infection by application of higher rifampicin doses actually improves killing of the bacteria and, ultimately, treatment outcome remains to be investigated.

Thus, the current dose of rifampicin used in internationally recommended regimens has not been based on careful evaluation of relationships between dosing, drug exposure achieved at the site of infection, and desirable and undesirable (surrogate parameter) responses. The wide acceptance and perceived success of the currently available regimens may have led to the relative paucity of studies evaluating the pharmacodynamics of rifampicin. Admittedly, the pharmacodynamics related to the slow-growing, intracellular M. tuberculosis bacteria and their capacity for dormancy may be too complex to be explained by simple pharmacodynamic parameters [33]. Nevertheless, recent pharmacodynamic studies suggest that the current dose of rifampicin is at the lower end of the dose-response curve [34, 38–40], as already suggested by the above-mentioned study by Kreis et al [19, 39]. In this respect, it should be mentioned that both early and recent pharmacokinetic studies have revealed a nonlinear increase of rifampicin concentrations upon increase of the rifampicin dose [13–17, 41]—that is, a relatively small increase in dose is associated with a more than proportional increase in rifampicin AUC. Clearly, this characteristic should be further assessed in future studies that explore the utility of higher doses of rifampicin.

**Toxicity**

The nonlinear pharmacokinetics of rifampicin would be expected to go along with a greater than proportional decrease in tolerability if higher doses are applied. Yet, this has not been observed in studies that did apply higher doses [14–17]; recent studies of higher rifampicin doses (13 mg/kg [41] and 20 mg/kg [40]), although hampered by small patient numbers and short-term use, also did not record increased hepatotoxicity or other adverse events. The toxicity reported for intermittent high-dose rifampicin treatment [21] has been retrospectively ascribed to the intermittency of dosing rather than the magnitude of the dose [39]; nonetheless, it may have prevented the research community from identifying the correct dosage regimen for rifampicin.

Higher doses of rifampicin (900–1,200 mg) have been used in other disease, including brucellosis, legionnaires disease, and leishmaniasis, without significant tolerability problems. In these contexts, rifampicin is coadministered with less toxic drugs such as erythromycin, doxycycline, or co-trimoxazole and is used for weeks rather than months [42–44].

Rifampicin may not be the most toxic drug in the multidrug regimen currently used for tuberculosis. In studies of 4-month rifampicin monotherapy for latent tuberculosis, hepatotoxicity was rare compared with its frequency in rifampicin-pyrazinamide treatment. This may be due to the pyrazinamide or to drug interactions rather than to rifampicin itself [45]. The arrival of novel antituberculosis drugs and novel combinations may shed more light on this issue and allow higher doses of rifampicin to be used safely. Although there are significant safety concerns about the use of high intermittent doses of rifampicin, an extrapolation to daily dosage is not warranted without clinical trial evidence.

**Cost**

In their review of 40 years of BMRC studies on tuberculosis treatment, Fox, Ellard, and Mitchison repeatedly reminded us that the first short-course therapy trials were designed “to use the minimum amount of expensive rifampicin” (in East Africa) or did not include rifampicin because of the high cost (Hong Kong and Singapore) [29]; rifampicin made up 90% of the cost of drugs in rifampicin-based short-course regimens [23]. These financial restrictions are no longer warranted; the price of a complete treatment regimen for a single patient, based on the 2HRZE4HR regimen, is now $38.15, through the Stop TB Partnerships’ Global Drug Facility (http://www.stoptb.org/gdf/). This price equals the price of 1 week of rifampicin monotherapy in 1973.

**LOOKING FORWARD**

It is important to re-engage with the question of the optimal dose of rifampicin. Most importantly, the tuberculosis pandemic is still uncontrolled; there is a pressing need to improve the treatment of tuberculosis so that patients test negative on smear and culture as quickly as possible. In small-scale studies, high doses (20 mg/kg) of rifampicin have already been shown to have bactericidal activity up to twice that of the 600-mg dose (10 mg/kg) [40, 46]. Moreover, rifampicin has a sterilizing effect—the capacity to kill the remaining mycobacteria that undergo sporadic metabolism and that remain after the initial phase of treatment [47]. The sterilizing effect of rifampicin provides the most exciting reason to address this issue: if higher doses of rifampicin are safe and well...
tolerated and kill tubercle bacilli more rapidly, then we may be able to shorten tuberculosis treatment further. This will have an immediate effect on completion and cure rates. The original 600-mg dose has helped to reduce treatment duration of the multidrug regimen to 6 months but failed to reduce the duration of treatment to 4 months, as 5%–15% of the patients experienced bacteriological relapses in the BMRC Study 4 trials [29, 48]; a further reduction should still be our goal. In addition, faster smear and culture conversion decreases the size of the infectious pool of patients in the community and can reduce further transmission of tuberculosis. Second, higher doses of rifampicin may expose the bacteria to AUC/MIC values that prevent the emergence of resistance or, according to the concept of mutant prevention concentration [49], increase concentrations to a level that prevents the emergence of rifampicin-resistant mutants, thus decreasing the risk of the emergence of multidrug-resistant tuberculosis. Currently, 3.6% of all individuals with incident tuberculosis worldwide have multidrug-resistant tuberculosis, although this percentage is likely underestimated because access to drug susceptibility testing is limited in many high-incidence areas [50]. Optimizing first-line regimens is an important strategy to limit the emergence of multidrug-resistant tuberculosis. Third, there has been a recent study that higher-dose rifampicin may play a role in infections caused by low-level resistant strains (ie, MICs of 1–2 μg/L, just above the 1-mg/L break-point concentration). Such resistance may be overcome by applying higher doses of rifampicin (J. van Ingen, in press). Fourth, the drug is available and affordable, and there is widespread experience with its clinical use. If higher doses prove to be more efficacious and tolerable, a new regimen could be implemented quickly.

From the above points, it is clear that dose-ranging, tolerability, and extended bactericidal activity studies of high doses of rifampicin are warranted; the time is now. Fortunately, this field is currently in motion. Dose-ranging and tolerability studies are in the planning phase, and phase 2 studies of high-dose rifampicin are now being performed in Tanzania and planned in Peru and Brazil.

In summary, we present evidence that the current 600-mg once daily dose of rifampicin in tuberculosis treatment may not be optimal. The reason behind this dose is obscure, but arguments are largely pharmacokinetic and economical in nature, with a concern about toxicity on the basis of intermittent high-dose rifampicin. The 600-mg dose is at the lower end of the dose-response curve, and the nonlinear pharmacokinetics and dose-dependent activity of rifampicin mean that studies of higher dosages within the multidrug antituberculosis treatment regimens are urgently required. More active regimens including higher doses of rifampicin may help to reduce the duration of tuberculosis treatment with immediate benefits on treatment completion rates and the emergence of multi-drug-resistance.

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