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Evolving Larger: Dosing Anti-Tuberculosis (TB) Drugs in an Obese World

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Abstract: Current clinical practice guidelines recommend dosing anti-tuberculosis drugs according to ideal body weight and provide dosing caps for most first-line agents. However, this recommendation may be placing corpulent patients with tuberculosis at risk as increased total body weight is associated with an increased risk of clinical failure. Patients with diabetes are at an increased risk of developing tuberculosis and typically weigh more than patients with tuberculosis alone. All these factors in-combination stress the importance of evaluating the effect of weight on the pharmacokinetics of first-line anti-tuberculosis drugs.

Multiple studies suggest the use of total body weight based dosing for rifampin. Less data are available for pyrazinamide and ethambutol, but both appear to be candidates for total body weight based dosing. The study evaluating levofloxacin concluded that no adjustment is required. However, the larger variability in obese patients is concerning as to whether "one size fits all" dosing is optimal for levofloxacin. The vast majority of the isoniazid's pharmacokinetic variability is due to NAT2*4 status. However, more extensive analysis of slow and fast metabolizers is needed to determine the effect of weight within each subgroup. Moxifloxacin does not appear to be affected by weight, but doses of at least 800 mg are likely needed to optimize its pharmacokinetic/pharmacodynamic target attainment.

Future pharmacokinetic evaluations should focus on recruiting a wide range of patient weights. These analyses should take advantage of the full weight distribution instead of arbitrarily dichotomizing patients into obese vs. non-obese persons. A subsequent evaluation of the safety and effectiveness of optimized dosing regimens is needed.

Keywords: Dose optimization, ethambutol, isoniazid, obesity, pharmacokinetics, pyrazinamide, rifampin, tuberculosis.

INTRODUCTION

Tuberculosis (TB) has historically been regarded as a "thin-man's" disease as many patients were those affected by low consumption of food. This assumption has now been challenged by the global obesity pandemic with approximately 2 of the world's 9 billion humans being obese [1-4]. In addition, people who are overweight or obese are more likely to develop diabetes, and these people with diabetes are three times more likely to develop TB [5]. Some investigators have postulated that diabetes even affects the pharmacokinetics and/or clinical outcomes of anti-TB therapy [6, 7]. This hypothesis has been challenged upon further scrutiny with the increased weight of patients with diabetes and TB most likely being responsible for the earlier findings [6, 8, 9].

We have observed that clinical failure rates for TB increase as patient's weight increases [8, 10]. One potential reason for this is that mass (M) or patient weight significantly impacts the pharmacokinetics of anti-TB agents. Recent evidence suggests that low drug exposures from pharmacokinetic variability may be a greater risk for the development of multidrug-resistant TB than lack of directly observed therapy [11]. A concept known as fractal geometry has been utilized to explain relationships across large scales of dimensions, recursive scaling patterns, and non-regular shapes. This concept was utilized in the 1930s to discover the "¾ power law". This law explains that ¾ is the dimension that scales metabolic rate over a large span of mass M. The relationship between systemic clearance (SCL) of other antimicrobials has been shown to obey this law [12-14]. Therefore, patient weight likely plays a vital role in dose optimization. This view contradicts current clinical practice guidelines which state that ideal body weight should be considered when utilizing weight-based dosing recommendations for anti-TB drugs (Table **1**) [15].

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Many studies have sought to determine the pharmacokinetic profiles of anti-TB drugs, but few have utilized overweight and/or obese patients. Therefore, the evidence to support dosing recommendations of anti-TB agents for obese persons is limited. Furthermore, the ability of these studies to evaluate the effect of weight on the pharmacokinetics of anti-TB drugs has been limited by the narrow weight range of persons included. This review will discuss the available evidence as well as identify future research needed to provide optimal dosing for the obese patient. The information in the review will be limited to data regarding first-line anti-TB drugs and fluoroquinolones in adults.

RIFAMYCINS

A maximum dose of 600 mg of rifampin is recommended for patients weighing 60 kg or greater, regardless of the number of doses per week [15]. The more intermittent dosing strategies are particularly concerning since rifampin's effect on microbial killing is driven by the ratio of the area under the curve (AUC) to minimum inhibitory concentration (MIC) or AUC:MIC [16, 17]. These lower total weekly doses (1200 mg for twice weekly or 1800 mg for thrice weekly) are quite likely to produce a lower AUC over a week. This pharmacodynamic premise has been demonstrated practically with more intermittent rifampin regimens having higher risks of relapse [18].

Furthermore, higher daily rifampin dosing may be needed in all patients. This was first noted by Peloquin and colleagues who observed a negative correlation between weight and the peak concentration (C_{max}) of rifampin in 24 healthy males receiving a single dose of rifampin, isoniazid, and pyrazinamide [19]. A hollow-fiber model study determined that achieving a C_{max} to MIC ratio, or C_{max}:MIC, of 175 or greater was associated with a decreased risk of developing resistance to rifampin [16]. Increasing the dose of rifampin would therefore help achieve greater microbial kill (AUC/MIC) and decrease the risk of developing resistance (C_{max}:MIC). Doubling the rifampin dose has been shown to double the rate of killing of bacilli in sputum during the first two days of

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Table 1. Pharmcokinetic-Pharmacodynamic Indices for Anti-tuberculosis Drugs and Daily Dosing Recommendations.

	Pharmacokinetic-Pharmacodynamic Index	Maximum Guideline-Recommended Daily Dose	Maximum Dose for Obese Patients	Notes &Research Needs
Rifampin	MK: AUC/MIC RP: Cmax/MIC	600 mg 10 mg/kg (IBW)	1200 mg ≥10 mg/kg (ABW)	Daily doses of 1200 mg per day have been used for staphylococcal infections. Long-term safety and efficacy data of 20 mg/kg dosing in all patients are needed. Safety and effectiveness data for daily rifampin doses > 1200 mg are also needed.
Isoniazid	MK: AUC/MIC	300 mg 5 mg/kg (IBW)	300 mg 5 mg/kg (IBW)	Data regarding the impact of weight on isoniazid pharmacokinetics within acetylation status.
Pyrazinamide	MK: AUC/MIC RP: T>MIC	2 grams 15-30 mg/kg (IBW)	2 grams 20-30 mg/kg (ABW)	Doses > 2 grams per day are likely needed based on target attainment rates in simulation studies. A retrospective analysis of high-dose pyrazinamide suggests 40-60 mg/kg/d can be used without significantly increasing the risk of nephrotoxicity. However, more data are needed to confirm this approach.
Ethambutol	MK: AUC/MIC RP: T>MIC	1.6 grams 15-20 mg/kg (IBW)	1.6 grams 15-20 mg/kg (ABW)	Increased doses beyond the maximum are likely needed, but data supporting the safety and effectiveness of higher doses are not available.
Levofloxacin	MK: AUC/MIC	1000 mg No weight adjustment	1000 mg No weight adjustment	Currently available data evaluating the impact of obesity on levofloxacin pharmacokinetics relies on the influence of body mass index. An analysis of the data using TBW is needed.
Moxifloxacin	MK: AUC/MIC	400 mg No weight adjustment	400 mg No weight adjustment	Data regarding the safety and effectiveness of moxifloxacin 800 mg daily is needed as this is the dose required in simulation studies to optimize the attainment of the AUC/MIC target.

Legend: AUC = area under the curve, Cmax = peak concentration, IBW = ideal body weight, MIC = minimum inhibitory concentration, MK = microbial killing, RP = resistance prevention, T>MIC = percent time above the MIC, TBW = total body weight

therapy [20]. These results require confirmation as the study only included 14 patients and the study follow-up was only two weeks.

Nijland and colleagues evaluated the pharmacokinetics of rifampicin in 17 patients with TB and diabetes and 17 patients with TB only [7]. Each patient received rifampicin 450 mg (10 mg/kg) and isoniazid 600 mg thrice weekly. A 53% decrease in the AUC_{0-6h} was observed in patients with both TB and diabetes (12.3 mg x h/L vs. 25.9 mg x h/L, p = 0.003). However, the patients with TB and diabetes were corpulent (55.6 kg vs. 46.2 kg, p = 0.01) and received a lower dose of rifampicin (8.1 mg/kg vs. 9.7 mg/kg, p = 0.08). Body weight was a significant independent predictor of rifampicin exposure in both regression analyses performed in spite of the heaviest patient weighing 75.2 kg. The same group conducted a follow-up study in 18 patients with TB and diabetes matched for gender and body weight with 18 patients with TB only who received rifampin, isoniazid, pyrazinamide and ethambutol [9]. No differences were observed for the AUC_{0-24}, C_{max}, time to peak concentration (T_{max}), and half-lives of rifampin, isoniazid, or ethambutol. Therefore, it is more likely that increased body weight is responsible for the pharmacokinetic changes in diabetic patients with TB receiving rifamycins than the diagnosis of diabetes.

ISONIAZID

The maximum isoniazid dose recommended by clinical practice guidelines is 5 mg/kg for daily administration and 15 mg/kg for intermittent administration with patients weighing more than 60 kg receive a capped dose (300 mg daily; 900 mg intermittent) [15]. A study of 18 Caucasian volunteers (13 slow, 2 intermediate, 2 rapid metabolizers) demonstrated that 88% of the variability in isoniazid's systemic clearance is driven by the number of N-acetyltransferase 2 gene *4 (NAT2*4) alleles [21]. The authors concluded that patient demographics, sex, and body weight were responsible for very little variability when dosing isoniazid regardless of NAT2*4 status. However, no data were presented regarding the effect of weight within each metabolizer group and the weight distribution of the persons evaluated was limited (mean 74 ± 10 kg).

PYRAZINAMIDE

Pyrazinamide dosing is based on ideal body weight, but the current maximum recommended dose is recommended for all persons weighing 90 kg or more [15]. A population pharmacokinetic analysis of 227 South African patients receiving pyrazinamide for active pulmonary TB revealed that pyrazinamide serum clearance increased by 0.545 $L/hour^{-1}$ for every 10 kg increase in weight over 48 kg [22]. Pyrazinamide's volume of distribution also increased by 4.3 L for every 10 kg weight increase over 48 kg. The median weight of the study population was 51.5 kg with an interquartile range of 45.0 kg, 59.0 kg. Peloquin and colleagues observed a negative correlation between weight and pyrazinamide C_{max} in 24 healthy male volunteers [19].

Pyrazinamide's sterilizing effect is best explained by the AUC:MIC ratio, whereas suppression of resistance is best explained by percent time above the MIC (T>MIC) [23]. Both of these PK-PD indices are linked to systemic clearance. Monte Carlo simulations predict doses higher than 2 g/day are needed to achieve a 90% target attainment rate for pyrazinamide's sterilizing effect. Clinical trials are needed to evaluate the safety and efficacy of these proposed dosing recommendations in overweight and obese persons.

ETHAMBUTOL

Persons weighing greater than 90 kilograms are recommended to receive a flat dosing regimen according to current clinical guidelines [15]. A case series suggested that heavier patients receiving ethambutol may be at an increased risk of optic neuropathy [24]. However, our results in 18 persons (6 normal weight, 6 overweight/obese, 6 class III obese) receiving a single dose of ethambutol suggest that its systemic clearance is proportional to $(M/45.6)^{3/4}$, obeying fractal geometry-based laws [13]. Ethambutol's optimal microbial killing is associated with AUC:MIC, whereas prevention of resistance is association with the percentage of the dosing interval that the drug concentration is above the MIC (T>MIC), meaning that heavier persons are more likely to experience clinical failure with standard dosing of ethambutol [25].

FLUOROQUINOLONES

Clinical practice guidelines currently recommend the same dose of levofloxacin (500-1000 mg daily) and moxifloxacin (400 mg daily) for all adults, regardless of patient weight [15]. A study evaluating levofloxacin pharmacokinetics in 12 hospitalized patients and 3 volunteers found no difference in the mean values when compared to four normal weight volunteers from a previous study [26]. The authors did note an increased amount of variability in pharmacokinetic parameters with the group of obese persons. This increased pharmacokinetic variability could place some patients at risk of clinical failure or others at risk of concentration associated adverse events. The study did not take advantage of the wide distribution of weights of the people receiving levofloxacin due to the dichotomization into non-obese versus obese groups. Furthermore, we have observed that body mass index may be a poor covariate candidate compared to body weight [12-14].

Moxifloxacin pharmacokinetics were evaluated in 12 persons weighing 98-166 kg (BMI 43.0-58.2 kg/m^2) [27]. The authors concluded that the plasma pharmacokinetics were similar to historical data for normal weight persons including an AUC of 43.7+11.8 mg.h/L. This is likely due to the finding that volume of distribution was better correlated with lean, ideal, or fat-free mass measures than total body weight. Clearance was not significantly associated with any of the size descriptors used in the analysis. A previous study demonstrated that a moxifloxacin dose of 800 mg is likely needed for a target attainment rate of $\geq$ 90% [28]. Safety data regarding moxfiloxacin 800 mg are needed, especially given the long duration of therapy recommended by current guidelines [15].

CONCLUSION

The increasing prevalence of obesity and diabetes makes research investigating the impact of total body weight on the pharmacokinetics and outcomes of patients with TB paramount. The existing data have demonstrated that rifampin, pyrazinamide, and ethambutol are affected by weight. Isoniazid is more heavily influenced by N-acetyltransferase, but the effect of weight should be more extensively evaluated in a wide range of persons with known NAT2*4 status. Retrospective evaluations have shown that increased weight is significantly associated with an increased risk of clinical failure. However, only data from hollow fiber and animal models evaluating the microbial killing of *M. tuberculosis* are available to help us estimate the impact of the pharmacokinetic alterations associated with increased total body weight and outcomes. Further studies to establish pharmacokinetic-pharmcodynamic targets of combination regimens are needed. The safety and effectiveness of anti-TB drug dosing regimens utilizing total body weight to provide dose optimization has yet to be evaluated. These studies are needed to ensure that more aggressive dosing can be tolerated by patients and that the optimized regimens produce the expected improvement in clinical outcomes.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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