

Caution when treating tuberculosis in malnourished children

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Tuberculosis (TB) is one of the 10 leading causes of death worldwide.¹ The WHO in 2016 estimated that 1 million children <15 years old suffer from TB and 250 000 died of this condition (including children with HIV-associated TB).²

Malnutrition and TB are problems of enormous magnitude in most low-income and middle-income countries, which carry the burden of 95% of cases and deaths from TB,³ and both problems are compounded in a high proportion of affected children. Nutrition is significantly poorer among patients with active TB compared with healthy controls.⁴ Both macronutrient and micronutrient deficiencies increase the risk of developing TB and of having poorer outcomes from TB.^{4,5} Malnourished patients with TB have delayed recovery and higher mortality rates than well-nourished patients; however, the nutritional status of patients with both conditions invariably improves when they receive effective TB chemotherapy.³ The high prevalence of HIV infection in low-income and middle-income countries further aggravates the problem of malnutrition and TB.

The WHO and various countries with high burden of TB have published guidelines for nutrition in TB and HIV infection. These guidelines have limited information on the gaps in knowledge regarding the disposition of anti-TB drugs in individuals suffering from TB and malnutrition, or TB, HIV infection and malnutrition.⁶ This is, however, an area that ought to be prioritised for research.

The clinical response to medications differs between patients, and TB chemotherapy is no exception. A known source of individual variability is the nutritional status.⁷ The quality and quantity of hepatic metabolising enzymes are

significantly reduced in malnourished children,^{7,8} yet doses of anti-TB drugs, which are primarily metabolised in the liver, are rarely modified during acute malnutrition. In malnutrition there is reduced renal clearance of drugs that are primarily excreted through the kidney, and doses of such drugs are not routinely modified in clinical practice or treatment guidelines.⁸ Thus, administering to malnourished children the doses of drugs, especially those with narrow therapeutic index, recommended for well-nourished children can potentially result in adverse drug toxicities, morbidity and mortality. However, the impact of impaired anti-TB drug disposition on the morbidity and mortality of severely malnourished children has not been adequately investigated.

Important pharmacokinetic parameters used to describe drug metabolism include the maximum plasma concentration after a single dose (C_{max}), time taken to attain the maximal plasma concentration (T_{max}), area under the curve (AUC) of a plot of plasma drug concentration versus time, clearance (CL) and half-life ($t_{1/2}$). Results from a recent systematic review showed that the disposition of two anti-TB drugs (isoniazid (INH) and ethambutol) had been evaluated in malnourished children.⁸ Among children with kwashiorkor, the total clearance (CL) of INH significantly decreased, while the half-life ($t_{1/2}$) significantly increased. However, there was no significant difference in the half-life of INH in underweight compared with well-nourished control children.⁸ Roy *et al*⁹ reported no significant difference in the serum concentrations of INH in moderately malnourished and well-nourished children. Among children treated for TB with thrice-weekly pyrazinamide (PZA) or ethambutol, the maximum concentration (C_{max}) for PZA was significantly reduced in severely malnourished compared with their well-nourished counterparts. However, the C_{max} for ethambutol showed no significant difference when compared for both groups of children.¹⁰ This suggests that various degrees of malnutrition impact on drug disposition differently. Ethambutol is eliminated primarily in the kidney; its CL and $t_{1/2}$ did

not differ for underweight and marasmic children compared with well-nourished control group.⁸ Mukherjee *et al*¹¹ evaluated several pharmacokinetic parameters (C_{max} , T_{max} and area under the curve from 0 to 4 hours (AUC_{0-4h})) of INH, rifampicin (RMP), ethambutol and PZA in severely malnourished and well-nourished children after administering the WHO standard and revised doses for children. There was no significant difference in each pharmacokinetic parameter when the two groups of children were compared. In spite of these data, INH and other anti-TB drugs are prescribed for children based on their weight band for age according to the revised WHO guidelines. The WHO recommends the use of standard-dose combination anti-TB therapy that includes rifampicin (R), isoniazid (H), pyrazinamide (Z) or ethambutol (E) in all children; however, there is a lack of adequate information on the disposition of these drugs in severely malnourished children. In drug-susceptible pulmonary TB, the 6-month RMP-based regimen 2HRZE/4HR remains the recommended first-line regimen, hence the need for more studies on the disposition of these drugs in malnourished children to guide their appropriate dosing.

In this issue of *Archives of Disease in Childhood*, Singh *et al* report the impact of age and nutritional status on the population pharmacokinetic study of INH and PZA in 37 children. The study excluded children with other clinical conditions that are associated with malnutrition, such as HIV infection, and chronic hepatic or renal diseases. The study was limited to children aged 1–15 years with pulmonary or extrapulmonary TB in the initiation phase of the four combined first-line anti-TB (2HRZE) and for at least 15 days of anti-TB treatment. The nutritional status of children under 5 years of age was assessed according to the WHO standards for weight-for-height (<−2: wasting), weight-for-age (<−2: underweight) or height-for-age (<−2: stunting) z-scores. The authors also classified the nutritional status of older children based on body mass index (BMI) as severe malnutrition (BMI<−2) and well-nourished (BMI≥−2). However, the normally nourished control groups that were used to compare each malnourished group differ and can potentially influence the findings.

The major outcomes measured were the C_{max} and the area under the curve from 0 to 8 hours (AUC_{0-8h}) for both INH and PZA for different categories of malnutrition. Similar to some previous studies, other important pharmacokinetic parameters

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such as the CL and $t_{1/2}$ of both drugs were not determined. The C_{max} represents the rate of absorption and the AUC_{0-8h} represents the extent of total drug absorption over the 8-hour period. Both parameters therefore reflect the extent of drug availability and are sufficiently sensitive in determining the therapeutic level of INH and PZA in the blood, but are insufficiently sensitive in determining the likelihood of toxicity, since drug toxic level is much more dependent on its CL and $t_{1/2}$. For INH, the C_{max} and AUC for underweight, stunted, wasted and severely malnourished children did not significantly differ from those of their respective well-nourished counterparts. However, the results were contrasting for PZA when severely malnourished older children (low BMI) were compared with well-nourished children of similar age (with normal BMI). Both C_{max} and AUC_{0-8h} were significantly reduced in malnourished children compared with their normally nourished counterparts. The C_{max} for PZA in underweight, stunted and wasted children did not significantly differ from those of their respective well-nourished controls. But the AUC_{0-8h} for stunted and wasted children was significantly lower compared with their well-nourished counterparts. Regardless of the study limitations, Singh *et al* did not make a definitive conclusion on the clinical outcome of TB in malnourished children with low availability of PZA.

The results from this study reiterate the importance of recognising the differences in the spectrum of malnutrition, rather than seeing it as a single disease entity. Since different degrees of malnutrition affect drug disposition differently, a rational approach is advocated to appropriately evaluate the influences of malnutrition on drug disposition. The current data are limited to two of the first-line anti-TB drugs that have been previously studied and did not include the pharmacokinetic parameters that are most closely linked to drug toxicity. Other studies evaluating the pharmacokinetic parameters of first-line anti-TB drugs in malnourished and well-nourished children rarely assessed the hepatic or renal clearance and half-life of the drugs (table 1). In a few cases where these parameters were assessed, the results were inconsistent and did not provide adequate data regarding their potential toxicity. To confound the situation malnourished children may have extrapulmonary TB or experience a multi-drug-resistant TB that requires prolonged treatment and the use of second line anti-TB drugs, about which even less is known. The risk of potential toxicity of the second-line anti-TB is much higher in malnourished children compared with those who are well-nourished. This is attributed to the reduced hepatic or renal clearance of the drugs in malnourished children.⁷ Furthermore, malnutrition

often coexists with bacterial infections, malaria, TB and/or HIV infection and may require treatment with complex and potentially interacting drugs and newer antibiotics. In general there is paucity of population pharmacokinetic studies of many of the drugs frequently administered to malnourished children. To further advance this field, collaboration between experts in child nutrition and those in drug disposition is required.

In vivo studies evaluating the potential toxicity of INH or RMP in children are scarce. However, there are case reports of potential clinical toxicity of these drugs. A 5-year-old boy with latent TB infection developed fulminant hepatic failure 5 months after commencing INH (11 mg/kg daily).¹² This was characterised by severe jaundice, markedly elevated aspartate transaminase and alanine transaminase, prolonged international normalised ratio, and signs of hepatic encephalopathy. Following INH discontinuation, all the problems resolved completely after 6 months. Similar idiosyncratic drug-induced reaction has been reported in two different studies in the USA among children with latent TB infection treated with INH only.^{13,14} In one of the studies, a child with fulminant hepatitis had a liver transplant.¹⁴ INH is used in combination with rifampicin as chemoprophylaxis, and it may be difficult to know which drug is responsible for an adverse toxicity. Hepatotoxicity and

Table 1 Effect of malnutrition on total clearance (CL) and half-life ($t_{1/2}$) of first-line anti-TB drugs primarily metabolised by the liver or primarily eliminated in the kidneys

Anti-TB drug	Severity of malnutrition	Mean CL (mL/min/kg)			Mean $t_{1/2}$ (hour)			Reference
		Normal healthy controls	Malnourished children	Comment on drug CL (based on p values)	Normal healthy controls	Malnourished children	Comment on drug $t_{1/2}$ (based on p values)	
Isoniazid	Severe.	125.7±0.0*	329.4±0.0*	Significantly increased in malnutrition.	1.03±0.0	0.73±0.0	Significantly decreased in malnutrition.	19
	Non-severe.	4.1±0.5	2.9±0.3	Not significantly decreased in malnutrition.	3.6±0.3	3.90±0.3	Not significantly increased in malnutrition.	9
	Non-severe.	–	–	Insufficient evidence.	1.78±0.0	1.82±0.0	Not significantly increased in malnutrition.	20
	Severe and non-severe.	–	–	Parameter not assessed.	–	–	Parameter not assessed.	11
Rifampicin	Severe and non-severe.	–	–	Parameter not assessed.	–	–	Parameter not assessed.	21
	Severe and non-severe combined.	8.2±0.0	8.2±0.2	No significant change.	2.7±0.1	2.9±0.0	Not significantly increased in malnutrition.	22
Pyrazinamide	Severe and non-severe.	–	–	Parameter not assessed.	–	–	Parameter not assessed.	11
	Severe and non-severe.	–	–	Parameter not assessed.	–	–	Parameter not assessed.	11
	Severe and non-severe.	–	–	Parameter not assessed.	–	–	Parameter not assessed.	21
Ethambutol	Non-severe.	33.6±14.2	67.0±91.2	Not significantly increased in malnutrition.	9.7±4.0	7.4±5.6	Not significantly decreased in malnutrition.	10
	Severe and non-severe.	–	–	Parameter not assessed.	–	–	Parameter not assessed.	11

*Value in mL/min.
TB, tuberculosis.

hepatitis risks are increased with concomitant use of INH and RMP, carbamazepine or phenobarbital.¹⁵ Other observational studies have indicated hepatotoxicity of RMP in children when used alone or used concurrently with INH.^{16–17} In all these reports, the plasma levels of the anti-TB drugs were not determined among patients who had hepatotoxicity.

The WHO revised guidelines for the treatment of TB in children recommend increased INH, RMP and PZA dosages according to body weight. These recommendations were based on evidence from pharmacokinetic studies suggesting that young children require higher dosages of the drugs than adolescents and adults to achieve desired serum concentrations, and observational cohort studies reported that the higher dosages were rarely associated with increased risk of toxicity in children.¹⁸ This is rather a practical approach. However, many of the anti-TB toxicity studies are observational and not specific for malnourished children. It may therefore not be appropriate to generalise such safety data to children who are severely malnourished and/or HIV-infected children.

Until more data are available, routine monitoring by the clinicians of malnourished children receiving weight-based drug regimens is necessary. Clinical studies would be helpful to know the impact of reduced total drug clearance on the incidence of drug effectiveness and toxicity, morbidity and mortality in malnourished children with TB.

In summary:

- ▶ It may be safe to use doses lower than the WHO recommended doses of INH, RMP and PZA for acutely malnourished children with TB. However, doses should be increased gradually following nutritional recovery, according to the change in BMI, or weight-for-age and weight-for-height z-scores.
- ▶ The current WHO guidelines for TB treatment should be modified for severely malnourished children and should clearly define dosing of anti-TB drugs for malnourished and well-nourished children.

- ▶ The existing algorithms for TB management in children should be revised to accommodate malnourished and well-nourished children with or without HIV infection. Scaling down the anti-TB doses during acute malnutrition and reverting to the WHO recommended doses according to the change in nutritional status of a child should form an integral part of the algorithms.

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