

Children and tuberculosis medicines: bridging the research gap

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The incidence and prevalence of tuberculosis (TB) in children are increasing and becoming a particular problem in countries that are also affected by the HIV epidemic.¹ Tuberculosis in children has been seen as hard to diagnose but, at least in developed countries, relatively easy to treat. However, in children with HIV, severe disease is more frequent and this has led to a re-examination of treatment regimens.

In adults, the approach to first-line treatment of TB is well established. Success depends on being able to provide a standardized short-course chemotherapy regimen with four drugs (isoniazid, rifampicin, ethambutol and pyrazinamide) reliably for 2 months, then 2, 3 or 4 drugs for up to a further 4 to 5 months, depending on the sensitivities of the infection and the circumstances of the patient (especially the history of previous treatment). To enhance the adherence that is critical to successful treatment, use of fixed-dose combination products is recommended as standard care. However, there are currently very few fixed-dose combination products available that are of good quality and formulated for treating children.

In 2006, WHO revised its recommendations on the use of ethambutol in children, following an extensive review of efficacy and safety.² The outcome of that review was to amend the recommended daily dose of ethambutol for children of all ages to 20 mg/kg, with a range of 15–25 mg/kg. The process of carrying out that review and amending the recommendations highlighted two issues: first, that children metabolize TB medicines differently to adults, and second, that there was evidence available to inform dosage recommendations about “old” drugs. Neither of these findings are new but the systematic

consideration of them to inform WHO recommendations is important.

To ensure optimal treatment of TB in children, the dosage recommendations for the other first-line drugs required equivalent reassessment. In particular, pharmacokinetic studies of other first-line drugs needed to be collated to determine whether current WHO dosage recommendations are likely to result in plasma concentrations that are sufficient for a therapeutic effect in children of all ages. The existing pharmacokinetic evidence on pyrazinamide, isoniazid and rifampicin in both adults and children was therefore compiled and considered at a meeting in July 2008 (PR Donald, unpublished data, 2008).

The review summarized the results of over 50 published pharmacokinetic studies of antituberculous medicines in children, including recent data from studies in children carried out in India and South Africa. There are clearly gaps in knowledge that complicate making evidence-based recommendations and the overall quality of the pharmacokinetic evidence is low. Importantly, the dosage form of medicines used in the studies, the method of administration of the medicine and dosage regimens are not consistently described.

Notwithstanding these limitations, it is likely that the recommendations for doses of rifampicin, isoniazid and pyrazinamide will need to be changed to recommend higher doses per kilogram per day in children up to 12 years of age and, ideally, these new dosage recommendations should become internationally harmonized. Before the changes can be confirmed, however, a formal assessment of the safety of higher doses in children needs to be carried out, as well as identification of any evidence

to define safe and effective use of the medicines in neonates.

Current dosage forms of the first-line medicines may then need to be modified. There are only a limited number of products available and it is not possible to reliably administer the recommended doses to children of a range of weights and ages. Tablets of existing medicines that are not scored and cannot be split accurately are one problem; having to take multiple tablets to achieve ideal doses is a second; and administration practices, such as crushing medicines to mix them with food or fluids with resulting uncertain effects on bioavailability, is a third. The existing fixed-dose combination products, in particular, need further assessment to determine how best to use them if higher doses are needed for efficacy.

Other questions need to be considered. Can existing products be used safely and effectively in intermittent treatment regimens? What doses can be used in neonates? What should be the treatment regimens for tuberculous meningitis? What should be used in children infected with HIV and TB? While more clinical trials may provide some answers, existing evidence needs to be used as the basis for refining the recommendations for these problems now, as well as defining what further work needs to be done. This process of improving the way we treat tuberculosis in children has finally been initiated and must now be carried forward. ■

References

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