Pharmacokinetics

Isoniazid treatment of children: can genetics help guide treatment?

N Cranswick, K Mulholland

Commentary on the paper by Schaaf *et al* (see page 614)

Half of the world's population are children, yet many of the most important developments in drug therapy ignore the needs of this most vulnerable population. With *Mycobacterium tuberculosis* as the cause of one of the most important chronic infectious diseases worldwide,[1] it is gratifying to see research that describes the integration of modern molecular techniques to improve the delivery of the most important component of tuberculosis treatment for the world's children. The study by Schaaf and colleagues,[2] reported in this issue of the journal, focuses our attention on isoniazid therapy which is still the mainstay of tuberculosis therapy for both adults and children.

For most drugs, children need specific doses, usually defined in terms of body weight. Extrapolation of the dose from adult studies by body weight would result in the under-dosing of many drugs, as children are proportionally more efficient at clearing the drugs.[3] Isoniazid is a good example. The study by Schaaf *et al* highlights the fact that not only are higher doses required in childhood to achieve the same levels as adults, but also that children are as metabolically heterogeneous as adults. Correct dosage is important to maximise the chances of effective treatment, and to minimise the chances of adverse effects, both serious and minor. Adherence in tuberculosis treatment of children is poor[4] and may be improved by minimising adverse effects of therapy.

Where a drug is being used for the treatment of infections, the appropriate efficacious dose is defined by the characteristics of the organism as well as host factors such as absorption. Drug exposure must be adequate to control or eliminate the infection.[5 6] Adverse effects are host dependent and may be dose related or idiosyncratic. Many of the serious side effects associated with isoniazid, such as hepatotoxicity, although thought to be idiosyncratic, may be dependent to some extent on the dose chosen and the serum drug levels achieved.[7 8] Fortunately, serious side effects, such as dose related peripheral neuropathy are less common in children than adults.[9] However, children who are severely malnourished may be at increased risk of side effects; especially those involving the nervous system.[10] This is particularly important in the treatment of tuberculosis, as children with tuberculosis are often severely malnourished at the time they start treatment, as were almost half of the children in the Schaff *et al* study. In these cases, supplementation with pyridoxine rather than dose adjustment may be more important as this has been shown to reduce the risk of toxicity.[10] Tolerability is dictated by dose related minor side effects such as nausea, vomiting, and anorexia. These may not require withdrawal of the drug but can influence adherence to a regimen, and could therefore influence efficacy.

The current approach to dosing children is procrustean (see box) with a one size fits all approach. WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD) recommend, for all patients regardless of age, a dose of 5 mg/kg/day where the drug is given daily and 10 mg/kg/day where the drug is given three times a week. Higher doses have been recommended in severe disease.[11] The study of Schaaf *et al* presents a strong argument that dosage should be tailored based on age and possibly genotype. Pharmacogenetics has identified differences in drug clearance based on the genetic profile of the metabolising enzymes; this is most relevant for drugs that are primarily cleared by hepatic elimination.[12] The CPY450 pathways have been the most extensively investigated and reported upon. However, for INH, it is phase II acetylation by N-acetyltransferase 2 (NAT2) which is the rate limiting step in drug elimination.[13 14] The enzyme is subject to genetic polymorphism, which results in fast (FF), slow (SS), and intermediate (FS) metabolisers. Schaaf *et al* investigated a group of 64 children less than 13 years of age with a standard 10 mg/kg dose of isoniazid. They showed that, following a single dose of the drug, the slow metabolisers had concentrations at two hours approximately double those of the fast group and total drug exposures over three times those of the fast group. The intermediate group had a profile that was between the two, although the total exposure to the drug (as measured by the area under the drug concentration by time curve) was closer to the fast group. These differences were primarily related to differences in the drug elimination. While there were statistically significant differences between groups, there is still considerable overlap between the fast, intermediate, and slow populations as shown in fig 1. This indicates that there are other important determinants of elimination, such as age, nutritional status, disease burden, and the interactions with other drugs. There may also be random individual variation not explained by such factors. Thus, the genotype may not necessarily always be a good predictor of the phenotype. As fig 1 indicates, the combined curve showing the AUC measures for children in all three genetic groups is biphasic rather than triphasic. The FF and FS genotype have a similar phenotype, while those with the SS genotype have greater AUC values. The combined data reveals a bimodal distribution, with considerable overlap between the two groups. Through the use of modern technology, particularly microarray technology, it should be possible to develop a rapid test to assist physicians in the management of a child (or adult) with tuberculosis.[15] The question that remains is, would such a step be a useful addition to the management of tuberculosis?

In children, metabolic rate is determined mainly by size. Traditionally this has been interpreted as a function of liver size such that younger children have more liver per body weight. Often allometric scaling is used to define the relation between size and metabolic processes.[16] This relation states that the metabolic rate of an organism is proportional to $(\text{weight})^{3/4}$:

$$\text{Drug elimination} \propto \text{Wt}^{3/4}$$

Several pharmacokinetic studies have shown that this relation holds for drug metabolism in children such that dose scales to $(\textit{body weight})^{3/4}$ better than *body weight* alone.[17 18] This may also explain why body surface area also scales well for dose as the commonly used equation approximates the allometric model.

Tuberculosis, like most infectious diseases, is predominantly a disease affecting developing countries. The World Health Organisation is the authority on which most developing countries rely for guidance on the use of drugs and vaccines. For good reasons, WHO always endeavours to produce recommendations that are practical and simple to

The procrustean approach

Procrustes was the ancient champion of enforced conformity. He was a highwayman in Greek antiquity. He would measure each of his victims on his standard bed. If they were too short he would stretch them, while if they were too tall, he would cut off their legs; thus one size (bed) fits all.

apply in the field, thus the Procrustean approach. For many drugs this can be achieved and despite the competing influences that affect the dose-effect equation, most drugs can be adequately administered using a one size fits all approach for adults and a simple age or weight related schedule for children. Only a few drugs require dose adjustment based on therapeutic drug monitoring as, for most drugs, the therapeutic window is wide enough to ensure that the minimum effective dose is well below the toxic dose.[19] The need for monitoring drug levels would make the use of a drug virtually impossible to implement in the context of the developing world, due to the costs involved and the complexity of the test and its interpretation. INH appears to be in an intermediate group between these two extremes. The currently recommended dose in children of 10 mg/kg treats the vast majority of children adequately without an unacceptably high rate of side effects. However, there are some dose dependent adverse effects, and identifying a group of children likely to have higher drug levels, and therefore at higher risk of side effects may improve treatment adherence and safety, as this group would be adequately treated with a lower dose. Identification of this group may also enable the use of a larger standard dose in children. Thus, knowledge of the patient's metaboliser status could further optimise INH therapy.[20] While the technology to perform this is presently available, it is currently too expensive and inconvenient.[21 22] It is conceivable that in the not too distant future polymorphisms at a single locus could be defined by a simple bedside test on blood, urine, or cheek swab. To know whether this is a concept worth pursuing we need to know much more about the dose related toxicity of isoniazid among malnourished children living in rural areas of the developing world, at the current dose, and possibly at a higher dose. If there is significant dose related toxicity, there would be a strong argument to develop this as a bedside test for the developing world to improve the safety and acceptability of tuberculosis treatment. Isoniazid may be the ideal candidate drug to investigate the impact of the widespread application of a simple pharmacogenetic test on clinical outcomes in a whole world environment.

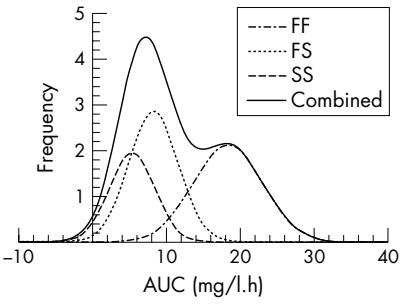

Figure 1 Distribution of AUC values based on genotype. This graph is based on the isoniazid AUC distribution data from Schaaf *et al*.

WHO treatment guidelines reach into all corners of the world in the form of an army of health workers and countless guidelines and training materials developed at country level. Any change in the guidelines is difficult and expensive and creates the risk of confusion in the field. Although Schaff *et al* do not specifically recommend a change in the guidelines, the fact that almost half the children in their fast acetylator group do not achieve the recommended levels at two and three hours raises the possibility that the dose for children under 5 years of age should be raised. WHO's Tuberculosis Control Programme has paid little attention to the problem of childhood tuberculosis, despite growing evidence that the disease is underdiagnosed in children. The paper by Schaff *et al* should prompt WHO to undertake a careful review of isoniazid dosage in children. Perhaps it is time for a randomised controlled trial comparing the current dosage with a higher dose in children, examining toxicity, tolerability, and perhaps effectiveness. Based on the results of such a trial, consideration should then be given to the need for a rapid test to identify the group of slow acetylators who may be at higher risk of toxicity. Such developments could lead to fewer side effects, better adherence to therapy, and possibly more effective therapy.

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Authors' affiliations

N Cranswick, Australian Paediatric Pharmacology Research Unit, Royal Children's Hospital and Murdoch Children's Research Institute, University of Melbourne, Australia
K Mulholland, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel Street, London, UK

Correspondence to: Prof. K Mulholland, Infectious Disease Epidemiology Unit, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine (University of London), Keppel Street, London WC1E 7HT, UK; kim.mulholland@wch.org.au

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Immunisation

Childhood immunisations and the development of atopic disease

C Grüber

Commentary on the paper by Bremner *et al* (see page 567)

Parents of children at heightened risk for atopy are frequently concerned about early immunisations. Apart from concerns about rare allergic reactions to the vaccine antigens or contaminants themselves (reviewed in Grüber and colleagues[1]), there exists a fear that immunisations may promote the development of atopic disease, leading to delayed or incomplete vaccination of these children. Some reports about an association of immunisation and atopic disease have fuelled this fear.

Moreover, the rising prevalence of allergic diseases in many industrialised countries has been associated with improvement in hygiene standards. It is thought that a lack of microbial stimuli delays the maturation from the fetal Th2 skewed immune system towards the more Th1 balanced immune system of the school child, and thus renders children more susceptible to Th2 dependent allergic disease. In this context, early childhood vaccinations have been viewed as a promoter of atopy development, either directly by the administration of agents which induce a Th2-type immune response or indirectly by the prevention of infections which otherwise would induce a preferential Th1-type immune response, and would thus skew the cytokine balance away from atopy.[2]

What is the currently available evidence for an atopy promoting effect of early childhood immunisations? An IgE response to vaccine antigens is commonly detectable in the sera of vaccinated children. About 50% of infants have detectable IgE against diphtheria/tetanus after primary vaccination,[3] and after booster vaccination later in life more than 90% of vaccinees have detectable IgE against the vaccine antigens.[4] The IgE response to vaccine antigens seems to be more pronounced among atopic individuals,[3 5] but the correlation of IgE and protective IgG against the vaccine antigens is poor.[6 7] IgE formation against vaccine antigens should thus be regarded as a regular component of the immune response, although exaggerated in atopics. It should be noted that an IgE response to vaccine antigens is not predictive of allergic side effects to the vaccine.

By contrast, there is no convincing evidence that IgE formation against nutritive or inhalant allergens is enhanced by routine vaccinations. Longitudinal data from infants in a Swedish controlled pertussis vaccine trial and from a German observational birth cohort show no increased sensitisation rate following pertussis vaccination.[6 8] In fact, better general vaccination coverage in the latter cohort was dose dependently associated with a transient reduction of the risk for allergic sensitisation to allergens up to age 5 years.[9] Two cross-sectional studies, however, suggested an association of vaccination and allergic sensitisation against environmental allergens by deprivation of natural infections. Among pupils from a Swedish anthroposophic school, likely to follow a more traditional lifestyle, including diet and healthcare, measles/mumps/rubella vaccination (MMR) was less common than in regular schools (18% *v* 93%), as was allergic sensitisation (24% *v* 34%, respectively), but a history of measles was more common (61% *v* 1%, respectively).[10] In Guinea-Bissau, surviving measles cases from a devastating measles epidemic were less frequently sensitised to environmental allergens than children who were vaccinated against measles.[11] It is unclear, however, to what extent a selection bias due to a loss of children with a less efficient Th1 immune response to the measles infection has flawed the results.

Does routine immunisation promote the development of allergic disease? In many cases, atopic dermatitis is the earliest clinical manifestation of the ''atopic march''. Parents frequently report an onset of atopic dermatitis after primary immunisation, but this is generally what would be expected with regard to the peak incidence of the disease. A recent longitudinal survey with 9744 children followed up from birth to 3–15 years reported an almost twofold incidence ratio of atopic dermatitis among measles, mumps, and rubella vaccinated children versus non-vaccinated children; the incidence ratio for measles infected children, however, was similar.[12] For pertussis vaccination, no effect was seen in the Swedish trial.[13] In the German cohort, measles/mumps vaccinated children with a family history of atopic disease were less likely to experience atopic dermatitis up to age 5 years than non-vaccinated children (OR 0.50, 95% CI 0.29 to 0.86), and a dose dependent inverse association of atopic dermatitis and better vaccination coverage in general was noted.[9] A large international cross-sectional study involving more than 100 000 children (ISAAC) showed a weak negative association of atopic dermatitis and better diphtheria-tetanus-pertussis or measles vaccination coverage.[14]

Some cross-sectional studies suggested an association of asthma symptoms and vaccination. In a retrospective, non-randomised study, 11% of 243 children vaccinated against diphtheria, tetanus, and pertussis but only 2% of 203 non-vaccinated children developed subsequent asthma.[15] In New Zealand, none of 23 children without documented vaccination against diphtheria, tetanus, pertussis, and polio developed asthma, but 23% of 1242 vaccinated children had asthma episodes.[16] The Swedish pertussis trial showed no association of pertussis vaccination and asthma symptoms.[13] In ISAAC, there was a weak negative association of asthma symptoms with local birth-year immunisation rates for DTP and measles,[14] and in the German birth