

What are the major antituberculous drug toxicities in children?

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The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

This review addresses the question: *What are the major antituberculous drug toxicities in children?*

The WHO Pocketbook of Hospital Care for Children recommends that:

In the majority of cases (ie. in the absence of smear-positive pulmonary TB or severe disease):

First 2 months (initial phase): isoniazid + rifampicin + pyrazinamide daily or 3 times a week

followed by EITHER

Next 6 months (continuation phase): isoniazid + ethambutol or isoniazid + thioacetazone daily

OR

Next 4 months (continuation phase): isoniazid + rifampicin daily or 3 times a week

In the case of smear-positive pulmonary TB or severe disease:

First 2 months (initial phase): isoniazid + rifampicin + pyrazinamide + ethambutol (or streptomycin) daily or 3 times a week

followed by EITHER:

Next 6 months (continuation phase): isoniazid + ethambutol daily:

OR

Next 4 months (continuation phase): isoniazid + rifampicin daily or 3 times a week

It does state however to follow National TB Programme (NTP) guidelines. More recently published WHO guidelines (2006) do not include recommended use of thiacetazone.[1]

The following are listed in the appendix of the WHO pocketbook as recommended doses of first-line anti-TB drugs for children.

Drug	Daily dose (mg/kg) (range)	Intermittent dose 3 x/week (mg/kg) (range)
Ethambutol	20 (15-25)	30 (25-35)
Rifampicin	10 (8-12)	10 (8-12)
Isoniazid	5 (4-6)	10 (8-12)
Pyrazinamide	25 (20-30)	35 (30-40)
Streptomycin	15 (12-18)	15 (12-18)
Thioacetazone	3	Not applicable

It should be noted that a recent WHO review has agreed to increase the recommended dosages of isoniazid, rifampicin and pyrazinamide for children but these revisions are yet to be published.

INTRODUCTION

It is estimated that at least 1 million children develop TB disease worldwide each year [1, 2] but difficulties with confirming diagnosis and previous poor surveillance of child TB by National TB Programmes (NTP's) in high-burden countries means that it is difficult to know the true burden of TB disease in children. Reports from TB-endemic countries of the proportion of the total caseload being treated for TB that are children (0-14 years) vary from 10% to more than 30%.[2-6]

The great majority of children being treated for TB in the world live in resource-limited TB endemic countries. In communities where TB incidence has increased due to the HIV epidemic, the numbers of children being treated for TB has increased markedly.[7] These are also regions where surveillance and reporting of adverse reactions to anti-TB therapy are poor or non-existent, and co morbidities such as malnutrition and HIV infection are common. This adds emphasis to the important issue that recommended dosages of anti-TB therapy for children must be safe and well tolerated.

Only recently has World Health Organization (WHO) directed NTP's to routinely report child TB data and outcomes. [8]Available data from resource-limited settings suggest that treatment adherence is poor in children.[3-6] Adverse reactions

to anti-TB drugs could potentially cause significant morbidity as well as adversely affect treatment adherence and outcomes [5, 9] and management of TB in HIV-infected children is complicated by the addition of other medications with potential toxicities. Finally, recommended drug dosages for children are currently under review and are likely to be increased for isoniazid (INH), rifampicin (RMP) and pyrazinamide (PZA), as they were recently for ethambutol (EMB). [1, 10, 11] We therefore aimed to review the frequency and manifestations of toxicities in children to currently recommended first-line anti-TB therapy.

METHODOLOGY

Articles were identified through Pub Med by use of the 'Clinical Queries' framework. The search strategy employed was as follows: (antitubercul* agents OR tuberculosis OR rifampicin OR isoniazid OR pyrazinamide OR ethambutol OR streptomycin OR thioacetazone and (adverse drug reaction OR adverse effect OR side effect OR poisoning OR toxicity). Search was initially limited to English language and humans and "all child (0-18years)" and then expanded to all ages. Search was limited initially to review article OR randomized controlled trial. A similar strategy was adopted to search EMBASE databases and the Cochrane Library Reference. Reference lists were hand searched and relevant articles retrieved.

Results

Isoniazid

The extensive experience with the use of INH either alone or in combined chemotherapeutic regimens has revealed a low order of toxicity. [12] There are two major adverse reactions to INH: neurologic and hepatic. Both are rare in children. [13]

INH competes with vitamin B6 (pyridoxine) in its action as a cofactor in the synthesis of synaptic neurotransmitters. Resulting dose-related neurologic side effects include peripheral neuropathy, ataxia and paraesthesia. In adult patients receiving INH therapy in a daily dosage of 3-5mg/kg/day, clinical deficiency of vitamin B6 has been reported to occur in 2% of cases, but in 10% or more of those receiving a higher dose (16-24mg/kg/day). [14-16] Children receiving INH are less susceptible to developing pyridoxine deficiency or peripheral neuritis than adults. [17, 18] A study in children found 13% to be vitamin B6 deficient but none had definitive clinical symptoms or signs consistent with pyridoxine deficiency. [16] A prospective, single blind, placebo-controlled trial of vitamin B6 supplementation of INH therapy in 85 children with TB in Zaire, showed no case of neurological or neuropsychiatric disorder in either group. [19]

INH hepatotoxicity is well described in the literature. [20, 21] It is rare in children receiving INH up to 10mg/kg but can manifest as subclinical, asymptomatic transient serum transaminase elevations observed in 0-13.6 %; [22-24] or less commonly as clinical hepatitis that is reversible with discontinuation of medication (0.1-7.1%); [13, 21, 25, 26] There are also rare case reports of severe hepatitis and hepatic failure. [21, 27, 28]

Less commonly INH has been associated with a variety of rheumatologic complications (including arthralgias and drug-induced lupus syndrome), dermatologic (rash, urticaria), gastrointestinal (abdominal pain, nausea, vomiting, diarrhoea) and rare haematologic abnormalities. (agranulocytosis, eosinophilia, thrombocytopenia, anaemia). [12]

INH is often used in combination with other potentially toxic drugs such as RMP and PZA either as treatment for active disease or as chemoprophylaxis. In this context, it may be difficult to know which drug is responsible for an adverse event. A prospective, randomised, controlled study of treatment of latent TB in children over an 11-year period detected no serious drug related adverse effects. [24] Of 232 patients that received INH for 9 months, 6.5% developed nausea/epigastric pain and 6% had transient increase in liver enzymes. Of 650 patients who received INH and RMP for 3 to 4 months, 1.2% had transient increase in liver enzymes, 0.7% experienced nausea/epigastric pain, 1.3% had transient macular/papular rash and 0.7% had photosensitivity. Discontinuation or modification of treatment was not required in any patient.

Young children eliminate INH faster than older children and adults and require a higher dosage to achieve similar levels. [29] The recommended dosage for INH is the subject of current review commissioned by WHO [11] and it is likely that the dosage will be increased. The level of INH at any given dosage also depends on whether the patient is a fast or slow acetylator, and this differs between ethnic groups. [30, 31] Slow acetylator status has been associated with hepatotoxicity in studies of adults. [9]

There is already some experience with using higher dosages of INH (10-20mg/kg) in children including for latent TB infection, treatment of TB disease including TB meningitis and treatment of multidrug resistant (MDR) TB. [13, 24, 32-34]. Doses of 20mg/kg appear to be commonly associated with a transient rise in liver enzymes and clinical jaundice. [33, 35, 36] However, it is generally used at the higher dose of 20 mg/kg in the context of tuberculous meningitis when there are likely to be other potential co-factors for hepatotoxicity such as the use other anti-TB drugs and anticonvulsants.

Rifampicin

Rifampicin (RMP) given in currently recommended doses (10mg/kg/day) is well tolerated. The most common side effects of RMP are orange discolouration of urine, sweat and tears and discolouration of soft contact lenses. [37] More serious adverse events are predominately allergic or hepatotoxic.

Reactions to RMP labelled as allergic include fever, rash, flu-like syndrome, eosinophilia and much less often haemolytic anaemia, haemoglobinuria and kidney damage with acute renal insufficiency. Thrombocytopenia and anaphylactic events have also been reported. [38] In a review of 20,667 adult patients treated with 600mg/day of RMP for 3 months for leprosy, flu-like syndrome developed in 54 (0.26%) patients, rash in 15 (0.07%) patients, acute renal failure in 20 (0.1%), thrombocytopenia in 2 (0.01%) and hypotension in 2 (0.01%). [39] There were only 2 cases of flu-like syndrome in children (aged 10-19) and no cases of acute renal failure. Allergic reactions are more commonly observed in cases of intermittent (usually less than twice-weekly), high-dose administration and with increasing age. [38, 39] These events occur in about 1% of patients treated with RMP 600mg twice weekly. [38]

RMP is a potentially hepatotoxic drug, as are INH and PZA. No hepatotoxicity has been described for EMB or SM. [40] Active TB disease is treated with multiple drugs and so there are limited data on toxicity rates of RMP alone. Hepatitis is infrequently associated with RMP alone and is more often seen when RMP is used in combination with INH. [41] Hepatotoxicity occurs in 1-2% of patients treated with prophylactic RMP monotherapy. [40, 42] No adverse events were reported in a study of children

that received RMP alone or in combination with PZA as chemoprophylaxis. [43]

A retrospective review of rates of hepatotoxicity in children in the USA reported that 14 (3.3%) of 430 children receiving INH and RMP had a hepatotoxic reaction. [44] Studies of children receiving INH, RMP and PZA for at least 2 months in the intensive phase report a very low incidence of any adverse events including hepatotoxicity. [26, 45-50] One study reported that the rate of hepatitis reactions rose significantly and linearly with age from less than 1% for 0-19 years to 5% for those over 60 years. [51] Advanced age is a well-recognised, consistent factor associated with hepatotoxicity to anti-TB drugs. [9]

Less common adverse effects associated with RMP include gastrointestinal (nausea, vomiting, diarrhoea), central nervous system (headache, fever), dermatologic (rash, itching, flushing) and haematologic (thrombocytopenia and acute haemolytic anaemia) reactions. [38]

Pyrazinamide

Pyrazinamide (PZA) is most commonly used in combination with other agents in the first two months of therapy for active TB disease. The most frequent or clinically significant adverse events associated with PZA are hepatotoxicity, gastrointestinal intolerance, non-gouty polyarthralgia and asymptomatic hyperuricaemia. A slight increase in serum concentration of uric acid has been reported in a number of studies. [48, 52, 53] This may be accompanied by clinical manifestations in adults but not in children. [52] Other adverse effects of PZA reported in adults have been: hepatotoxicity which is generally dose-related and after long periods of treatment [9] myoglobinuric renal failure, gastrointestinal disturbances, aseptic meningitis and rash (case reports only in children). [52, 54]

The incidence of toxicity in British Medical Research Council trials was low: 3 (0.2%) of 1845 patients in East and Central Africa, 13 (0.6%) of 2219 patients in Hong Kong and 11 (2.8%) of 397 patients in Singapore. [55] There are few data on tolerance and adverse effects of PZA in children. Reports of the use of PZA in children have found it to be well tolerated and hepatic enzyme abnormalities were infrequent and limited to the first month of treatment. [52, 53, 56] Pharmacokinetic studies show that as for other anti-TB therapy, levels achieved using recommended dosages in children are lower especially in children of less than 5 years. [57, 58]

Ethambutol

Recommendation for the use of EMB in children of all ages and usage of EMB in young children has increased in TB endemic countries. EMB was introduced to replace thiacetazone, which commonly caused severe, often fatal Stevens-Johnson reactions in HIV-infected adults and children. [59-63] At the time, this caused concern about using EMB in children too young to report early symptoms of optic neuritis and resulted in a number of literature reviews of efficacy and toxicity of EMB. [64, 65] WHO also commissioned a review, which supported the use of EMB in infants and young children and also recommended increasing the dosages. [66]

The most serious toxic effect of EMB is retrobulbar neuritis, which exists in two forms. The more common form affects the central fibres of the optic nerve causing blurred vision, decreased visual acuity, central scotomas and often the loss of ability to detect green and sometimes red, and is generally reversible. The more unusual form involves the peripheral fibres of the optic nerve. Visual acuity and colour vision may not

be affected, although peripheral constriction of the visual fields is found on examination. Because the neuritis is retrobulbar in both forms, the fundus appears normal on ophthalmoscopic examination. [65]

The occurrence of ocular toxicity is related to dose and duration of therapy. [10, 64, 66] Over 40% of adults developed toxicity at doses of greater than 50mg/kg compared to 0-3% at a dose of 15 mg/kg/daily. In only 2 of 3811 children (0.05%) receiving EMB doses of 15-30 mg/kg was EMB stopped due to possible ocular toxicity. [10, 64] The current recommended daily dose is 20 mg/kg and it is mainly used only in the intensive phase for duration of 2 months.

One study in adults found a higher incidence of ocular toxicity among patients with low zinc concentrations. [67] Children with TB, particularly those with HIV/AIDS are very likely to be zinc deficient. [68, 69] There are no available data on whether HIV infection might increase the risk of EMB toxicity. [64] A pharmacokinetic study in Malawian children found no difference in EMB levels between HIV-infected and HIV-uninfected children. [58]

Other adverse reactions to EMB reported in the literature include gastrointestinal upset, malaise, headache, mental confusion, disorientation, joint pain, increased serum uric acid and peripheral neuritis. [12]

Streptomycin

The potential toxic effects of Streptomycin (SM) are dose-related and inherent to aminoglycoside antibiotics in general: otovestibular toxicity, which can result in permanent deafness, and nephrotoxicity. [12] Difficulties associated with prolonged parenteral therapy and potential toxicity means its recommended use in children is now limited.

Treatment trials and adverse events

Adverse events such as hepatotoxicity may be more common when drugs are used in combination than when used alone. Further, intermittent regimens that for example use twice-weekly medication at higher dosages may have a different toxicity profile compared to daily regimens. Efficacy studies of treatment regimens where patients have been carefully monitored throughout the treatment regimen for treatment response also report important data of adverse events. A recent trial of 1335 adults in developing countries, using combinations of EMB, INH, RMP and PZA found that only 28 (2.1%) patients experienced adverse events that led to a change of treatment or an interruption of treatment of 7 days or longer. [70] Jaundice was the most frequent adverse event. Loss of visual acuity led to the termination of EMB in four patients. There were no deaths attributable to adverse events.

Treatment trials in children from various region report adverse events, although numbers are not as large as have been reported from studies of adults. No significant side effects were noted in a prospective randomised controlled trial of 206 South African children comparing 6 months daily regimen of RMP, INH and PZA to a higher dose twice-weekly regimen. [49] An earlier study of 76 Indian children also compared intermittent (twice weekly INH 20-30 mg/kg, RIF 10-15 mg/kg and PZA 50-60 mg/kg) to daily (INH 10-15 mg/kg, RIF 10-15 mg/kg, PZA 20-30 mg/kg) in intensive phase. [71] The patients were closely monitored including monthly liver function tests and no adverse effects requiring modification of treatment occurred. Six

patients complained of vomiting initially and 2 had mild joint pains.

A prospective trial in 83 Indian children using a variety of regimens, all including INH at 15 mg/kg and RIF at 10-15 mg/kg, reported side-effects to be uncommon and mild: transient hepatitis (4), vomiting (1) and skin rash (1).[45] A subsequent study reported hepatotoxicity in 2% of 323 children receiving daily INH, RMP, PZA and EMB in intensive phase compared to 1% of 120 children who received INH, RMP and PZA. [72] A prospective study of 36 Greek children treated with RMP, INH and PZA resulted in no serious problems with drug tolerance or toxicity. Temporary asymptomatic hyperuricaemia and transient elevation in serum transaminases were observed in 11 patients but no drug modification was required. [48].

In a recent randomised clinical trial of the treatment of lymph node TB with RMP, INH and PZA, in 268 patients, of which 87 were children: adverse events occurred in 1% of patients treated daily and 11% of patients treated twice weekly. [73] Gastrointestinal symptoms were the commonest reported event with one patient developing jaundice. All the other reactions were in adults.

In an observational study of 175 children receiving a 6-month directly observed regimen including INH, RMP and PZA, only 2 (1%) had significant adverse events of vomiting and skin rash, which interrupted drug treatment for 1-2 months. [50] An additional 9 patients had episodes of gastrointestinal disturbance (vomiting or abdominal pain) that did not require discontinuation of therapy or change in drug doses. These occurred in young children during the first month of therapy and were thought to be caused by the large volume of medications. No patient developed hepatitis, peripheral neuritis or joint pain.

In an uncontrolled prospective study of short course chemotherapy for 6 months in children in Papua New Guinea treated with RMP, INH, PZA and SM, 15 (2%) of the 639 children developed side effects. [47] Twelve developed rash during the initial 2 months daily treatment and it was attributed to SM in 8 cases, PZA in 3 cases and INH in 1 case and two developed jaundice. One child who had received SM and INH for several months in an earlier incomplete treatment course complained of deafness. Four children were considered to be allergic to either PZA or INH and were desensitised with increasing dosages and had no further problems.

DISCUSSION

First-line anti-TB therapy at currently recommended dosages in children is well tolerated. Serious adverse reactions are rare and even mild, reversible side effects are uncommon. Poor treatment completion rates are reported in children in resource-limited settings [3-5] but it is unlikely that adverse reactions are a major factor for this.

Review of the literature shows that children tolerate anti-TB drugs better than adults. One reason for this may be because children have lower serum concentrations for anti-TB drugs than adults when receiving equivalent mg/kg doses as recommended.[29, 57, 58] In the past, this has not been considered a problem as clinical response and outcomes have generally been very favourable in children with TB using these recommended dosages. However, past studies in children that have reported toxicity have not included HIV-infected children with TB. The poorer outcomes noted in children with TB/HIV co-infection [74, 75] has increased attention on the need for appropriate dosages in children to achieve optimal serum levels

and the need for more careful surveillance in such settings. As the recommended doses of RMP, INH and PZA are likely to be increased in the near future, it will be extremely important to monitor for the possibility of an increasing incidence of side effects. Some studies in adults have found that HIV infection is associated with an increased risk of hepatotoxicity to anti-TB drugs. [9] There are no published data for children.

Anti-TB drugs, mainly RMP, have important interactions with antiretroviral therapy (ART) and have many similar side effects. RMP reduces the serum levels of almost all protease inhibitors except ritonavir by more than 75% [76] and levels are also decreased for non-nucleoside reverse transcriptase inhibitors such as efavirenz and nevirapine. [77]It is also recommended that all HIV/TB co-infected children should receive cotrimoxazole preventive therapy as well as pyridoxine while on anti-TB treatment. [1] Hepatotoxicity, skin rash, gastrointestinal upset, leucopaenia, anaemia and peripheral neuropathy are all side effects that could be caused by either anti-TB drugs or ART. It is therefore difficult to distinguish which drug is responsible for these side effects when treatment for both diseases is combined. [78] As HIV and TB are frequent co-morbidities in children in developing countries, and with the increasing use of ART in HIV infected children, it will be important to monitor for adverse effects in these populations.

In conclusion, anti-TB drugs at current recommended doses are well tolerated in children. Although occasional fatal hepatotoxic events are described in children, the incidence of serious toxicity is very low. There are few data from resource-limited TB endemic countries and monitoring for adverse effects in children will need to be improved if increased doses are to be used in children especially in regions where co- morbidities such as HIV and malnutrition are common.

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