Antituberculosis drug-induced hepatotoxicity in children

Peter R. Donald
Department of Paediatrics and Child Health, Faculty of Health Sciences, University of Stellenbosch and Tygerberg Children’s Hospital, Tygerberg, South Africa

Abstract

Recent increases in the dosages of the essential antituberculosis agents isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA) for use in children recommended by World Health Organization have raised concerns regarding the risk of hepatotoxicity. Published data relating to the incidence and pathogenesis of antituberculosis drug-induced hepatotoxicity (ADIH), particularly in children, is reviewed. Amongst 12,708 children receiving chemoprophylaxis, mainly with INH, but also other combinations of INH, RMP and PZA only 1 case (0.06%) of jaundice was recorded and abnormal liver function documented in 110 (8%) of the 1225 children studied. Excluding tuberculous meningitis (TBM) 8984 were children treated for tuberculosis disease and jaundice documented in 75 (0.83%) and abnormal liver function tests in 380 (9.9%) of the 3855 children evaluated. Amongst 717 children treated for TBM, however, jaundice occurred in 72 (10.8%) and abnormal LFT were recorded in 174 (52.9%) of those studied. Case reports document the occurrence of ADIH in at least 63 children. Signs and symptoms of ADIH were frequently ignored in the recorded cases. ADIH can occur in children at any age or any dosage of INH, RMP or PZA, but the incidence of ADIH is considerably lower in children than in adults. Children with disseminated forms of disease are at greater risk of ADIH. The use of the higher dosages of INH, RMP and PZA recently recommended by WHO is unlikely to result in a greater risk of ADIH in children.

Introduction

All pharmacological interventions balance efficacy and toxicity; there are few efficacious agents that do not have some toxicity risk. In the case of antituberculosis agents the major risk is hepatotoxicity and three agents identified by World Health Organization (WHO) as essential, isoniazid (INH), rifampicin (RMP) and pyrazinamide (PZA), carry such a risk. In view of recent recommendations for increased dosages of INH (5-15 mg/kg), RMP (10-20 mg/kg) and PZA (30-40 mg/kg) for children, this paper reviews knowledge of antituberculosis drug induced hepatotoxicity (ADIH) occurring amongst children. The role of the essential drugs INH, RMP and PZA implicated in ADIH is considered alone and in concert and factors that might influence ADIH in adults and children are discussed and literature relating to ADIH in children is reviewed and summarized.

Materials and Methods

A PubMed search used keywords hepatotoxicity, hepatitis, liver injury, antituberculosis treatment, chemoprophylaxis, chemotherapy, isoniazid, rifampin and rifampicin, pyrazinamide, childhood, children and paediatric. All papers published from 1944 up to December 2009 referring to children in the title or published in paediatric journals were reviewed. A personal collection of childhood tuberculosis literature was also scanned, particularly for earlier literature, and bibliographies of identified papers searched for additional references. Papers quantifying the occurrence of ADIH in children in any manner are included; this might mean, in some instances, the regular determination of serum transaminases and bilirubin or may refer only to the documentation of jaundice. Papers relating primarily to hepatotoxicity in adults have also been reviewed, particularly regarding the principles underlying hepatotoxicity. Papers in English, German, French, Italian and Spanish were included. Unless otherwise stated drugs were administered daily and dosages are given as mg/kg implying that this is the daily dosage. The term hepatotoxicity, hepatitis, liver damage and liver injury are used interchangeably in the literature, but for purposes of this review the term ADIH has been adopted and indicates any significant deviation from normal in liver function tests (LFT) or clinical signs that indicate liver dysfunction in the presence of antituberculosis treatment. Importance is placed on the identification of jaundice as an indisputable clinical sign of serious hepatic pathology. Data relating to ADIH under different circumstances was extracted from relevant papers and summarized under three headings: case reports, the use of INH, RMP and PZA in chemoprophylaxis and the use of the same agents in tuberculosis treatment. Account was taken of different drug dosages, especially that of INH, however classification as regards dosage is imprecise as many authors give a dosage range without indicating the mean or median dosage.

Several definitions of ADIH and approaches to possible ADIH appear in different texts including those of the American Thoracic Society (ATS), the Council for International Organizations of Medical Sciences and the World Health Collaborating Centre for International Drug Monitoring. These definitions have not been applied to papers reviewed, but the opinions of authors accepted as to what constituted ADIH. Each laboratory has its own normal values, these are seldom provided and there is little uniformity as to the definition of ADIH.

Results

Before any discussion of ADIH it is relevant to note that liver biopsy studies and autopsies reveal that a significant proportion of adults, before and after antituberculosis treatment commencement, have hepatic abnormalities including granulomata, histiocytic nodules and non-specific reactive hepatitis. The role these abnormalities might play in the development of symptoms and signs of ADIH during chemotherapy must remain speculative. Similar studies in children have been reported. Needle biopsy of the liver in 120 children (age range 31/2 months to 14 years), with different forms of primary tuberculosis, produced histological evidence of bacillary dissemination in
17% of children. Among 71 children with uncomplicated primary tuberculosis, tubercles were noted in four and epithelioid nodules, consisting mainly of histiocytes, fibrocytes and lymphocytes, in eight cases; in 46 with more serious forms of disease, tubercles were seen in two children and histiocytic nodules in a further three. Similar results have been described by others.10,11

It should also be noted that LFT performed before the start of treatment or chemophrophylaxis may be abnormal in a significant proportion of adults and children; this is particularly likely with more severe disease.12-16 A recent official statement of the ATS also pointed out that individual transaminase values may vary as much as 45% during a single day or 10-30% on successive days.2

INH was introduced in 195217,18 and brought about an unprecendented rapid improvement in tuberculosis patients. Following its introduction for chemophrophylaxis, studies enrolling several thousands of participants were undertaken.19 This enthusiasm was dampened when hepatitis was reported in 19 individuals from Baltimore, USA, receiving prophylactic INH; jaundice developed in 13 and 2 died.20 It was later noted that Baltimore City experienced a simultaneous increase in liver cirrhosis deaths during this period, creating an excessively negative picture of the hepatotoxic propensity of INH.21 None the less these events led to a reassessment of the hepatotoxicity of INH and questioned the wisdom of INH chemophrophylaxis.22 It was soon apparent that in any group receiving INH for tuberculosis disease management, or chemophrophylaxis, a significant proportion developed signs and symptoms of ADIH.22,23-27 With hindsight early INH animal studies did demonstrate liver damage28 and early case reports documented liver damage and jaundice associated with INH use (and overdosage).29-34 studies of series of patients receiving INH revealed increases in AST, ALT and disorders of other LFT.35,36 Rereading documentation of early chemophrophylaxis studies also reveals cases of jaundice, the significance of which was not appreciated.37

When INH hepatotoxicity was recognized it was already known that exposure to INH and its metabolites varied; there were probably three N-acetyltransferase 2 (NAT2) phenotypes, rapid, intermediate and slow acetylators of INH and there was great interest in the NAT2 phenotype in relation to ADIH. With definite genotyping it is now indisputable that SS acetylators of INH are more likely to experience a rise in serum hepatic transaminases than rapid acetylators.38-41 Whether this translates into susceptibility to overt hepatotoxicity with all the manifestations of jaundice and liver failure is less obvious, although some investigators have identified slow acetylators as also being more susceptible to severe hepatotoxicity.42 By contrast the incidence of hepatotoxicity with jaundice in a series of clinical trials in Chennai, India, over a 20 year period was 1.9% amongst 1757 patients phenotyped as slow INH acetylators and 1.2% amongst 1238 rapid acetylators; the difference was not significant.43 Similarly in a randomized, double-blind, placebo-controlled INH chemophrophylaxis trial 20 838 individuals received INH and 6991 placebo.26 Ninety five cases of hepatitis occurred in the INH group, but only 7 in the placebo group; the difference was highly significant; furthermore 75 of the INH group became jaundiced, but only 5 in the placebo group. The individuals who developed ADIH were phenotyped as regards their NAT2 status and the distribution of rapid and slow acetylators was 50:50 which was that expected in the Middle European population evaluated.

Following the introduction of INH there was, initially, little awareness of possible ADIH complicating antituberculosis chemotherapy in children. Early descriptions of INH therapy in children by experienced clinicians also record dosages of INH, calculated as mg/kg body weight varying from 10-15 mg/kg body weight44 to 20 mg/kg and higher45-47 and there is frequent comment that children do not experience undue toxicity. Similarly reports of INH chemotherapy trials during which children received INH in dosages of 5 or 10 mg/kg made little comment regarding possible ADIH.48,50 With the introduction of RMP and PZA, also potentially hepatotoxic agents, much greater concern emerged regarding ADIH in children.

The role of RMP in ADIH is still subject to considerable discussion. In guinea pigs and mice no hepatic lesions were demonstrable following RMP administration.51 In earlier experiments with rats RMP alone caused no hepatic damage, however the addition of INH caused major histological lesions in the liver.52 Several adult studies compared experience with RMP combined with INH and with EMB. Amongst pulmonary tuberculosis patients treated for the first time with INH and RMP some disturbance of LFT was noted amongst 13 (35%) of 37; amongst 72 retreatment patients given RMP and EMB only 6 (8%) developed a transient rise in transaminase values and one a rise in serum bilirubin.53 Later the same group described 110 previously untreated pulmonary tuberculosis patients receiving INH and RMP and a transient rise in transaminase values occurred in 21 (23%) and a rise in serum bilirubin in 8 (11%).54 An extensive review of RMP published in 1971 summarized experience with RMP hepatotoxicity following monotherapy and as part of multidrug therapy; amongst 1366 individuals receiving RMP monotherapy 5 (0.37%) became jaundiced and 1 (0.07%) developed biochemical abnormalities;55 amongst 4280 patients treated with RMP and other drugs, including INH, 80 (1.87%) developed jaundice and another 27 (0.6%) other biochemical abnormalities. The case report of Askgaard et al. also provides an instructive window on the interplay of INH and RMP in ADIH.56 Precisely why RMP should have such a deleterious influence on INH hepatotoxicity is uncertain; RMP may induce INH hydrolyase and thus increase the amount of INH directly converted to isonicotinic acid and hydrazine; slow acetylators of INH might then be more exposed to hydrazine and hepatotoxicity.57

In 1954 McDermott et al enthusiastically described experience with INH and PZA combined in daily dosages of 5 mg/kg and 50 mg/kg respectively given twice daily.58 Of 53 patients with 3 month and 6 month bacteriological results 92% remained culture negative; unfortunately hepatitis occurred in six (10%) patients, four became jaundiced and one died of fulminant hepatitis. The first four cases of hepatitis occurred during the 5th month of treatment and the PZA treatment duration was shortened to 90 days, but the fatal hepatitis case occurred at 55 days treatment and PZA use was stopped altogether. A later study by the same group gave PZA in a lower dosage of 20-30 mg/kg, however efficacy was also lower and the risk of hepatotoxicity was not eliminated.59 However when PZA was studied at daily dosages of 30-40 mg/kg together with other drugs in British Medical Research Council (MRC) trials the incidence of ADIH 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.60 The demonstration of the unique sterilizing capacity of RMP and PZA revolutionized antituberculosis regimens and introduced six months short-course chemotherapy.61 The identification of the first two months of therapy as critical for the action of PZA in combination with the powerful sterilizing activity of RMP led to the evaluation of this combination for two month chemophrophylaxis regimens. An early study of two months RMP and PZA, however, found a significant incidence of adverse events that contributed to non-compliance,62 but larger studies in HIV-infected patients of the combination of RMP and PZA given daily63 or twice weekly64,65 in comparison to INH also given daily or twice weekly, suggested that the RMP/PZA combination was both safe and efficacious and it was recommended by the ATS.66 Unfortunately further studies found the combination of RMP and PZA to be associated with an unacceptable incidence of ADIH,67-71 and Lee et al. emphasized the need for careful monitoring of patients receiving RMP and PZA.72 Some studies also included a small number of children. Randula et al. managed 10 children with two months RMP/PZA; one child aged 15 years developed severe ADIH.73

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Concerns regarding chemoprophylaxis with RMP and PZA were confirmed in an extensive programme survey in the USA of RMP/PZA usage for latent tuberculosis.74 The incidence of ALT values higher than X5 normal and ADIH per 1,000 RMP/PZA initiations was 25.6 (95% CI 22.3-29.3) and 18.7 (CI 15.9-21.9) respectively; there were seven fatalities (rate 0.9) and 23 hospitalizations (rate 2.8 per 1,000 RMP/PZA initiations). Hong Kong researchers also presented a cohort and nested case study of pulmonary tuberculosis management with combinations of INH, RMP and PZA; adding PZA to INH and RMP during the continuation phase of therapy increased the ADIH risk appreciably.75 None of the less some studies of adults76 and children77 have reported acceptable levels of hepatotoxicity associated with the chemoprophylactic use of 2 months of RMP and PZA and emphasized the advantages of improved compliance with shorter regimens.

Le Bourgeois et al. studied PZA in 42 children receiving a mean dosage of 23.3 mg/kg (range 20-37 mg/kg) with INH and RMP at recommended dosages.78 AST and ALT values at 1 month and at treatment conclusion rose to more than X3 normal in only 2 children (5%); treatment was not interrupted and the increased values normalized. Sánchez-Albisua et al. described the use of PZA (20-25 mg/kg), INH (10 mg/kg) and RMP (15 mg/kg) in a cohort of 114 children. Eleven children (19.6%) with normal ALT values before treatment experienced an increase in values; however the highest value was 193 U/L and only four children had values > 65 U/L.79 In a retrospective study from Japan 99 children aged 0-16 years treated for tuberculosis were assessed.80 In 22 children (22.2%) AST or ALT values were increased, but < X3, the upper limit of normal; severe ADIH, (an elevation of AST or ALT values to more than X5 normal in those with normal values pre-treatment), occurred in 8 (8.1%) children, and young age and PZA use were associated with ADIH. It should be noted that only 12 children received PZA in this study and that 4 were amongst those developing ADIH and that 4 of these 8 children had severe disease in the form of tuberculous meningitis. In univariate analysis disease severity was an ADIH risk factor, but not in multivariate analysis. A single case report also suggested that RMP and PZA combined might have contributed to serious ADIH in a 10 year old child.81

The influence of infectious hepatitis

Viral infectious hepatitis, is common in developing countries, may predispose to ADIH, and be confused with ADIH and thus have a significant influence on the interpretation of results of many studies.82-85 The ATS, in a review of ADIH, concluded that it was not possible to reach firm conclusions about the role of hepatitis B virus infection in precipitating or exacerbating ADIH.2 HIV-infection and its treatment add another element to this problem. In a cohort of African patients receiving antiretroviral therapy, although there was a low incidence of hepatotoxicity, carriage of HBsAg and antituberculosis therapy increased the risk of hepatotoxicity significantly.86 Türktaş et al. studied infectious forms of hepatitis amongst 705 adult Turkish tuberculosis patients.87 Serologic markers (IgM) for viral hepatitis were studied amongst 57 (8.1%) patients who developed acute ADIH with jaundice during treatment with INH and RMP and confirmed hepatitis B in 6 (10.5%) patients, while 4 (7%) were hepatitis C positive. Four patients (7%) were HBsAg-positive, and this was within the range reported for Turkey. The authors comment that the reported incidence of ADIH is often higher in developing countries, but that not all cases of hepatitis during antituberculosis treatment may be due to ADIH. Similar conclusions were drawn by other researchers88 and three recent studies from India have also identified viral hepatitis as a common complicating factor in 10-15% of patients presenting with apparent ADIH.89-91

With regard to children early reports of possible INH ADIH often carried suggestions that infectious hepatitis, or other intercurrent infections, might mimic INH ADIH or increase susceptibility to ADIH.12,92-95

Dieu, after describing a high jaundice incidence amongst his patients discusses the subject at length and, in the absence of epidemiological evidence of an infectious hepatitis outbreak in the relevant ward, considered this an unlikely explanation for the high incidence of severe ADIH encountered.93 Several reports of ADIH also document infectious forms of hepatitis in children presenting with jaundice while receiving antituberculosis treatment.16,96,97

Such forms of hepatitis are particularly likely in children hospitalized with more serious forms of tuberculosis for a prolonged period. Kumar et al. studied serological markers for hepatitis viruses amongst 40 children who developed ADIH characterized by jaundice and raised serum ALT and bilirubin during INH and RMP therapy, both in dosages of 10-20 mg/kg body weight daily.98 Hepatitis A and B were shown to be associated with apparent ADIH in 7.5% and 35% of children respectively. Epidemiological evidence suggested that non-A and non-B viruses could have been responsible for hepatitis amongst at least some of the remaining 23 children. The authors conclude that the high ADIH incidence reported from some developing countries may be due to infectious forms of hepatitis; the risks for infection being exacerbated by poor hygiene and the need for parenteral therapy in severely ill children. As the fatality rate was 20% amongst the 40 children described the problem has serious implications. Studies by Dieu, Burghard, Ramachandran, Rugamini & Mehta, Tsagaropoulou -Stinga et al.99-103 all reported very high incidences of jaundice associated with high dosages of INH and RMP, but others using equally high INH and RMP dosages have not experienced this level of serious liver disease.16,104,105 Part of these reported differences may well be due to the occurrence of undetected infectious hepatitis.

Antituberculosis drug-induced hepatotoxicity in children

There is now no doubt that children experience ADIH and 26 papers summarized in Table 1 give details of possible ADIH in 33 children. While evidence supporting ADIH in some cases might be regarded as flimsy, there are several cases, where rechallenge with the relevant agent confirmed the etiology. The median age of children was five years and eight (24%) received an INH dosage of 20 mg/kg or more, five (15%) a dosage of 15 mg/kg and the remaining 19 (58%) 10 mg/kg or less. A recent report describes a further 20 children (0-17 years) who experienced fulminating INH-related hepatic failure;109 in this last report the median age of the children was 10.5 years and all the dosages of INH were <12 mg/kg (6 not available). An earlier paper reviewed possible INH related deaths in the USA between 1965-1989, and identified 14 cases <20 years of age, but these probably also include older adolescents and may well include cases described in this present review.110

It must be emphasized that a common theme in these reports is the frequency with which INH treatment, either alone or accompanied by RMP and PZA, was continued in the face of symptoms indicating possible ADIH.

ADIH in children receiving chemoprophylaxis

Eighteen papers report INH chemoprophylaxis in children and comment on adverse events. Seven give details of 2149 children receiving an INH dosage of 4-6 mg/kg; serum transaminase values were determined regularly in 461 children and 56 (12.1%) had increased values; treatment was discontinued in five (0.23%), no child developed jaundice.77,111-116 Four studies enrolled 1451 children who received an INH dosage of 10 mg/kg,117,118,119 of 369 whose LFT were routinely determined
Table 1. Case reports of antituberculosis drug-induced hepatotoxicity associated with antituberculosis treatment in children.

| Authors                      | Age   | Sex | INH Dosage | RMP Dosage | Other Drugs | Time after treatment start | Features                                                                                                                                            | Outcome findings | Pathology                                                                 |
|------------------------------|-------|-----|------------|------------|-------------|-----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|------------------|---------------------------------------------------------------------------|
| Sweetnam & Murphy 1952      | 6 years | Female | 8 mg/kg   | -          | -           | 8 weeks                     | Nausea, vomiting, jaundice. Recent contact with infectious hepatitis. INH stopped.                                                                     | Recovery         | -                                                                         |
| Brügger 1956                | 7 months | Male | 9.5 mg/kg | 9 mg/kg    | -           | 5 months                    | Fever, toxic, loss of consciousness. Pertussis-like coughing fever and toxicity.                                                                         | Death            | Fatty infiltration of liver                                              |
|                             | 18 months | Male | 9 mg/kg   | 12 mg/kg   | -           | 5 months                    | Measles-like rash, fever, oedema. Fever, toxic, liver edge hard on palpation.                                                                           | Death            | Fatty infiltration of liver                                              |
| Davies & Glowinski 1961     | 81/2 years | Female | 6 mg/kg  | PAS 6 g    | 3-6 weeks     | Lymphadenopathy, rash and jaundice. Role of INH confirmed on rechallenge.                                                                        | Survived         | -                                                                         |
| Bonnet et al. 1972          | 4 years | Male | 10 mg/kg, but increased to 20 and then 30 mg/kg | 30 mg/kg | PAS 300 mg, 4 weeks | Jaundice. Dosages of drugs reduced and INH continued at 10 mg/kg | Survived | Liver biopsy:\ Inflammation, intralobular and intracellular bile retention and fatty infiltration |
| Rudoy et al. 1973           | 6 years | Male | 20 mg/kg, SM 10 mg/kg | - | PAS 300 mg | 4 weeks | Fever, arthralgia, maculopapular rash, abdominal pain. Role of INH confirmed on rechallenge | Survived | Liver biopsy:\ Focal mesenchymal reaction with non-tuberculous granulomas |
| Merlin et al. 1974          | 3.75 years | Female | 10 mg/kg  | SM 400 mg  | 10 months | Routine liver evaluation found raised transaminase values, findings; resolved when INH stopped. | Survived | Liver biopsy: Histological evidence of hepatitis, infectious and drug-induced hepatitis indistinguishable. |
| Casteels-VanDaele et al. 1975 | 13 years | Female | 12 mg/kg  | 11 mg/kg | EMB 20 mg/kg | 7 days | Lethargy, confusion. INH recommenced on recovery | Survived | Liver biopsy: Histology compatible with hepatitis. |
| Allué et al. 1976           | 8 years | Male | 20 mg/kg  | 20 mg/kg  | PAS 200 mg/kg | 14 days | Jaundice, liver enzymes and serum bilirubin elevated. RMP stopped, jaundice resolved and INH continued. Jaundice, LFT elevated. Loss of consciousness. Drugs stopped. Treatment continued with EMB & PAS | Survived | - Cellular infiltration of portal spaces, fatty infiltration and cholestasis |
|                             | 9 years | Male | 15 mg/kg  | 15 mg/kg  | PAS 200 mg/kg | 4 th day | Jaundice, loss of consciousness. RMP discontinued, but deterioration continued. | Survived after exchange transfusion | Death | Liver necrosis and regeneration |
|                             | 1 yr 7 months | Female | 30 mg/kg  | 18 mg/kg  | PAS 200 mg/kg | 3 days after RMP started | Jaundice, transaminases increased. INH stopped, RMP and EMB substituted. On rechallenge LFT again increased. INH given during steroid therapy for ulcerative colitis; fever, nausea and jaundice | Survived | - |
| Brasfield 1976              | 12 years | Female | Dosage not given | SM & PAS, dosages not given | 12 weeks | Jaundice, transaminases increased. INH stopped, RMP and EMB substituted. On rechallenge LFT again increased. INH given during steroid therapy for ulcerative colitis; fever, nausea and jaundice | Survived | - |
| Vanderhoof et al. 1976      | 15 years | Female | 300 mg    | -          | -           | -                           | -                                                                                                                                                    | Death            | -                                                                         |

Continued next page
Table 1. Continued from previous page.

| Authors                      | Age  | Sex  | INH Dosage | RMP dosage | Other Drugs     | Time after treatment start | Features                                                                 | Outcome findings | Pathology                  |
|------------------------------|------|------|------------|------------|-----------------|----------------------------|---------------------------------------------------------------------------|------------------|----------------------------|
| Walker & Park-Hah 1977115    | 2 yrs| Male | 16.6 mg/kg | -          | -               | 1 day                      | Fever, nausea, vomiting; INH stopped. Recomenced and 1 day later rash, fever, vomiting, raised AST | Recovery         | -                          |
| Chapin et al. 1978116       | 12 yrs| Female | 15 mg/kg | 15 mg/kg | PAS             | 3 months                  | Fluothane anaesthetic given within 10 days of starting INH. 3 months later jaundice occurred followed by liver failure; jaundice with increased transaminases; RMP stopped, INH substituted, but no improvement, INH and prothionamide stopped | Death            | -                          |
|                             | 4 yrs| Female | 20 mg/kg | -          | Prothionamide 15 mg/kg, EMB 20 mg/kg | 8 months                  | -                                                                         | Recovery with liver atrophy | -                          |
| Gutman 1978117              | 5 months | Female | 20 mg/kg | 20 mg/kg | SM 30 mg/kg, PAS 300 mg/kg, diltiazem 5 mg/kg | 9 days | Jaundice, LFT increased; RMP discontinued, and LFT better, but child experienced a bleeding duodenal ulcer | Death            | -                          |
| Stein & Liang 197995        | 2 yrs| Male | 20 mg/kg | -          | PAS 150 mg/kg   | 2 months                  | ALT and AST raised, infectious hepatitis contact. INH continued and 3 weeks later all drugs stopped, EMB started, INH rechallenge caused transaminases to rise again | Recovery         | -                          |
| Eistrizter et al. 1980118   | 11 months | Male | 10 mg/kg | 10 mg/kg | -               | 2 days                     | Vomiting and lethargy followed by loss of consciousness and grossly abnormal LFT. | Recovery         | Liver biopsy: architecture preserved, isolated centrilobular necrosis, cholestasis and fatty degeneration. |
| Bonora et al. 1981119       | A baby | Not stated | 20 mg/kg | 10 mg/kg | -               | 9 days                     | Nausea, vomiting and abdominal tenderness, transaminases increased. INH and RMP stopped. INH later reintroduced with SM. | Recovery         | -                          |
| Uhrainqui et al. 1983120    | 6 yrs| Female | 10 mg/kg | 10 mg/kg | EMB 20 mg/kg    | 6 days                     | Nausea, vomiting and anorexia, AST and ALT raised, but normalized when INH was stopped. Nausea, vomiting, anorexia and hepatomegaly. INH stopped; reintroduced at an 8 mg/kg dosage after normalization of LFT. | Recovery         | -                          |
|                             | 9 yrs| Male | 15 mg/kg | 15 mg/kg | SM 20 mg/kg     | 9 days                     | -                                                                         | Recovery         | -                          |
| Palusci et al. 1985121      | 16 yrs| Female | 4.3 mg/kg | -          | -               | 18 weeks                  | Insomnia, weakness, tachycardia; INH continued and patient presented a week later in liver failure | Recovery after liver transplantation | -                          |
| Gal & Katt 1986122          | 5 yrs| Male | 10 mg/kg | -          | -               | 10 weeks                  | Jaundice, diffuse abdominal pain; LFT raised; progressed to liver failure. | Death            | -                          |
| Van Aalderen et al. 1987124 | 10 yrs| Male  | 10 mg/kg | 15 mg/kg | PZA 35 mg/kg, EMB 15 mg/kg | 10 weeks                  | Initial symptoms headache, itching skin rash and gastrointestinal symptoms. | Death            | Liver biopsy: Acute atrophy, no sign of viral disease. |
| Moulding et al. 1989123     | 5 yrs| Not stated | -          | -          | -               | 3 months                  | Lethargy, weakness and loss of appetite. Liver failure | Death            | -                          |
| Hasasawa et al. 1994128     | 16 yrs| Female | Not stated | -          | -               | 3 months                  | -                                                                         | Recovery after liver transplantation | -                          |
| Meyers et al. 1994125       | 51/2 yrs | Female | 15 mg/kg | -          | -               | 14 weeks                  | Liver failure | Recovery after liver transplantation | -                          |
| Berkowitz et al. 1998126    | 10 yrs| Male | 300 mg | 450 mg | PZA 1 g, EMB 400 mg, carbamazepine | 5 days                     | Lethargy and abdominal tenderness, Tuberculosis treatment stopped. | Recovery         | -                          |
| Cillo et al. 2005127        | 10 yrs| Male  | Not stated | -          | -               | 3 months                  | Fulminant liver failure | -                          |
| Lobato et al. 2008128       | 4 yrs| Female 8 months | 9 mg/kg | -          | -               | 3 weeks | Vomiting, anorexia, pale stools and abdominal pain, jaundice followed by fulminant liver failure. | Recovery after liver transplantation | -                          |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; EMB, ethambutol; INH, isoniazid; LFT, liver function test; PAS, para-amino salicylic acid; RMP, rifampicin; SM, streptomycin; yrs, years.

In addition to the cases listed above a further twenty cases of INH-related hepatic failure in children (mean age 9.8 years; range 1.3-17) were identified by Wu et al. (2007)129.
Hepatotoxicity of Antituberculosis agents in children treated for tuberculosis

Despite initial complacency regarding hepatotoxicity the introduction of RMP and later PZA into routine treatment, together with reports of hepatotoxicity in adults, created circumstances in managing children; from approximately 1970 reports of treatment of children with tuberculosis disease frequently refer to LFT evaluation or the occurrence of jaundice in children receiving INH, RMP and PZA. In this review 69 papers are referenced giving details of children treated for tuberculosis that evaluate or comment on ADIH.

The majority of papers document daily therapy, but partial or total intermittent therapy was described in several papers.97,156-163 In general, intermittent regimens were associated with less hepatotoxicity, but were also frequently used for less serious forms of tuberculosis.

Two papers report early studies in which INH monotherapy was used to manage tuberculosis disease in 218 children;163,164 in only one were liver functions studied and four of 50 (8%) children had increased LFT values.164 One child (0.46%) developed jaundice.

Thirteen studies recorded treatment of 3053 children with INH dosages of 10-20 mg/kg and drugs other than RMP;12,182,156,163,165-173 The additional drugs commonly used were SM, PAS and EMB and in one study PZA.12,181 Jaundice occurred in 12 children (0.39%); serum transaminase values were routinely determined in 443 children and increased in 49 (11.1%). There were several interesting observations. Mantero et al. phenotyped 54 children as rapid (22) or slow (32) INH acetylators; of 14 children developing increased AST levels only two (9.1%) were rapid INH acetylators and 12 (37.5%) slow, suggesting an influence of INH concentrations on ADIH.170 Jaundice occurred in 12 children and in nine this was associated with INH dosages of ≥20 mg/kg and in one case ≥15 mg/kg; it is noteworthy that eight of 12 cases of jaundice were reported in one study.169 Three papers give details of the management of children with INH 8-15 mg/kg and RMP;99,174,175 All 224 children entered in these studies had AST and ALT regularly evaluated and 32 (14.3%) had increased values on at least one occasion. Two children (0.9%) became jaundiced and three (1.3%) experienced symptoms compatible with ADIH. The study of Dieu is frequently referred regarding the interaction of INH and RMP and the influence of increased INH dosages.99

Seven studies record details of 453 children receiving INH dosages of 10-20 mg/kg together with RMP, but no other agents.99,100,102,156,158,160,176 AST and ALT levels were not reported in 3 studies and amongst the remaining 5 studies 413 children were evaluated and increased AST or ALT values found in 64 (15.5%). Jaundice occurred in 52 children (11.5%). The percentage of children with jaundice is high and strongly influenced by the studies of Dieu,99 Burghard et al.,100 Bassetti et al.176 and Rugamini & Mehta.102 However, whether or not infectious causes of hepatitis underlie some of these cases, it remains true that the incidence of jaundice was influenced by the INH dosage; the studies of Dieu,99 Burghard et al.100 and Rugamini & Mehta 102 provide evidence that reducing the INH dosage to a maximum of 15 mg/kg has a considerable influence on susceptibility to severe ADIH.

Sixteen papers describe the findings in 2714 children receiving an INH dosage of approximately 10 mg/kg (range 5-14 mg/kg), together with RMP and other agents.9,13,37,78,80,94,157,161,177,186 In four studies LFT were not evaluated; amongst 1762 children regularly evaluated 141 (8.0%) had increased transaminase levels and amongst the whole group jaundice was observed in three children (0.11%). Symptoms or clinical signs of ADIH were observed in 35 children (1.3%).

Nine studies enrolled 2332 children who received an INH of dosage 10-20 mg/kg together with RMP and other drugs.160,171,172,186-191 In two studies LFT were regularly evaluated in 1406 children;187,189 AST and/or ALT levels were increased in 139 (9.9%). Jaundice occurred in five (0.22%).

Fifteen papers described 717 children treated for TBM; in four 259 children received INH dosages of 10-15 mg/kg.12,100,192,193 In only one study were LFT determined and these children...
were probably treated with INH alone.12 Amongst these 14 eight (57%) had increased LFT levels before treatment and at four weeks after treatment commencement four (29%) still had increased values. The author implies that the only children with abnormal values were those with increased values pre-treatment. He also describes 9 of 21 children treated with INH who developed measles or varicella and in whom LFT increased by a factor of X4 to X6 normal values, but INH was continued without any deleterious effects.

Jaundice was reported in 26 children (10.04%) and all 26 cases come from the studies of Ramachandran et al.101 and Parasarathy et al.192. In the study of Parasarathy et al. ADIH was almost entirely confined to patients (adults and children) receiving INH and RMP.192 When ADIH did occur it was mainly in the intensive phase and was also more frequent in phenotypically slow acetylators of INH, implying that exposure to higher INH concentrations plays a role in ADIH. When RMP was given intermittently the incidence of jaundice was also lower. The authors also point out that viral hepatitis is endemic in South India; both INH and RMP might contribute to exacerbating subclinical viral hepatitis and this effect could be more marked with higher drug dosages.

Eleven papers described 458 children treated for TBM with INH dosages ranging from 15-20 mg/kg.16,96,101,103-105,168,192,194,195,196. Again a very high proportion (174; 52.9%) of 329 children in whom concentrations of transaminases were determined had increased values.

### Table 2. Antituberculosis drug-induced hepatotoxicity in children receiving chemoprophylaxis.

| Dosage mg/kg | Studies | n   | Liver function tests abnormal | Symptoms of hepatotoxicity | Jaundice | Treatment |
|--------------|---------|-----|--------------------------------|----------------------------|----------|-----------|
| INH 4-6      | 7       | 2149| 56/461 (12.1%)                | 2 (0.05%)                  | 0        | 5 (0.23%) |
| INH 10       | 4       | 1451| 25/969 (6.8%)                 | 64 (4.4%)                  | 1 (0.07%)| 2 (0.14%) |
| INH 10-20    | 7       | 7528| 17/116 (14.7%)                | 4 (0.05%)                  | 0        | 0         |
|              | 18      | 11128| 98/946 (10.4%)               | 70 (0.63%)                 | 1 (0.01%)| 7 (0.06%) |

| RMP containing chemoprophylaxis regimens |
|------------------------------------------|
| RMP 10                                   |
| 2                                        |
| 182                                      |
| 11/182 (6%)                             |
| 0                                        |
| 0                                        |
| 1 (0.55%)                               |
| INH 10, RMP 10                          |
| 4                                        |
| 1301                                     |
| Not routinely measured                   |
| 13 (1.0%)                               |
| 0/1301                                   |
| 0                                        |
| RPM 10 PZA15-30                         |
| 3                                        |
| 97                                       |
| 1/97 (1%)                               |
| 0/97                                     |
| 0                                        |

| All forms of chemoprophylaxis |
|------------------------------|
|                              |
| 27                           |
| 12708                       |
| 110/1225 (8.0%)             |
| 83 (0.55%)                  |
| 1 (0.01%)                   |
| 8 (0.06%)                   |

| INH, isoniazid; PZA, pyrazinamide; RMP, rifampicin. |

### Table 3. Antituberculosis drug-induced hepatotoxicity in children treated for tuberculosis.

| Drugs                | INH Dosage mg/kg | Studies | N   | Liver function tests abnormal | Symptoms or signs of liver disease |
|----------------------|------------------|---------|-----|--------------------------------|-----------------------------------|
| INH                  | 6-10             | 2       | 218 | 4/50 (8.0%)                    | Jaundice in 1 (0.46%)             |
| INH & other agents   | <10-20           | 13      | 3053| 49/443 (11.1%)                 | Jaundice 12 (0.39%)               |
| INH & RMP            | 8-15             | 3       | 224 | 32/224 (14.3%)                 | Symptoms of ADIH 3 (1.3%).        |
| INH & RMP            | 10-20            | 7       | 453 | 64/413 (15.5%)                 | Jaundice 2 (0.89%).               |
| INH & RMP and other agents | 5-14           | 16      | 2714| 141/1762 (8.0%)                | Symptoms of ADIH 5 (1.1%).        |
| INH & RMP and other agents | 10-20       | 9       | 2322| 139/1406 (9.8%)                | Symptoms of ADIH 6 (0.2%).        |
|                      |                 | 50      | 8984| 380/3855 (9.9%)                | Jaundice 5 (0.22%).               |
|                      |                 |         |     |                                 | Symptoms of ADIH 32 (0.38%)       |
|                      |                 |         |     |                                 | Jaundice 75 (0.91%)               |

| Tuberculous meningitis |
|------------------------|
|                        |
| INH, RMP and other agents | 10-15          | 4       | 259 | Not routinely determined        | Other drugs substituted 23 (8.9%). |
|                        |                 |         |     |                                  | Jaundice 26 (10.0%)               |
| INH, RMP and other agents | 10-20          | 11      | 458 | 174/329 (52.9%)                 | Jaundice 46 (10.0%)               |
|                        |                 | 15      | 717 | 174/329 (52.9%)                 | Jaundice 72/717 (10.04%)          |

| INH, isoniazid; RMP, rifampicin. |

### Table 4. Selected studies of adults with tuberculosis receiving INH and RMP recording an increase in transaminase values above normal.

| Authors           | n  | Increased transaminase values |
|-------------------|----|-------------------------------|
| Lees et al. 197113| 105| 37 (35%)                      |
| Lal et al. 1972201| 63 | 14 (22%)                      |
| Lees et al. 1972214| 110| 21 (23%)                      |
| Grönhagen-Riska 1978202| 319| 58 (18%)                      |
| Musch et al. 1982412| 86 | 30 (34%)                      |
| Hwang et al. 1997413| 240| 63 (26%)                      |
| Agal et al. 2005413| 200| 221 (11%)                     |
|                   | 1123| 244 (22%)                     |
Jaudice was also reported in a high proportion, affecting 46 (10.04%) and in the studies of Rahajoe et al.,188 Ramachandran,101 Tsagaropoulou-Stinga et al.,103 and Parasarathy et al.,192 the proportion of children becoming jaundiced varied from 29% to 50%; other studies using similar regimens with equally high drug dosages, although reporting a high proportion of children with increased transaminase values14,96,104,105,194 found a much lower incidence of jaundice or no cases of jaundice.

Table 3 summarizes ADIH amongst children treated for tuberculosis disease. Excluding TBM, 8984 children were treated for disease with jaundice reported in 75 (0.83%); LFT were evaluated in 3855 children and were abnormal in 380 (9.9%). TBM treatment was recorded for 717 children and jaundice occurred in 72 (10.04%) and abnormal LFT in 174 (52.9%) of 329 children. The study of Diekoff was not included in the tabulation of LFT results due to the early methodologies used.12

Discussion

The most important finding of this review is that ADIH, however defined, occurs in children, but that the incidence is lower than in adults receiving comparable drug dosages and regimens. The contrast between children and adults is clearest in chemoprophylaxis studies enrolling children and adults in the same study. Amongst children approximately 10%, receiving either INH alone or INH accompanied by RMP or RMP and PZA, experience a rise in serum transaminase values or (in older studies) an abnormality in LFT. Less than 1% are recorded as having symptoms of ADIH and only 1 child amongst more than 12,000 receiving INH chemoprophylaxis is recorded as developing jaundice. Very similar results are found amongst much smaller numbers of children receiving RMP containing prophylactic regimens. As regards PZA only 97 children entered in 3 studies are recorded who received PZA with RMP for chemoprophyaxis, but the risk of ADIH does not appear serious.

Amongst children treated for tuberculosis disease a different picture emerges. Although a similar proportion of children (approximately 10%) experience increased serum transaminase values, a considerably larger proportion presented with jaundice than amongst those managed for latent infection; this proportion varies from less than 1-50% in some studies of children treated for TBM. Several factors may be important in this regard.

Disease severity plays a role in the frequency of ADIH11,171 and underlying hepatic abnormalities present in both adults5-8 and children15 before the start of treatment, especially in disseminated forms of tuberculosis, may be relevant in this regard; a large proportion of children will also have abnormal LFT before treatment. This is particularly likely in children with disseminated disease that might accompany TBM. The study of Diekoff12 found no abnormal LFT amongst children with uncomplicated primary tuberculosis prior to treatment, but abnormal LFT amongst 57% of 14 children with TBM not complicated by miliary tuberculosis and 68% of 63 children with miliary tuberculosis without TBM.

In regimens including INH and drugs other than RMP there are indications that the INH dosage may play a role in ADIH: of 12 cases of jaundice reported following the use of INH with drugs other than RMP, 9 occurred in children receiving an INH dosage of 20 mg/kg or higher.102,168,169 With regard to children receiving only INH and RMP a number of authors commented on a reduced incidence of severe ADIH and jaundice, when the INH dosage was reduced to less than 15 mg/kg99,101,168,169,192,196 or less than 10 mg/kg.102 Amongst the 3 studies giving details of 224 children treated with only INH and RMP and receiving an INH dosage of approximately 8-15 mg/kg, only 2 (0.9%) children became jaundiced99,174,175 compared to 52 (11.5%) of 453 children receiving INH in dosages of 10-20 mg/kg99,100,102,156,158,169,176. Turning to those studies where INH and RMP were combined with other agents, often including PZA, jaundice occurred in only 2 (0.07%) of 2714 children receiving RMP and INH in a dosage of approximately 10 mg/kg, compared to 5 (0.21%) of 2413 children receiving an INH dosage of 10-20 mg/kg, which does not suggest an influence of INH dosage.171,172,186-191 There is also not a significant influence of dosage regarding those with increased serum transaminases; increased values were reported in 141 (8%) of 1762 children receiving an INH dosage of 10 mg/kg and 139 (9.8%) of 1406 children receiving dosages of 10-20 mg/kg.

However support is lent to the risk of increased concentrations of INH, or its metabolites, by the finding that, as in adults, children who are phenotypically slow acetylators of INH were more likely to experience a rise in transaminase values above normal.175 In the study of Martinez-Roig et al. all children presenting with clinical signs and raised enzyme values were phenotypically slow INH acetylators.119 The importance of INH dosage in precipitating severe hepatotoxicity also receives support from adult studies.185 In contrast to INH, the dosage of RMP does not appear to be a critical factor in precipitating hepatotoxicity,109,99 although O’Brien et al. found that RMP dosage became a significant factor in hepatotoxic reactions indicated by AST values above 100 U/L or increased serum bilirubin.171 Several paediatric studies of groups of similar children receiving INH, both with and without RMP, suggest that merely adding RMP to the regimen was sufficient to precipitate severe hepatotoxicity.102,166-169,196

PZA is an acknowledged hepatotoxic agent but few publications have addressed its potential to cause ADIH in children; a single case report suggested that RMP and PZA combined might have contributed to serious ADIH in a 10 year old child.81 Two studies of the combination of INH, RMP and PZA for chemothera- py75,79 found no evidence that PZA constituted an hepatotoxic risk, but a retrospective study found the use of PZA associated with AST or ALT values >5× the upper limit of normal, but only 8 of 90 children received PZA and several of these children had more severe disease.80

In considering the role of PZA it is also of interest that PZA was not used in studies reporting particularly high incidences of jaundice during the treatment of TB, although it was used in several studies using similarly high dosages of INH and RMP during which jaundice was unusual or did not occur.16,96,104,116. It should also be noted that several literature reviews concluded that the risk of hepatotoxicity associate with PZA dosages of 30-40 mg/kg in adults was not excessive.198-200

Comparisons of the results of this review with those of adults receiving similar regimens for tuberculosis disease treatment are difficult. ADIH associated with treatment of disease is more complex and few studies include both adults and children allowing a direct comparison of the same regimens in the same populations. Amongst groups of children treated for tuberculosis, other than TBM, the incidence of increased transaminase values is approximately 10% and similar to that amongst children receiving chemoprophylaxis; the percentage of children becoming jaundiced is, however, considerable higher, overall 1.2% compared to 0.01% amongst those receiving chemoprophylaxis and it should be emphasized that this figure is strongly influenced by very high rates of jaundice in a small number of studies, in nearly all of which cases the children were receiving INH dosages of 20 mg/kg or 10-20 mg/kg.

Table 4 summarizes selected studies reporting adult pulmonary tuberculosis patients receiving INH and RMP with documented increases in serum transaminase values above the upper limit of normal after the start of treatment; the mean percentage (22%) is approximately twice that in children suggesting a greater propensity for ADIH in adults. While it might be more valid to consider those children with transaminase values that were >2X or >3X or >5 normal this information is seldom provided.

In the meta-analysis of Steele et al. 6155 adult patients were evaluated in 19 studies and 168 (2.73%) diagnosed with clinical hepatitis.204 In this present review, excluding chil-
Children with tuberculous meningitis, and accepting the occurrence of jaundice as evidence of severe ADIH, 70/8984 (0.78%) children developed severe clinical hepatitis and an additional 31 (0.35%) developed symptoms indicative of ADIH. These figures are, again, strongly influenced by the occurrence of jaundice amongst the 453 children receiving INH and RMP only, with INH in a dosage of 10-20 mg/kg. Omitting these groups, only 18 (0.36%) cases of jaundice occurred amongst 8494 children treated for tuberculosis disease.

A tentative conclusion of this review might thus be that INH dosages of 5-15 mg/kg alone or in the company of other drugs do not constitute and undue risk for the development of ADIH in children.

As regards RMP it seems likely that RMP itself carries a relatively small risk of ADIH, but, for reasons not fully understood, can precipitate ADIH particularly with INH dosages of >15 mg/kg. The dosage of RMP does not appear critical in this interaction. From what is known of the serum concentrations of RMP achieved in children it would appear that dosages of 10-20 mg/kg can be safely recommended for children up to the age of 13 years with a proportionately lower dosage with increments in weight.205 Despite recent concern about the hepatotoxicity of PZA in adults, both in chemoprophylaxis and in disease treatment, this review produced little evidence that PZA makes a major contribution to ADIH in multidrug regimens in children. In only one study was there an indication that PZA made a significant contribution to ADIH, and this depended upon the influence of eight children receiving PZA.80 In several studies the highest incidences of ADIH occurred amongst children not receiving PZA. The dosage of PZA used in the studies reviewed varied from 25 mg/kg to 40 mg/kg and there was no suggestion that the dosage of PZA made any contribution to the development of ADIH. Thus it is likely that a PZA dosage of 30-40 mg/kg, with appropriate adjustments for age, can be recommended for use in children.

There is little information regarding the interaction of other infectious diseases in particular HIV-infection and ADIH in children. Evidence from adults is conflicting at present and while some studies suggest that HIV-infected individuals may be exposed to a reduced risk of ADIH,86 other studies found that the risk was unaltered amongst those who are HIV-infected,206,207 and yet other studies found HIV infection an independent risk factor for ADIH.88 In a recent randomized controlled study of INH prophylaxis in 263 HIV-infected children serum ALT was raised in 2 (0.02%) of 131 children receiving placebo, but none of the 132 receiving INH.208 Particularly in developing countries the various forms of infectious hepatitis play a role in ADIH, both in possibly precipitating toxicity and in confusing the diagnosis of ADIH. Amongst adults and children there is ample evidence that a significant proportion of patients with ADIH may have underlying infectious hepatitis.67,89-91 Amongst 85 Indian patients, mainly adults, presenting with acute liver failure associated with ADIH 15 (17.6%) had associated hepatitis virus infection.209 In children this combination may be associated with a high mortality and it is thus a potentially serious problem.96

**Limitations**

The papers reviewed stretch back over more than 50 years and their scientific quality therefore varies considerably. The terms hepatotoxicity, hepatitis, liver damage and liver injury are used interchangeably and each could be debated. In many instances the purpose of the study was the evaluation of chemoprophylaxis or treatment efficacy; in only a minority was the purpose the documentation of hepatotoxicity. Much data relating to ADIH is thus fragmentary; LFT were seldom performed routinely in early studies and cases of hepatotoxicity might well have been missed or not reported. None the less the occurrence of an outstanding event such as jaundice, or indeed death, as result of liver failure in a child, is most unlikely to have been missed by astute clinicians. Criteria for suspending treatment also vary and where some studies follow the recommendations of the ATS in this respect, other clinicians, for example, suspended treatment following a two-fold rise in transaminase values, irrespective of the presence of symptoms. Despite these reservations a substantial body of data has been assembled that may be valuable when assessing the risks of ADIH and also vary and where some studies follow the recommendations of the ATS in this respect, other clinicians, for example, suspended treatment following a two-fold rise in transaminase values, irrespective of the presence of symptoms. Despite these reservations a substantial body of data has been assembled that may be valuable when assessing the risks of ADIH associated to different dosages of INH, RMP and PZA to be used in children.

In conclusion this review confirms that ADIH does occur in children and that vigilance is always necessary if the tragedy of acute liver failure is to be prevented in children. None the less the incidence of ADIH in children is considerably lower than in adults and the newly recommended dosages of INH, RMP and PZA for children do not appear to constitute an added risk factor for ADIH.

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