

ORIGINAL ARTICLE

Adherence to isoniazid preventive chemotherapy: a prospective community based study

B J Marais, Susan van Zyl, H S Schaaf, M van Aardt, R P Gie, N Beyers



Arch Dis Child 2006;91:762-765. doi: 10.1136/adc.2006.097220

See end of article for authors' affiliations

Correspondence to:
Dr B J Marais, Department of Paediatrics and Child Health, Desmond Tutu TB Centre, Faculty of Health Sciences, Stellenbosch University, PO Box 19063, Tygerberg, 7505, South Africa; bjmarais@sun.ac.za

Accepted 18 May 2006
Published Online First
31 May 2006

Background: Current international guidelines recommend 6–9 months of isoniazid (INH) preventive chemotherapy to prevent the development of active tuberculosis in children exposed to a susceptible strain of *M tuberculosis*. However, this is dependent on good adherence and retrospective studies have indicated that adherence to unsupervised INH preventive chemotherapy is poor.

Aim: To prospectively document adherence to six months of unsupervised INH monotherapy and outcome in children with household exposure to an adult pulmonary tuberculosis index case.

Methods: From February 2003 to January 2005 in two suburbs of Cape Town, South Africa, all children <5 years old in household contact with an adult pulmonary tuberculosis index case were screened for tuberculosis and given unsupervised INH preventive chemotherapy once active tuberculosis was excluded. Adherence and outcome were monitored.

Results: In total, 217 index cases from 185 households were identified; 274 children <5 years old experienced household exposure, of whom 229 (84%) were fully evaluated. Thirty eight children were treated for tuberculosis and 180 received preventive chemotherapy. Of the children who received preventive chemotherapy, 36/180 (20%) completed ≥5 months of unsupervised INH monotherapy. During the subsequent surveillance period six children developed tuberculosis: two received no preventive chemotherapy, and four had very poor adherence.

Conclusion: Adherence to six months of unsupervised INH preventive chemotherapy was poor. Strategies to improve adherence, such as using shorter duration multidrug regimens and/or supervision of preventive treatment require further evaluation, particularly in children who are at high risk to progress to disease following exposure.

A large percentage of children with household exposure to a sputum smear positive adult tuberculosis index case become infected with *Mycobacterium tuberculosis*.^{1–3} Following infection, the risk of developing disease is highest (20–50%) in very young (<2–3 years of age) and/or immune compromised children.⁴ These high risk children may experience rapid disease progression, which identifies them as the priority group to receive preventive chemotherapy.⁵

Currently the World Health Organization (WHO) and the International Union against Tuberculosis and Lung Disease (IUATLD) recommend that all children <5 years of age who are in household contact with a sputum smear positive index case, should be actively traced and screened for tuberculosis.^{5,6} Six months of isoniazid (INH) is recommended as preventive chemotherapy once active tuberculosis has been excluded, because with good adherence, 6–9 months of INH monotherapy has proven efficacy to prevent tuberculosis in children infected with a susceptible strain of *M tuberculosis*.^{7–10}

Screening of children is difficult in resource limited settings,¹¹ and several reports have shown that even when screening is performed, adherence to 6–9 months of unsupervised INH preventive chemotherapy is often very poor.^{12–16} These studies have been criticised, mainly for their retrospective methodology, and international guidelines have remained unchanged. However, adherence is a crucial component of any preventive chemotherapeutic regimen. We prospectively documented adherence to six months of unsupervised INH monotherapy, and outcome in children with household exposure to an adult pulmonary tuberculosis index case.

METHODS

Setting

The study was conducted from February 2003 to January 2005 in two suburbs of Cape Town, South Africa. The

estimated size of the study population was 36 334 (census data 2001), and the incidence of new smear positive tuberculosis was high (average notification rate of new bacteriologically confirmed tuberculosis 320/100 000).¹⁷

Patients received antituberculosis treatment from two primary healthcare clinics. Facility based tuberculosis treatment registers were used to prospectively identify all new adult (>15 years) pulmonary tuberculosis cases. Household contacts were defined as those living at the same residential address as the adult index case at the time of diagnosis. A social worker visited the homes of new adult index cases and recorded the names and ages of all children resident at that address. According to South African National Tuberculosis control Programme (NTP) guidelines,¹⁸ children with suspicious symptoms and all children <5 years old were invited for evaluation at the local primary healthcare clinic.

Evaluation and treatment

Evaluation included a tuberculin skin test (TST, 2TU PPD RT23 intradermally) and chest radiograph (antero-posterior and lateral views). A single expert read all chest radiographs in a standardised fashion and identified children with probable tuberculosis that required antituberculosis treatment. A rapid human immunodeficiency virus (HIV) screening test (Determine Rapid HIV test, Abbott) was offered, together with standard pre- and post-test counselling, if the mother was known to be HIV infected or if the child was diagnosed with tuberculosis.

Antituberculosis treatment consisted of directly observed INH, rifampicin (RMP), and pyrazinamide (PZA) for two months, followed by INH and RMP for a further four months.

Abbreviations: HIV, human immunodeficiency virus; INH, isoniazid; PZA, pyrazinamide; RMP, rifampicin; TST, tuberculin skin test

Table 1 Demographics and tuberculosis screening results in children <5 years old in household contact with an adult pulmonary tuberculosis index case (n = 274)

	No. (%)
Gender	
Male	129 (47)
Age	
<3 years of age	178 (45)
HIV	
Mother known HIV+	0
Children tested	34 (12)
Children positive	0/34
TST	
Tested	243 (89)
Positive (≥ 10 mm)	122/243 (50)
Screening	
Not screened	14 (5)
Partially screened*	31 (11)
Fully screened†	229 (84)
Treatment	
Treated for tuberculosis	38 (14)
Preventive chemotherapy	180 (66)
No treatment	56 (20)

HIV, human immunodeficiency virus; TST, tuberculin skin test.

*Partially screened: either a TST or chest radiograph performed and read.

†Fully screened: both a TST and chest radiograph performed and read.

Preventive chemotherapy consisted of unsupervised INH monotherapy for six months, with monthly collection of tablets from the clinic. Adherence was documented after completion of the six month preventive treatment period. Adherence was considered reasonable if tablets were collected for 5 months or more, poor if collection occurred for 2–4 months, and very poor if monthly tablets were collected once or twice only (treatment period <2 months). Surveillance was carried out during the study period and for an additional 6 months after study enrolment stopped, to document children who were subsequently diagnosed with tuberculosis.

Parents gave written informed consent for study participation and approval was obtained from the City of Cape Town Health Department, local health committees, and the institutional review board of Stellenbosch University.

RESULTS

In total, 217 adult index cases from 185 households were identified, of whom 171 (79%) were sputum smear positive,

17 (8%) were culture positive, and 29 (13%) were diagnosed by chest radiography. Enumeration of household contacts <5 years of age identified 274 children. Demographics and tuberculosis screening results are reflected in table 1. No mothers were known to be HIV infected; 89.5% (34/38) of the children diagnosed with tuberculosis were tested for HIV and none tested positive. Of the 38 children diagnosed with tuberculosis after the initial screening tests, 31 (81.6%) were <3 years of age.

Adherence to antituberculosis treatment and unsupervised INH preventive chemotherapy is reflected in table 2. No side effects (peripheral neuropathy or liver damage) were reported or observed with the use of INH monotherapy. The outcome of children treated for tuberculosis was good; one child was lost to follow up. Of the 236 children without signs of tuberculosis at initial screening, six (3%) subsequently developed tuberculosis: 2/56 (4%) who received no preventive chemotherapy, and 4/130 (3%) with very poor adherence. In total, 36/44 (81.8%) children diagnosed with tuberculosis were <3 years of age: 31/38 (81.6%) diagnosed at initial screening and 5/6 (83.3%) who developed tuberculosis subsequently.

DISCUSSION

The most striking observation was the poor adherence to six months of unsupervised INH preventive chemotherapy in the study setting. Nearly 80% of household contacts <5 years old either received no preventive treatment at all or showed very poor adherence (<2 months). Frequently the only criterion considered when evaluating the potential public health value of a chemotherapeutic intervention is its efficacy under ideal trial conditions, while little emphasis is placed on “real life” operations research. Both efficacy, which is usually established under conditions of optimal adherence, and actual adherence in “real life” are essential elements that determine the ultimate effectiveness of the intervention.

Poor adherence to unsupervised INH monotherapy is not a novel finding,^{11–15} but this study incorporated some design elements that were absent in most previous studies. It was a prospective study conducted in an endemic area with active tracing of all child contacts. This allowed us to accurately document the total number of child contacts, the number evaluated, and the number who received preventive chemotherapy. Previous studies usually documented adherence only in the children who turned up for screening or in whom preventive chemotherapy was initiated, which imposes a significant selection bias. The finding that 24% of all children <5 years of age with household exposure to a tuberculosis index case were not even offered preventive chemotherapy, is almost certainly a gross underestimate of the situation in most endemic areas. The study area was well resourced, had

Table 2 Adherence to antituberculosis treatment and preventive chemotherapy, and outcome according to preventive chemotherapy adherence

	Adherence (%)			
	Not given	Very poor	Poor	Reasonable
Treatment regimen				
TB treatment (n = 38)	0	1 (3)	3 (8)	34 (89)
Preventive chemotherapy 6H (n = 236)	56 (24)	130 (55)	14 (6)	36 (15)
Outcome				
Preventive chemotherapy group TB within 6/12	2/56 (4)	4/130 (3)	0	0

Very poor: received <2 months of therapy.

Poor: received 2–4 months of therapy.

Reasonable: received >4 months of therapy.

TB, tuberculosis.

What is already known on this topic

- Young children, particularly those <3 years of age, are vulnerable to develop tuberculosis following household exposure to an infectious index case
- With good adherence and following exposure to an index case with drug susceptible tuberculosis, 6–9 months of INH preventive chemotherapy provides good protection, although retrospective studies have reported poor adherence to unsupervised

easy access to TST and chest x ray screening tests, and additional effort was made during the study period to trace and invite all children for screening. A survey performed in Malawian hospitals showed that child contacts were screened for tuberculosis in only 12% of hospitalised adult tuberculosis cases.¹¹

The fact that 82% of children who received antituberculosis treatment were <3 years of age, illustrates the particular importance of providing preventive treatment to this high risk group. The pre-chemotherapy literature that documented the natural history of disease emphasises the vulnerability of this age group,⁴ and more recent reports from India also indicate that children <3 years of age are at highest risk to develop severe disease manifestations.¹⁹ In addition, in children ≥ 3 years of age the majority of transmission in endemic areas occurs outside the household.^{20–21} Therefore, in resource limited settings where tuberculosis services are overstretched even without offering screening or preventive chemotherapy to children in household contact with an adult index case, it seems warranted to focus the provision of preventive chemotherapy on those children who are at highest risk to progress to disease following household exposure (<3 years and/or immune compromised).^{4–5} This seems like the most realistic way to improve access to preventive chemotherapy for those children who are most likely to benefit.

A three month preventive chemotherapy regimen of INH and RMP has been evaluated in children and appears equally efficacious as 6–9 months of INH monotherapy,^{22–23} while significantly better adherence has been reported with this short duration multidrug preventive regimen.^{12–22} In theory, RMP and PZA are best suited for the treatment of latent infection as they are the two most important sterilising drugs available.²² Although this combination has proven efficacy in animal models,²⁴ adverse reactions in adult patients have limited initial enthusiasm.²⁵ However, these adverse reactions have not been recorded in children,²⁶ and the standard three drug combination of INH, RMP, and PZA is generally well tolerated. Further studies are required to establish the efficacy and safety of short course multidrug preventive regimens, but this seems like the most promising alternative, both to reduce the risk of INH resistance and to improve treatment adherence.

In general, children contribute little to the creation of the drug resistance problem, although they may suffer a great deal as a result of it. Children usually have pauci-bacillary disease and therefore their chance of acquiring random INH resistance is small and they rarely contribute to disease transmission within the community. The main factor that influences children's risk to become infected with an INH resistant strain is the prevalence of transmitted INH resistance within the community. Drug resistance patterns among children provide an accurate reflection of transmitted drug resistance within a community. A recent survey of drug resistance patterns among children from areas surrounding

What this study adds

- This is the first prospective study to investigate adherence to preventive INH chemotherapy in children; a special effort was made to limit selection bias
- The study confirms that poor adherence is achieved using unsupervised INH preventive chemotherapy in children, putting them at risk to develop subsequent tuberculosis and emphasising the need to develop new preventive therapy strategies

and including the study setting, showed that 12.4% of all children with culture positive disease were infected with an INH resistant strain.²⁷ The safety of persisting with INH monotherapy as the preventive chemotherapy option of choice should be questioned in similar settings. In addition to child safety concerns it is also conceivable that INH monotherapy will fail to eradicate INH resistant bacilli, providing them with a selective advantage to produce adult-type (reactivation) disease later in life, contributing to increased transmitted drug resistance within the community.

The study's main limitation is the fact that it was done in a single community, although the study community is thought to be representative of the situation in many endemic areas. No intervention was performed to improve adherence in children who defaulted, as the study aimed to document adherence in "real life". Preventive chemotherapy was provided in the routine fashion by the local clinic and adherence was documented only after completion of the six month treatment period. In addition, reasons for poor adherence were not well documented, but in limited parent interviews the issue of parental risk perception featured prominently. Parents who discontinued preventive chemotherapy often recounted how children from family and/or friends who also defaulted came to no harm. As children who receive preventive chemotherapy are completely healthy, healthcare personnel need to pay particular attention that the concept of risk reduction is effectively conveyed, which may strengthen the argument to focus preventive chemotherapy in endemic areas primarily on high risk children.

In conclusion, this study confirms that adherence to six months of unsupervised INH preventive chemotherapy is poor. It emphasises the need to develop chemoprophylaxis strategies with improved adherence, such as short duration multidrug regimens and/or utilising treatment supervision, particularly in children who are at high risk of disease progression following exposure.²⁸

ACKNOWLEDGEMENTS

We thank the primary healthcare clinics involved, the patients and their parents, and the City of Cape Town Health Department.

Authors' affiliations

B J Marais, S van Zyl, H S Schaaf, M van Aardt, R P Gie, N Beyers, Desmond Tutu TB Centre and Department of Paediatrics and Child Health, Tygerberg Children's Hospital, Stellenbosch University, Cape Town, South Africa

Competing interests: none declared

REFERENCES

- 1 Marais BJ, Gie RP, Schaaf HS, et al. The clinical epidemiology of childhood pulmonary tuberculosis—a critical review of the pre-chemotherapy literature. *Int J Tuberc Lung Dis* 2004;**8**:278–85.
- 2 Singh M, Mynak ML, Kumar L, et al. Prevalence and risk factors for transmission of infection among children in household contact with adults having pulmonary tuberculosis. *Arch Dis Child* 2005;**90**:624–8.

- 3 **Topley JM**, Maher D, Nyong'onya Mbewe L. Transmission of tuberculosis to contacts of sputum positive adults in Malawi. *Arch Dis Child* 1996;**74**:140–5.
- 4 **Marais BJ**, Gie RP, Schaaf HS, *et al*. The natural history of childhood pulmonary tuberculosis: a critical review of literature from the pre-chemotherapy era. *Int J Tuberc Lung Dis* 2004;**8**:392–402.
- 5 **Marais BJ**, Gie RP, Schaaf HS, *et al*. Childhood pulmonary tuberculosis—old wisdom and new challenges. *Am J Respir Crit Care Med* 2006;**173**:1078–90.
- 6 **World Health Organization**. Tuberculosis in children. In: *Treatment of tuberculosis: guidelines for national programmes*, 3rd edn. Geneva: WHO, 2003:61–6.
- 7 **Enarson DA**, Rieder HL, Arnadottir T, *et al*. Treating the disease. In: *Management of tuberculosis: a guide for low-income countries*, 5th edn. Paris: International Union against Tuberculosis and Lung Disease, 2000:11–24.
- 8 **American Thoracic Society**. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med* 2000;**161**:S221–47.
- 9 **Smieja MJ**, Marchette CA, Cook DJ, *et al*. Isoniazid for preventing tuberculosis in non-HIV infected persons. *The Cochrane Library* 1999;(issue 4):1–20.
- 10 **International Union against Tuberculosis Committee on Prophylaxis**. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. *Bull World Health Organ* 1982;**60**:555–64.
- 11 **Claessens NJM**, Gausi FF, Meijnen S, *et al*. Screening childhood contacts of patients with smear-positive tuberculosis in Malawi. *Int J Tuberc Lung Dis* 2002;**6**:362–4.
- 12 **Van Zyl S**, Marais BJ, Hesselning AC, *et al*. Adherence to antituberculosis chemoprophylaxis and treatment in children. *Int J Tuberc Lung Dis* 2006;**10**:13–18.
- 13 **Bibi H**, Weiler-Ravell D, Shoseyov D, *et al*. Compliance to treatment of latent tuberculosis infection in a region of Israel. *Isr Med Assoc J* 2002;**4**:13–16.
- 14 **Reichler MR**, Reves R, Bur S, *et al*. Treatment of latent tuberculosis infection in contacts of new tuberculosis cases in the United States. *South Med J* 2002;**95**:414–20.
- 15 **Bock CK**, Metzger BS, Tapia JR, *et al*. A tuberculin screening and isoniazid preventive therapy program in an inner-city population. *Am J Respir Crit Care Med* 1999;**159**:295–300.
- 16 **Nolan RJ**. Childhood tuberculosis in North Carolina: a study of the opportunities for intervention in the transmission of tuberculosis in children. *Am J Public Health* 1986;**76**:26–30.
- 17 **Verver S**, Warren RM, Munch Z, *et al*. Proportion of tuberculosis transmission that takes place in households in a high-incidence area. *Lancet* 2004;**363**:212–14.
- 18 **Department of Health, South Africa**. National Tuberculosis Control Programme, 2000.
- 19 **Seth V**, Singhal PK, Semwal OP, *et al*. Childhood tuberculosis in a referral center: clinical profile and risk factors. *Indian Pediatr* 1993;**30**:479–85.
- 20 **Schaaf HS**, Michaelis IA, Richardson M, *et al*. Adult-to-child transmission of tuberculosis: household or community contact? *Int J Tuberc Lung Dis* 2003;**7**:426–31.
- 21 **Ena J**, Valls V. Short-course therapy with rifampin plus isoniazid, compared with standard therapy with isoniazid, for latent tuberculosis infection: a meta-analysis. *Clin Infect Dis* 2005;**40**:670–6.
- 22 **Spyridis N**, Tsolia M, Gelesme A, *et al*. Treatment of latent tuberculosis infection in children and adolescents: a ten year randomized prospective study comparing monotherapy to short course regimens. *Int J Tuberc Lung Dis* 2005;**9**(suppl 1):S237.
- 23 **Iseman MD**. Less is more: short-course preventive therapy of tuberculosis. *Am Rev Respir Dis* 1989;**140**:1187.
- 24 **Lecour HF**, Truffot-pernot C, Grosset JH. Experimental short-course preventive therapy of tuberculosis with rifampin and pyrazinamide. *Am Rev Respir Dis* 1989;**140**:1189–93.
- 25 **Priest DH**, Vossell LF, Sherfy EA, *et al*. Use of intermittent rifampin and pyrazinamide therapy for tuberculosis infection in a targeted tuberculin-testing program. *Clin Infect Dis* 2004;**15**:1764–71.
- 26 **Magdorf K**, Arizzi Rusche AF, Geiter RJ, *et al*. Short-course preventive therapy for tuberculosis: a pilot study of rifampin and rifampin-pyrazinamide regimens in children. *Am Rev Respir Dis* 1991;**143**(suppl):A120.
- 27 **Schaaf HS**, Marais BJ, Hesselning AC, *et al*. Childhood drug-resistant tuberculosis in the Western Cape Province of South Africa. *Acta Paediatr* 2006;**95**:523–8.
- 28 **Donald PR**. Preventing tuberculosis in childhood. *Indian J Pediatr* 2000;**67**:383–5.

ARCHIVIST

Intranasal lorazepam for convulsions in Africa

The options for the treatment of prolonged convulsions when intravenous access is not available include intramuscular paraldehyde and benzodiazepines by various routes: rectal diazepam, buccal midazolam, or intranasal lorazepam. Intramuscular paraldehyde has been compared with intranasal lorazepam in Malawi (Shafiqe Ahmad and colleagues. *Lancet* 2006;**367**:1591–7; see also Comment, *ibid*: 1555–6).

Over a 12-month period in 2004–05 160 consecutive children aged 2 months to 12 years (mean 19 months) presenting to the emergency department with acute seizures lasting for more than 5 min were randomised to intranasal lorazepam (100 µg/kg into one nostril via a mucosal atomisation device) or intramuscular paraldehyde (0.2 ml/kg). The average duration of the seizure before treatment was 2 h and the main diagnoses were cerebral malaria (52%), prolonged febrile convulsion (19%), hypo- or hypernatraemia (15%), and acute bacterial meningitis (13%). Convulsions stopped within 10 min in 60 (75%) in the lorazepam group and 49 (61%) in the paraldehyde group, a nonsignificant difference ($p = 0.06$). The median time to seizure cessation was similar in the two groups (7.5 v 8 min). There was no significant difference in the number of children in each group who convulsed again within 24 h (8 v 11) or who died (15 v 13). The risk of death was related to HIV infection (7/19 HIV infected children v 21/141 non-infected) and to seizure duration before treatment (<2 h, 8/75; >2 h, 20/85). Significantly fewer children in the lorazepam group (8 v 21) needed two or more rescue anticonvulsant agents. No clinically important cardiorespiratory events occurred in either group. These researchers consider intranasal lorazepam to be preferable because of its ease of use and low cost (estimated cost of one dose for a 10 kg child; paraldehyde US\$6, intranasal lorazepam US\$0.25) and the well known potential adverse consequences of intramuscular paraldehyde. Rectal diazepam is considered socially unacceptable in some societies and, although buccal midazolam is effective, there is concern that its short duration of action may be a disadvantage in situations where acute underlying pathology may be continuing. One potential disadvantage of lorazepam is that it needs to be kept cool (2–8°C) whereas diazepam and midazolam can be kept at 25°C. Transmucosal benzodiazepines can be given in the form of a variety of drugs by several routes and there appears to be no convincing evidence that one drug and one route is superior in all settings. In developing countries the most important advance would be to improve access to care so that children do not convulse for 2 h or more before receiving treatment.