Attentional function in secondary school students receiving isoniazid prophylaxis for tuberculosis infection

D. ANDERSON[1]*, V. ANDERSON[1,2], L. PENTLAND[1], S. SAWYER[3,4], M. STARR[5] AND P. D. R. JOHNSON[4,5]

[1] *Department of Psychology, Royal Children's Hospital, Royal Parade, Parkville, Victoria 3052, Australia*
[2] *Department of Psychology, University of Melbourne, Parkville, Victoria 3052, Australia*
[3] *Centre for Adolescent Health, Royal Children's Hospital, Parkville, Australia*
[4] *Department of Respiratory Medicine, Royal Children's Hospital, Parkville, Australia*
[5] *Department of Microbiology & Infectious Diseases, Royal Children's Hospital, Parkville, Australia*
[6] *Clinical Epidemiology and Biostatistics Unit, Royal Children's Hospital, Parkville, Australia*

SUMMARY

Reports have suggested that isoniazid treatment may be associated with poor concentration and subtle reduction in memory. This study examines attentional function and processing speed in a group of 25 adolescents who received isoniazid prophylaxis for at least 6 months. As adolescents often face major educational assessment milestones, such cognitive side effects may have important implications. Participants were assessed before treatment, 1 month into treatment and at least 1 week after treatment cessation. Measures included the Paced Auditory Serial Addition Test and subtests of the appropriate Wechsler scale sensitive to attention and speed of information processing. Isoniazid does not appear to cause significant adverse effects on attentional function in adolescents.

INTRODUCTION

Isoniazid is widely used in combination chemotherapy regimens for tuberculosis (TB). The drug is rapidly absorbed and widely distributed throughout the body, including to the central nervous system [1]. Even in standard doses, patients sometimes report minor neurotoxic symptoms such as restlessness and insomnia, but the benefits of effective treatment far outweigh these disadvantages. When used for preventive therapy, however, individuals who receive isoniazid are typically young, healthy and active and only a minority of them will ever be aware that they have derived personal benefit from taking the drug. Clinical trials of isoniazid as preventative therapy for TB were first undertaken in the 1950s [2]. Since that time several studies have been published examining

psychological and cognitive side-effects of treatment. Olsen and Torning [3] compared performance before, during and after treatment for TB with drug regimens that included isoniazid. They documented a subtle memory deficit consistent with their clinical observations that isoniazid treatment does not affect ability to concentrate on important work but that more peripheral information is often forgotten. The underlying cognitive components of these deficits on memory testing were not investigated. It is possible that they were the result of interference by isoniazid on more primary level cognitive functions such as attention. This possibility is supported by Linnoila and Mattila [4] who found evidence of impairment in divided attention after a single dose of isoniazid compared with placebo. However, not all studies have concluded that isoniazid has a detrimental effect on cognitive function. Theodore and Wolff [5] compared

* Author for correspondence.

the school performances of children aged 6–18 years receiving isoniazid prophylaxis for one year to those of controls receiving placebo. No significant difference between the two groups was identified, suggesting that any effect was not great enough to have a detectable impact on performance in the classroom.

Adolescence carries an increased risk of development of TB in those with positive tuberculin tests [6]. In countries such as Australia, with significant migrant populations, most cases of TB occur in people who were born overseas. There is concern that although adults are screened at the time of migration, many young children who were not screened are now entering adulthood, and could be a source of future local transmission of TB. Some Australian authorities have suggested that screening and preventive therapy programmes be re-introduced as part of TB control strategies [7]. However, one of the many tasks of adolescence is to obtain the necessary educational qualifications for entry to tertiary education. If present, significant cognitive side-effects of current preventative therapies may warrant postponement of administration of isoniazid until secondary school is completed, or the provision of special interventions for individuals undergoing treatment.

The present study aimed to examine possible cognitive side effects of isoniazid, specifically in the domain of attentional function, in a group of adolescents with positive tuberculin tests. It was hypothesized that attentional function while taking isoniazid would be poorer than that recorded prior to, and after completion of isoniazid treatment.

METHODS

Participants

During 1995, a large cross-sectional tuberculin skin test (TST) survey of Melbourne secondary school students was conducted to identify subgroups of students who may benefit from future targeted screening and treatment programs [8]. All students identified with positive TSTs were referred to a medical review clinic at the Royal Children's Hospital. Isoniazid preventive therapy was offered provided there was no prior history of treatment for TB, TB had been excluded and no contraindications to taking the medication were present (e.g. epilepsy, hepatitis). The treatment regime was a once daily dose of 300 mg. Supplemental pyridoxine was not prescribed as all students were considered to be well nourished

and it is not routinely combined with isoniazid at this institution. Patients who agreed to treatment were then invited to participate in the present study of cognitive side-effects of isoniazid. A total of 42 adolescents were offered isoniazid therapy, 38 of whom completed a 6-month course. Of these, 25 agreed to enter the cognitive study and completed all components. The mean age of the group was 16 years 6 months (± 13 months) all were in their 9th or 10th year at secondary school and 9 were male.

Adherence to medication in a subgroup from the same epidemiological study, and including 13 subjects from the present study, was examined separately [11]. Students receiving isoniazid were encouraged to adhere to their prescribed treatment using best practice methods. High adherence rates of 66–91 % were reported using various measures including a microelectronic tablet-dispenser, urine isoniazid assays, clinic attendance and tablet counts.

Procedure

The study was approved by the Research in Human Ethics Committee, Royal Children's Hospital, Melbourne and subjects were recruited according to the ethics protocol.

In an ABA crossover design with subjects acting as their own controls, subjects were assessed cognitively on three occasions: once before commencement of medication (pre-medication), 1 month after the commencement of treatment (on-medication) and at least 1 week after the cessation of treatment (post-medication) by which time the isoniazid would be expected to be completely eliminated given its half-life of up to 4 h [12].

Fifteen of the participants were within the age range for the Wechsler Intelligence Scale for Children, Third Edition (WISC-III) [9]. The other 10 were tested using the Wechsler Adult Intelligence Scale, Revised (WAIS-R) [10]. The majority of subjects were migrants of South East Asian origin and, where requested, assessment was carried out with the assistance of an interpreter.

At the pre-medication assessment general intelligence was estimated using the Block Design subtest of the appropriate Wechsler test [9, 10]. This subtest is highly correlated with general intelligence and, as it does not require a verbal response, is appropriate for a population including subjects for whom English is a second language. At each of the three sessions,

Table 1. *Means and standard deviations for each Wechsler subtest across test conditions*

Wechsler subtest	Pre-medication		On medication		Post-medication	
	Mean	(S.D.)	Mean	(S.D.)	Mean	(S.D.)
Arithmetic ASS*	6·80	(2·66)	6·25	(3·23)	7·36	(3·07)
Coding/Digit Symbol ASS	9·08	(3·50)	10·68	(3·85)	10·56	(3·96)
Digit Span ASS	8·32	(2·88)	8·60	(3·69)	8·48	(3·70)
Symbol Search RS†	30·64	(7·54)	32·40	(7·74)	32·92	(6·74)

* ASS, age scaled scores; † RS, raw scores.

attention and information processing skills were examined using subtests from the appropriate Wechsler intelligence test (Coding/Digit Symbol, Digit Span, Arithmetic, Symbol Search) chosen because they constitute the 'freedom from distractability' and 'processing speed' indices on the WISC-III and as such they are considered indicators of attentional function and processing speed. Age scaled scores (mean = 10, S.D. = 3) were used to allow combination of the results of the two test versions with the exception of Symbol Search for which raw scores were used as the scaled scores are not available for subjects over 17 years of age.

As tests of attention and information processing were administered on three occasions within a short period, it was necessary to consider the impact of practice effects on test performances. Test–retest data for age scaled scores on Coding/Digit Symbol, Digit Span and Arithmetic subtests are provided in the WISC-III manual [9] for children aged 14–15 years of age and the WAIS-R manual [10] for adults aged 25–34 years of age. These practice effects range from 0·4 age scaled points for the WISC-III Arithmetic subtest to 1·9 age scaled points for the WISC-III Coding subtest.

The Paced Auditory Serial Addition Test (PASAT) [13] was used at each session to examine attention and information processing, skills integral for efficient memory performance although not testing memory per se. In this respect it was felt the PASAT may tap similar skills to the task used by Olsen and Torning [3]. The PASAT measures rate of information processing and provides an estimate of the subject's ability to register sensory input, respond verbally and inhibit encoding of one's own response while attending to the next stimulus in a series and performing at an externally determined pace. The subject adds pairs of randomly presented single digit numbers such that each number is added to the one immediately preceding it. Subjects were drilled on a practice trial of 10 numbers delivered at the slowest rate until it was clear they understood the task. If necessary, a written demonstration was provided. Four test trials comprising 61 digits were then presented at progressively faster rates of presentation (2·4, 2·0, 1·6 and 1·2 sec). The number of correct responses for each rate of presentation was recorded as the dependent variable.

In a 16–18 year old control group, Stuss and colleagues [14] reported a practice effect of approximately six points with a second administration of the PASAT significant at a $P < ·01$. A further study [15] demonstrated minimal practice effects (approx. 2 points) on subsequent administrations.

RESULTS

Scores on the Block Design subtest indicated that the group was of average intelligence (mean = 9·60; S.D. = 3·55). The mean and standard deviations for the Wechsler subtest scores across the three assessments are presented in Table 1. The Arithmetic subtest was the only variable to show the anticipated pattern of poor performance while taking isoniazid. These differences were small and were not statistically significant (ANOVA $F(2, 48) = 1·5$, $P = 0·233$). When the Arithmetic subtest scores for on-medication and post-medication tests were adjusted for the appropriate age scaled practice effect the difference became more apparent, almost reaching statistical significance ($t(24) = 2·03$, $P = 0·053$).

Similarly, the PASAT performances for each rate of presentation did not show a pattern consistent with impaired performance as a result of medication. Rather, the performances of the group improved with each administration, consistent with the findings of Stuss and colleagues [15]. The group's average performances were below the normative level but a pattern of decreased performance with increased
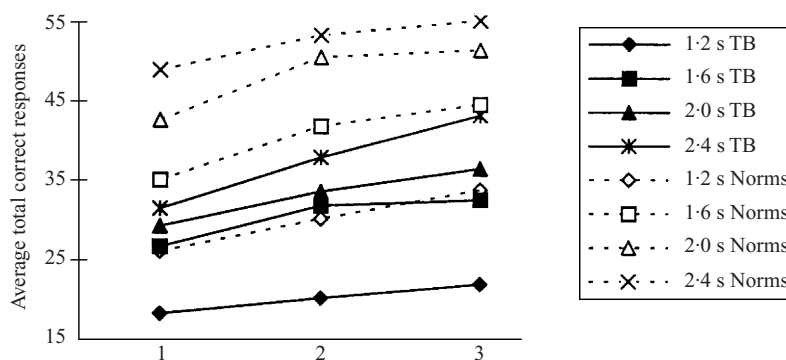
Fig. 1. Mean total correct responses for each presentation rate (in seconds) of the PASAT over 3 assessments plotted for TB subjects (solid lines) in comparison to normative data (dotted lines) [13].

speed of presentation was evident in keeping with test expectations, as illustrated in Figure 1. Furthermore, the difference for the group from administration 1 to administration 2 (4·5 points) was significantly different at a $P < 0.01$ level and was similar in magnitude to that reported in normative data [14]. While an improvement was also evident between administrations 2 and 3, the difference was not significant.

DISCUSSION

The present study does not support the hypothesis that isoniazid impairs attentional function or information processing speed in adolescents and is consistent with several previous studies.

Those studies which identified significant cognitive problems in people taking isoniazid may be explained by confounding factors. For example, Olsen and Torning [3] found a reduction in memory whilst their patients were taking 200–300 mg isoniazid per day. However, patients in that study were also concurrently receiving paraminosalicylic acid which is no longer used in TB treatment because of unacceptable side effects including diarrhoea, nausea and gastric discomfort. Furthermore, the effects of isoniazid may be greater in adults than adolescents. Olsen and Torning's study had a broad age range of 15–64 years, with only one subject below the age of 20.

Linnoila and Mattila [4] studied a younger and more homogeneous group of individuals (19–22 years of age) than Olsen and Torning [3] and found that single high doses of isoniazid (more than twice the daily dose used Olsen and Torning's study and the present study) produced significant attentional side-effects. A single high dose of isoniazid is not necessarily comparable with a prolonged course of standard dose therapy.

It is possible that the effects of isoniazid on attention and information processing speed are very subtle and may have been masked by practice effects. Given the repeated administration of the tests in this study, it would have been ideal to include a control group. However, normative data regarding practice effects of repeated administration of the PASAT are available [14, 15] and the pattern of improvement with repeated administration in this study was similar. Consequently, it would appear that the effects of isoniazid, if any, are not significant enough to prevent adolescents from gaining benefit from repeated exposure to test material.

The small size of our study sample means that we cannot conclude that isoniazid has no effect on attentional function. Any effect would, however, be small and unlikely to have a significant impact on classroom performance. Attentional side-effects are, therefore, unlikely to be a factor in prediction of compliance with isoniazid in secondary school students and isoniazid can be prescribed with confidence that it will not impact upon cognitive performance in adolescents.

ACKNOWLEDGEMENTS

REFERENCES

1. Forgan-Smith R, Ellard GA, Newton D, Mitchison DA. Pyranzinamide and other drugs in tuberculous meningitis. Lancet 1973; ii: 374.
2. Geiter LJ. Preventive therapy for tuberculosis. In: Reichman LB, Hershfield ES, eds. Tuberculosis a

comprehensive international approach. New York: Marcel Dekker, 1993: 241–50.

3. Olsen PZ, Torning K. Isoniazid and loss of memory. Scand J Resp Dis 1968; **49**: 1–8.

4. Linnoila M, Mattila MJ. Effects of isoniazid on psychomotor skills related to driving. J Clin Pharm 1973; **13**: 343–50.

5. Theodore A, Wolff M. The effect of isoniazid on performance in school. Am Rev Respir Dis 1970; **101**: 252–7.

6. Comstock GW, Livesay VT, Woolpert SF. The prognosis of a positive tuberculin reaction in childhood and adolescence. Am J Epidemiol 1974; **99**: 131–8.

7. Krause VL. Tuberculosis in the young: focusing on those at risk. Med J Aust 1998; **168**: 100–1.

8. Johnson PDR, Carlin JB, Bennett CM, et al. Prevalence of tuberculosis infection in Melbourne secondary school students. Med J Aust 1998; **168**: 106–10.

9. Wechsler D. Wechsler intelligence scale for children, 3rd edn manual. New York: The Psychological Corporation, 1991.

10. Wechsler D. Wechsler adult intelligence scale – revised manual. New York: The Psychological Corporation, 1981.

11. Starr M, Sawyer SM, Carlin JB, Powell CVE, Newman RG, Johnson PDR. A novel approach to monitoring adherence to preventive therapy for tuberculosis in adolescence. J. Paediatr. Child Health 1999; In press.

12. Bennett WM, Singer I, Golper T, Feig P, Coggins CJ. Guidelines for drug therapy in renal failure. Ann Intern Med 1977; **86**: 754–83.

13. Gronwall DMA, Sampson H. The psychological effects of concussion. Auckland, NZ: Auckland University Press, 1974.

14. Stuss DT, Stethem LL, Poirier CA. Comparison of three tests of attention and rapid information processing across six age groups. Clin Neuropsychol 1987; **1**: 139–52.

15. Stuss DT, Steihem H, Hugenholtz H, Richard MT. Traumatic brain injury: a comparison of three clinical tests, and analysis of recovery. Clin Neuropsychol 1989; **3**: 145–56.