



USAID
FROM THE AMERICAN PEOPLE



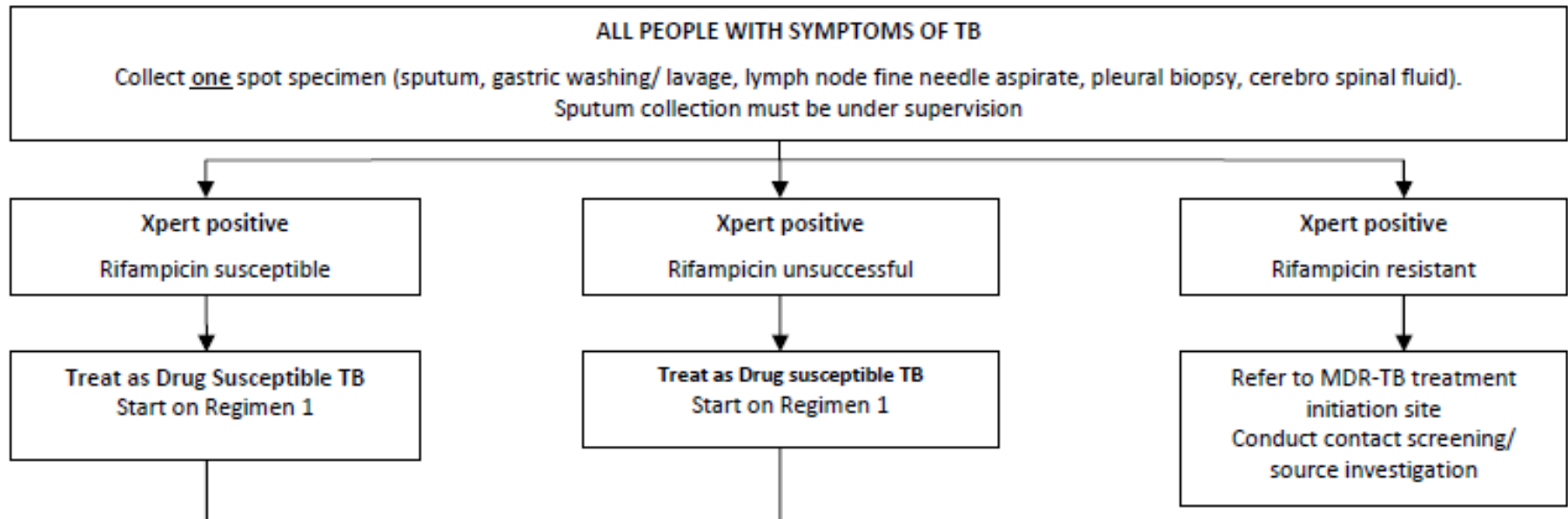
Has Regimen 1 reached its expiry
date?

Andrew Black

Wits Reproductive Health and HIV Research Unit

Diagnosis

4.1 XPERT DIAGNOSTIC ALGORITHM



National Tuberculosis Management Guidelines 2014

Regimen 1

Standardised first line treatment for all GeneXpert MTB/Rif Rifampicin sensitive or inconclusive PTB.

2HRZE/4HR



6HRZE



What can we expect?

- > 90% cure
- < 5% relapse
- Adverse events < 5%

Is this the South African reality? We need to move away from the fixation of Sm+ PTB.

- HIV co infected pre ART: higher relapse, use of rifamycins > 8 months improved relapse rate. Patients on cART ? Need for prolonged therapy.



RSA

2010: 55% cure rate, no province above 70%

2013 Q3: 75% cure rate, 3 provinces above 80%

Some districts >90%





High Morbidity during Treatment and Residual Pulmonary Disability in Pulmonary Tuberculosis: Under-Recognised Phenomena

Anna P. Ralph^{1,2*}, Enny Kenangalem^{3,4}, Govert Waramori⁵, Gysje J. Pontororing³, Sandjaja⁶, Emiliana Tjitra⁶, Graeme P. Maguire^{7,8}, Paul M. Kelly^{9,10}, Nicholas M. Anstey^{1,2}

1 Global and Tropical Health Division, Menzies School of Health Research and Charles Darwin University, Northern Territory, Australia, **2** Department of Infectious Diseases, Division of Medicine, Royal Darwin Hospital, Northern Territory, Australia, **3** Menzies School of Health Research-National Institute of Health Research and Development Research Program, Timika, Papua Province, Indonesia, **4** District Health Authority, Timika, Papua Province, Indonesia, **5** Public Health & Malaria Control Department, PT Freeport Indonesia, Timika, Papua Province, Indonesia, **6** National Institute of Health Research and Development, Jakarta, Indonesia, **7** Baker IDI Heart and Diabetes Institute, Alice Springs, Northern Territory, Australia, **8** School of Medicine and Dentistry, James Cook University, Cairns, Queensland, Australia, **9** Population Health Division, ACT Government Health Directorate, Canberra, Australian Capital Territory, Australia, **10** Australian National University Medical School, Canberra, Australian Capital Territory, Australia

Abstract

Background: In pulmonary tuberculosis (PTB), morbidity during treatment and residual pulmonary disability can be under-estimated.

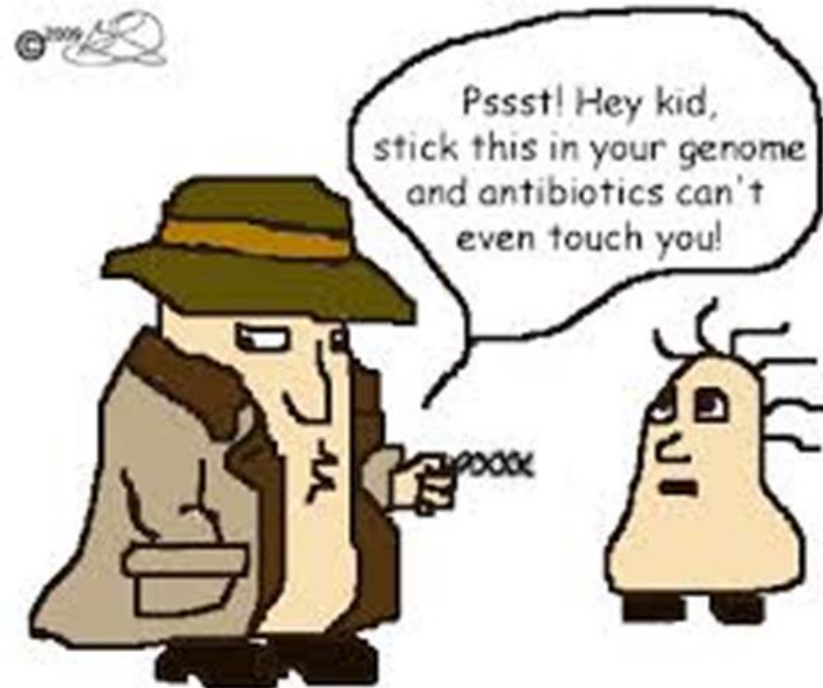
Methods: Among adults with smear-positive PTB at an outpatient clinic in Papua, Indonesia, we assessed morbidity at baseline and during treatment, and 6-month residual disability, by measuring functional capacity (six-minute walk test [6MWT] and pulmonary function), quality of life (St George's Respiratory Questionnaire [SGRQ]) and Adverse Events ([AE]: new symptoms not present at outset). Results were compared with findings in locally-recruited volunteers.

Results: 200 PTB patients and 40 volunteers were enrolled. 6MWT was 497m (interquartile range 460-529) in controls versus 408m (IQR 346-450) in PTB patients at baseline ($p<0.0001$) and 470m (IQR 418-515) in PTB patients after 6 months ($p=0.02$ versus controls). SGRQ total score was 0 units (IQR 0-2.9) in controls, versus 36.9 (27.4-52.8) in PTB patients at baseline ($p<0.0001$) and 4.3 (1.7-8.8) by 6 months ($p<0.0001$). Mean percentage of predicted FEV₁ was 92% (standard deviation 19.9) in controls, versus 63% (19.4) in PTB patients at baseline ($p<0.0001$) and 71% (17.5) by 6 months ($p<0.0001$). After 6 months, 27% of TB patients still had at least moderate-severe pulmonary function impairment, and 57% still had respiratory symptoms, despite most achieving 'successful' treatment outcomes, and reporting good quality of life. More-advanced disease at baseline (longer illness duration, worse baseline X-ray) and HIV positivity predicted residual disability. AE at any time during treatment were common: itch 59%, arthralgia 58%, headache 40%, nausea 33%, vomiting 16%.



TB treatment needs to be about more than just the bug

Need to find ways to increase the protective and decrease the destructive host immune mechanisms



Too Old



Too long



Correct dose

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2007, p. 2994–2996

0066-4804/07/\$08.00+0 doi:10.1128/AAC.01474-06

Copyright © 2007, American Society for Microbiology. All Rights Reserved.

Vol. 51, No. 8

Early Bactericidal Activity of High-Dose Rifampin in Patients with Pulmonary Tuberculosis Evidenced by Positive Sputum Smears[▽]

A. H. Diacon,^{1*} R. F. Patientia,² A. Venter,³ P. D. van Helden,³ P. J. Smith,⁴ H. McIlleron,⁴
J. S. Maritz,⁵ and P. R. Donald⁶

Department of Internal Medicine,¹ Department of Molecular Biology and Human Genetics and MRC Centre for Molecular and Cellular Biology, DST/NRF Centre of Excellence for Biomedical TB Research,³ and Department of Paediatrics and Child Health,⁶ Faculty of Health Sciences, University of Stellenbosch, Tygerberg, South Africa; Tiervlei Trial Centre, Karl Bremer Hospital, Bellville, South Africa²; Division of Clinical Pharmacology, University of Cape Town, Cape Town, South Africa⁴; and Biostatistics Unit of the South African Medical Research Council, Cape Town, South Africa⁵

Received 23 November 2006/Returned for modification 26 March 2007/Accepted 8 May 2007

We studied the early bactericidal activity of twice the standard dose of rifampin in subjects with pulmonary tuberculosis evidenced by positive smears. The observed mean 2-day activity was almost double that reported at the standard dose. Further studies are warranted to establish whether higher rifampin doses might assist in shortening tuberculosis treatment.



Serum Concentrations of Antimycobacterial Drugs in Patients with Pulmonary Tuberculosis in Botswana

Jordan W. Tappero,^{1,7} Williamson Z. Bradford,^{2,3,4} Tracy B. Agerton,^{1,4} Philip Hopewell,^{2,3} Arthur L. Reingold,⁴ Shahin Lockman,^{1,7} Aderonke Oyewo,⁷ Elizabeth A. Talbot,^{1,7} Thomas A. Kenyon,^{1,7} Themba L. Moeti,⁸ Howard J. Moffat,⁸ and Charles A. Peloquin^{5,6}

¹Centers for Disease Control and Prevention, Atlanta, Georgia; ²Department of Medicine, University of California, San Francisco, ³Medical Service San Francisco General Hospital, ⁴School of Public Health, University of California, Berkeley, California; ⁵National Jewish Medical and Research Center and ⁶The Schools of Pharmacy and Medicine, University of Colorado, Denver; and ⁷The BOTUSA Project and ⁸National TB Program, Ministry of Health, Gaborone, Botswana

Background. We conducted a pharmacokinetic study of antimycobacterial drugs involving a cohort of patients with pulmonary tuberculosis (TB) in Gaborone, Botswana, to assess the prevalence of and risk factors for low drug concentrations in serum.

Methods. Adults participated if they had a history of cough ≥ 2 weeks, had abnormal chest radiograph findings, consented to testing for human immunodeficiency virus (HIV), had sputum cultures positive for *Mycobacterium tuberculosis*, and were receiving antituberculous therapy for >7 days. Observed maximum serum concentrations were compared with published normal ranges.

Results. Of 91 patients enrolled, 89 (98%) were outpatients, and 59 (68%) of 87 patients tested had HIV infection. The following numbers of patients had low serum concentrations of the following drugs: isoniazid, 27 (30%) of 90; rifampin, 71 (78%) of 91; ethambutol, 37 (41%) of 91; and pyrazinamide, 1 (1%) of 91. Low serum concentrations of both isoniazid and rifampin occurred in 23 (26%) of 90 patients. Low serum concentrations of rifampin were found in both HIV-infected and non-HIV-infected patients, and such patients were less likely to have >4 weeks of symptoms, more likely to have lymphadenopathy, and more likely to have low serum albumin levels ($P < .05$ for all). The associations with noncavitary pulmonary disease ($P = .12$) and HIV infection ($P = .07$) did not reach statistical significance. Delayed absorption was most common with ethambutol, followed by rifampin.

Conclusions. These data, predominantly from HIV-infected patients with TB, suggest that low isoniazid, rifampin, and ethambutol concentrations are common in Botswana. In contrast, pyrazinamide usually is well absorbed.



Determinants of Rifampin, Isoniazid, Pyrazinamide, and Ethambutol Pharmacokinetics in a Cohort of Tuberculosis Patients

Helen McIlleron,^{1*} Peter Wash,^{2†} André Burger,² Jennifer Norman,¹ Peter I. Folb,³ and Pete Smith¹

Division of Clinical Pharmacology, University of Cape Town, Cape Town, South Africa¹; Brewelskloof Hospital, Worcester, South Africa²; and Medical Research Council of South Africa, Tygerberg, South Africa³

Received 7 June 2005/Returned for modification 21 August 2005/Accepted 9 January 2006

Evaluation of sources of pharmacokinetic variation can facilitate optimization of tuberculosis treatment regimens by identification of avoidable sources of variation and of risk factors for low or high drug concentrations in patients. Our objective was to describe the pharmacokinetics of rifampin, isoniazid, pyrazinamide, and ethambutol in a cohort of tuberculosis patients established on first-line treatment regimens and to evaluate the determinants of pharmacokinetic variation. Plasma concentration-time profiles were determined for each of the drugs in 142 patients with drug-sensitive pulmonary tuberculosis after 2 months of daily treatment in hospital. Pharmacokinetic measures were described by noncompartmental analysis. Multiple linear regression was used to evaluate the patient and the treatment factors associated with variation of the area under the concentration-time curve from 0 to 8 h. Several factors independently associated with variations in antituberculosis drug concentrations were identified: human immunodeficiency virus infection was associated with 39% and 27% reductions for rifampin and ethambutol, respectively; formulation factors were determinants of rifampin and isoniazid bioavailability; female patients had increased rifampin and isoniazid concentrations but reduced ethambutol concentrations; older patients had higher levels of isoniazid and ethambutol; patients with a history of previous antituberculosis treatment had lower ethambutol concentrations; and the dose per kilogram of body weight was associated with the concentrations of all four agents. Further studies are required to assess the implications of variations in antituberculosis drug concentrations for efficacy and safety before decisions are made to change the dosing strategy in patients at risk.

Early Therapeutic Drug Monitoring for Isoniazid and Rifampin among Diabetics with Newly Diagnosed Tuberculosis in Virginia, USA

Scott K. Heysell,¹ Jane L. Moore,² Debbie Staley,² Denise Dodge,² and Eric R. Houpt¹

¹ *Division of Infectious Diseases and International Health, University of Virginia, P.O. Box 801340, Charlottesville, VA 22908-1340, USA*

² *Tuberculosis Control and Prevention, Virginia Department of Health, Richmond, VA, USA*

Correspondence should be addressed to Scott K. Heysell; skh8r@virginia.edu

Received 18 July 2013; Accepted 3 October 2013

Academic Editor: T. Ottenhoff

Copyright © 2013 Scott K. Heysell et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Slow responders to tuberculosis (TB) treatment in Virginia have prolonged treatment duration and consume more programmatic resources. Diabetes is an independent risk factor for slow response and low serum anti-TB drug concentrations. Thus, a statewide initiative of early therapeutic drug monitoring (TDM) for isoniazid and rifampin at 2 weeks after TB treatment was piloted for all diabetics with newly diagnosed TB. During the period of early TDM, 12/01/2011–12/31/2012, 21 diabetics had C_{2hr} concentrations performed and 16 (76%) had a value below the expected range for isoniazid, rifampin, or both. Fifteen had follow-up concentrations after dose adjustment and 12 (80%) increased to within the expected range (including all for rifampin). Of 16 diabetic patients with pulmonary TB that had early TDM, 14 (88%) converted their sputum culture to negative in <2 months. Early TDM for diabetics was operationally feasible, may speed response to TB therapy, and can be considered for TB programs with high diabetes prevalence.



PROPHYLAXIS OF ISONIAZID NEUROPATHY WITH PYRIDOXINE*

H. BLAIR CARLSON, M.D.,† ELEANOR M. ANTHONY, M.D.,‡ WILLIAM F. RUSSELL, JR., M.D.,§
AND GARDNER MIDDLEBROOK, M.D.¶

DENVER, COLORADO

THE NEW ENGLAND JOURNAL OF MEDICINE

July 19, 1956



- Potential for interference by high doses of pyridoxine with the anti tuberculosis activity of INH no more than 10mg per day should be used.

McCune. American Review of Tuberculosis and Pulmonary Diseases 1957.



The Prevention and Treatment of Isoniazid Toxicity in the Therapy of Pulmonary Tuberculosis

2. An Assessment of the Prophylactic Effect of Pyridoxine in Low Dosage *

TUBERCULOSIS CHEMOTHERAPY CENTRE, MADRAS¹

A recent report from the Tuberculosis Chemotherapy Centre, Madras, showed that a vitamin-B-complex preparation containing a small amount of pyridoxine (as well as aneurine hydrochloride, riboflavine, nicotinamide, panthenol and cyanocobalamin) was effective in the treatment of peripheral neuropathy caused by daily high-dosage (12.5-15.2 mg/kg body-weight) isoniazid therapy of pulmonary tuberculosis. The present report gives results which show that the B-complex preparation is fully effective in preventing peripheral neuropathy in patients receiving the same high dosage of isoniazid, and that this is due to the small pyridoxine content of only 6 mg daily, and not to any of its other constituents. The low cost of this small dose of pyridoxine makes high-dosage isoniazid therapy, given in combination with other drugs or alone, a possible proposition in developing countries.

Studies in the Centre have produced clear evidence that there is an increase in the frequency of peripheral neuropathy when the dosage of isoniazid is increased from 7.8-9.6 mg/kg body-weight to 12.5-15.6 mg/kg daily, and that its incidence is higher among slow than among rapid inactivators of isoniazid.

The studies also show that increasing the dosage of isoniazid when given alone from a moderate daily dosage of 7.8-9.6 mg/kg to the high daily dosage of 12.5-15.6 mg/kg has not materially altered the radiographic or the bacteriological response to treatment.



Beyond PTB

Cerebrospinal fluid concentrations of antituberculosis agents in adults and children

P.R. Donald*

Department of Paediatrics and Child Health and Division of Molecular Biology and Human Genetics and the MRC Centre for Molecular and Cellular Biology, DST/NRF Centre of Excellence for Biomedical TB Research, Faculty of Health Sciences, University of Stellenbosch and Tygerberg Children's Hospital, PO Box 19063, 7505 Tygerberg, South Africa

S U M M A R Y

Tuberculous meningitis (TBM) causes a devastating morbidity and mortality in adults and children. Even in patients presenting at an early stage of disease, deterioration may occur despite apparently adequate therapy. The literature relating to cerebrospinal fluid penetration of antituberculosis agents is reviewed. Amongst the essential antituberculosis agents isoniazid has the best CSF pharmacokinetics reaching peak concentrations (C_{max}) only slightly less than in blood. Pyrazinamide also has good CSF penetration and in children receiving dosages of 40 mg/kg the CSF C_{max} exceeds the proposed minimal inhibitory concentration of 20 μ g/ml. Streptomycin other aminoglycosides and ethambutol have poor CSF penetration and cannot be agents of first choice for TBM treatment. Rifampicin at dosages used in adults seldom reaches CSF concentrations exceeding MIC, but does so more frequently in children when dosages of up to 20 mg/kg are used. The non-essential agents ethionamide, the fluoroquinolones, with the exception of cipro-



Initial Antituberculous Regimen with Better Drug Penetration into Cerebrospinal Fluid Reduces Mortality in HIV Infected Patients with Tuberculous Meningitis: Data from an HIV Observational Cohort Study

**Gerardo Alvarez-Uria, Manoranjan Midde,
Raghavakalyan Pakam, and Praveen Kumar Naik**

Department of Infectious Diseases, Bathalapalli Rural Development Trust Hospital, Kadiri Road, Anantapur District, Bathalapalli 515661, Andhra Pradesh, India

Correspondence should be addressed to Gerardo Alvarez-Uria; gerardouria@gmail.com

Received 9 June 2013; Revised 18 July 2013; Accepted 18 July 2013

Academic Editor: Luis E Cuevas

Copyright © 2013 Gerardo Alvarez-Uria et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Tuberculous meningitis (TM) is the deadliest form of tuberculosis. Nearly two-thirds of HIV infected patients with TM die, and most deaths occur within one month. Current treatment of TM involves the use of drugs with poor penetration into the cerebrospinal fluid (CSF). In this study, we present the mortality before and after implementing a new antituberculous regimen (ATR) with a higher drug penetration in CSF than the standard ATR during the initial treatment of TM in an HIV cohort study. The new ATR included levofloxacin, ethionamide, pyrazinamide, and a double dose of rifampicin and isoniazid and was given for a median of 7 days (interquartile range 6–9). The new ATR was associated with an absolute 21.5% (95% confidence interval (CI), 7.3–35.7) reduction in mortality at 12 months. In multivariable analysis, independent factors associated with mortality were the use of the standard ATR versus the new ATR (hazard ratio 2.05; 95% CI, 1.2–3.5), not being on antiretroviral therapy, low CD4 lymphocyte counts, and low serum albumin levels. Our findings suggest that an intensified initial ATR, which likely results in higher concentrations of active drugs in CSF, has a beneficial effect on the survival of HIV-related TM.



In conclusion

- The drugs we have work for sensitive TB
- We urgently need to start using the drugs correctly, and throw out the poor decisions made 40 years ago.



New drugs

- More effective (determined by outcomes)
- Less side effects and drug interactions
- Meaningfully shorter
- Affordable for a large programme

