Oral trimethoprim-sulphamethoxazole levels in stable HIV-infected children

Heather J Zar, Grant Langdon, Patti Apolles, Brian Eley, Gregory Hussey, Peter Smith

Background. Effective treatment of *Pneumocystis jiroveci* pneumonia (PCP) requires therapeutic serum concentrations of 5 - 10 µg/ml trimethoprim (TMP); consequently intravenous trimethoprim-sulphamethoxazole (TMP-SMZ) is recommended therapy. However, oral therapy is desirable as the intravenous route is costly, time-consuming, more difficult to administer and carries a risk of needlestick injury.

Objective. To investigate whether therapeutic TMP levels for treatment of PCP can be attained with oral therapy in HIV-infected children.

Methods. A prospective dose-escalation study was undertaken of serum TMP levels attained following oral doses of TMP of 5 mg/kg, 10 mg/kg or 20 mg/kg in stable HIV-infected children. Children who received a 20 mg/kg dose were randomised to get a second dose (5 or 10 mg/kg TMP) at 6 hours. TMP levels were measured at baseline, peak (3 hours), and trough (6 hours) using liquid chromatography. An additional TMP level was taken at 9 hours in those who received a second TMP dose.

Results. Median (25th - 75th percentile) peak serum TMP levels following a 5 mg/kg, 10 mg/kg or 20 mg/kg oral loading dose were 0.93 (0.5 - 1.5) µg/ml, 1.94 (1.4 - 2.2) µg/ml and 7.68 (6.1- 7.8) µg/ml respectively. Peak TMP levels at 9 hours after a second TMP dose of 5 or 10 mg/kg were 6.98 (3.4 - 8.8) µg/ml and 9.25 (8.2 - 10.3) µg/ml respectively.

Conclusion. Therapeutic concentrations of TMP for treatment of *P. jiroveci* can be attained with an oral loading dose of 20 mg/kg and sustained with a second dose at 6 hours of either 5 mg or 10 mg/kg in stable HIV-infected children.

S Afr Med J 2006; **96:** 627-629.

Pneumocystis jiroveci pneumonia (PCP) is an important cause of hospitalisation and death in HIV-infected children in Africa.[1-4] Untreated PCP is fatal in 100% of cases.[5] Recommended treatment is intravenous trimethoprim-sulphamethoxazole (TMP-SMZ) followed by oral therapy once clinical improvement occurs to complete 21 days of therapy.[5] Intravenous therapy should be used initially as serum levels of 5 - 10 µg/ml of TMP are recommended for effective treatment of PCP.[6,7] However, establishment of intravenous access requires specific skill, may be especially difficult in very young or malnourished children and is a painful procedure. Furthermore, as the response to therapy may be slow (4 - 8 days before clinical improvement occurs) repeated insertion of intravenous lines may be required.[5] In addition, this procedure poses a risk of transmitting HIV to health care workers via needlestick injury. Administration of intravenous TMP-SMZ is also more costly, difficult and time-consuming than oral medication and may result in fluid overload.[8] Because of these difficulties, oral TMP-SMZ is often used for treatment of PCP in South Africa and other developing countries despite lack of data on the efficacy of such therapy.

Poor response to treatment with TMP-SMZ has been described in a few patients with very low peak levels of TMP.[6] In addition, low serum TMP concentrations have been associated with failure to respond to TMP-SMZ during the first 3 days of treatment.[7] It is therefore important to attain therapeutic serum levels of TMP for treatment of PCP. Pharmacokinetic studies in non-HIV-infected patients suggest that serum TMP concentrations of 5 - 10 µg/ml are not attainable with standard oral doses of TMP-SMZ.[8] In HIV-infected children, altered absorption and metabolism of TMP-SMZ as a result of gastrointestinal, hepatic or renal disease may further reduce serum TMP concentrations. However, it is possible that therapeutic TMP levels may be attained with oral medication if increased dosages are used. The aim of this study was to determine whether therapeutic TMP concentrations of 5 - 10 µg/ml could be attained using oral therapy in the treatment of PCP.

Methods

A prospective dose-escalation study was undertaken to investigate serum TMP levels after administration of different oral dosages of TMP-SMZ to HIV-infected children. The study was approved by the Research and Ethics Committee of the University of Cape Town. Written, informed consent was obtained from a parent or guardian.

Fifteen stable HIV-infected children who were taking TMP-SMZ for PCP prophylaxis and who were attending the

School of Child and Adolescent Health, Red Cross War Memorial Children's Hospital, Cape Town

Heather J Zar, MB BCh, FAAP, PhD
Patti Apolles, RN, APCN
Brian Eley, MB ChB, FCPaed (SA), BSc Hons
Gregory Hussey, MB ChB, MMed, FFCH

Department of Pharmacology, University of Cape Town

Grant Langdon, BSc, BSc (Med) Hons
Peter Smith, BSc, BSc Hons, PhD

Corresponding author: *Heather Zar (hzar@ich.uct.ac.za).*

outpatient infectious diseases clinic at Red Cross Children's Hospital were studied. Exclusion criteria were inability to take oral medicine, ongoing chronic diarrhoea, known hypersensitivity to TMP-SMZ, severe anaemia (haemoglobin less than 8 g/dl), neutropenia (neutrophil count less than 1 000/µl) or thrombocytopenia (platelet count less than 80 000/µl), renal failure or any acute illness within the preceding 2 weeks.

Children were studied 48 - 72 hours after their last dose of TMP-SMZ prophylaxis.

An oral loading dose of 5 mg/kg, 10 mg/kg or 20 mg/kg TMP was administered to children using a suspension (40 mg TMP and 200 mg SMZ per 5 ml of Cozole suspension, Be-Tabs Pharmaceuticals, Roodepoort, South Africa). Thereafter those who received a 20 mg/kg dose of TMP were randomised using a computer-generated list to receive a second dose of either 5 or 10 mg/kg TMP 6 hours after the loading dose. Blood was drawn at baseline and at 3 and 6 hours after the oral loading dose for TMP levels using an indwelling catheter. Where children received a second TMP dose, an additional blood specimen was taken at 9 hours.

Measurement of serum TMP levels was based on the method of Laizure *et al*.[9] using high-pressure liquid chromatography. The technician performing TMP levels was blinded as to the dose of drug that had been administered. The drug was extracted from 200 µl of serum by solid-phase extraction. Buffered samples were eluted through a preconditioned solid-phase column with methanol and dried down at 37°C. Dried samples were reconstituted in mobile phase (35% acetonitrile: 65% heptane sulfonic acid, pH 3.0) and quantitated using a Luna 3 µm reverse-phase column (Phenomenex, Torrance, Calif.). Absorbance was monitored at 240 nm.

Results

Of the 15 children (median (25th - 75th percentile) age 23.5 (11 - 40) months) enrolled, 4 patients received a loading dose of 5 mg/kg TMP, 6 received a loading dose of 10 mg/kg TMP and 5 received a loading dose of 20 mg/kg TMP. The median weight of the children was 10.7 (8.5 - 14.1) kg.

Baseline serum TMP levels were undetectable in all children. The median (25th - 75th percentile) serum TMP levels (µg/ml) obtained with a 5 mg/kg loading dose at 3 and 6 hours were 0.93 µg/ml (0.5 - 1.5) µg/ml and 0.77 (0.3 - 2.0) µg/ml respectively. Levels obtained with a 10 mg/kg loading dose were also subtherapeutic at 3 hours (1.94 (1.4 - 2.2) µg/ml) and 6 hours (1.3 (1.2 - 2.3) µg/ml). However, therapeutic TMP concentrations were obtained with a 20 mg/kg loading dose at both these time intervals (7.68 (6.1 - 7.8) µg/ml and 6.74 (6.4 - 6.8) µg/ml respectively) (Fig. 1). In children who had received a 20 mg/kg loading dose, serum TMP levels at 9 hours after a second dose of either 5 or 10 mg/kg TMP were 6.98 (3.4- 8.8) µg/ml and 9.25 (8.2 - 10.3) µg/ml respectively and were therefore maintained within the therapeutic range (Fig.1). TMP-SMZ was well tolerated by all children and no adverse events were noted.

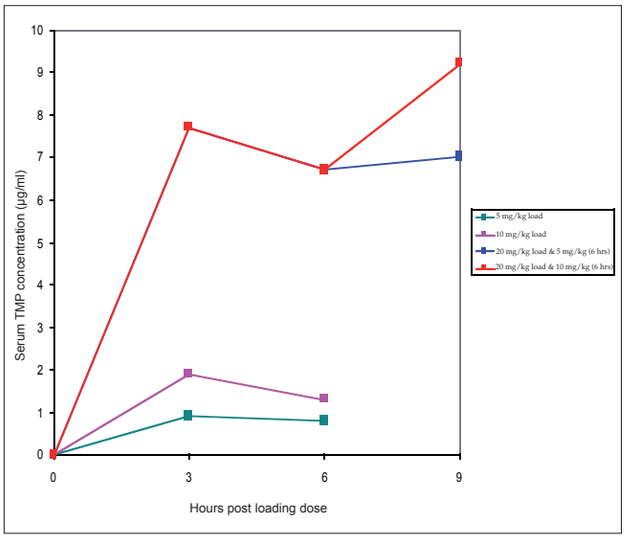

Fig. 1. Serum TMP concentrations in HIV-infected children following different oral doses of TMP-SMZ.

Discussion

In this study, therapeutic serum TMP levels for treatment of PCP were attained with an oral loading dose of 20 mg/kg TMP and sustained with a second dose of either 5 mg or 10 mg/kg TMP given 6 hours later in a group of stable HIV-infected children. However, subtherapeutic levels occurred in children given a lower loading dose. The importance of therapeutic serum TMP levels has been suggested by studies[6,7] in which peak serum TMP levels of less than 5 µg/ml were associated with a poor response to PCP therapy. Low peak TMP levels have been associated with failure of TMP-SMZ therapy in adult non-HIV-infected patients in whom histological confirmation of PCP was obtained at autopsy.[6] Hughes *et al*.[7] reported that children who failed to respond to TMP-SMZ within the first 3 days of therapy had lower serum TMP concentrations than those who demonstrated a rapid clinical response; differences in TMP peaks were particularly evident during the first day of therapy. Such data underscore the importance of rapidly establishing a therapeutic TMP level in children with PCP, hence the use of a loading dose. In our study an oral loading dose 4 times the conventionally administered dose was necessary to establish a therapeutic TMP concentration.

Although intravenous TMP-SMZ has been recommended for treatment of PCP, this study suggests that adequate TMP levels can be attained with high-dose oral therapy. This is consistent with pharmacokinetic studies of adults that have reported oral TMP-SMZ to be well absorbed.[10,11] However, a pharmacokinetic

study of HIV-uninfected patients[8] found that significantly higher mean increments of serum TMP levels were obtained following intravenous compared with oral administration. Moreover, our study involved stable HIV-infected children; the results may therefore not be generalisable to those who are acutely ill and who may have impaired absorption or metabolism of drugs. In addition, the children in the current study were older than those in whom PCP usually occurs, who are commonly infants aged 3 - 6 months.[1-5] However, a pharmacokinetic study of HIV-uninfected patients[8] found similar peak TMP concentrations in all ages. Further study is warranted on the efficacy and tolerability of oral TMP-SMZ in HIV-infected children with acute pneumonia in the doses shown in this study to achieve therapeutic levels before high-dose oral treatment can be routinely recommended as first-line therapy.

In the absence of data on ill children, intravenous TMP-SMZ therapy should preferably be used in very sick children, but where this is not feasible, oral therapy may be used. Increasingly, oral antibiotic therapy has been reported to be as effective as intravenous treatment for ill children, as demonstrated by a study in which oral amoxicillin and intravenous ampicillin were found to be equally effective in treating children with World Health Organization-defined severe pneumonia.[12] TMP-SMZ is well absorbed orally. Nevertheless, before oral TMP-SMZ therapy can be routinely recommended for very sick children with suspected PCP, an optimal dosage needs to be established in this patient population. Such a study could only be done where subjects tolerate oral therapy, where there is close monitoring of TMP levels with the capacity to adjust the dose, and where careful monitoring of clinical response and adverse events is feasible. Although no adverse events occurred in our patients, adverse events including nausea, vomiting, diarrhoea and skin rashes have been reported frequently; bone marrow depression has rarely occurred. With prolonged therapy and higher doses careful monitoring for adverse events is warranted, including measurement of a full blood count.

Establishment of an effective oral TMP-SMZ regimen for PCP is important for the treatment of HIV-infected children, particularly in countries with limited resources. PCP has been reported to occur frequently as an AIDS-indicator disease among HIV-infected infants in Malawi and South Africa in association with a high mortality.[2-6] As a result of the HIV pandemic in sub-Saharan Africa, increasing numbers of HIV-infected children may develop PCP, necessitating the development of effective, affordable management strategies.[13] Use of an effective oral TMP-SMZ regimen could provide a cost-effective, available alternative to intravenous therapy. In addition, use of an effective oral TMP-SMZ regimen may provide a safer alternative than intravenous therapy as the latter must be diluted in a large volume thus increasing the risk of fluid overload especially in young HIV-infected infants who may also have an HIV-associated cardiomyopathy.[14]

Finally, measurement of TMP levels may prove useful for therapeutic monitoring of children who are treated for suspected or proven PCP. By adjusting the TMP-SMZ dose to maintain TMP levels at 5 - 8 µg/ml, toxicity was decreased while efficacy was maintained in HIV-infected adults with PCP.[15] Monitoring of serum TMP concentrations may be one way of adjusting dosage to ensure that drug concentrations remain within the therapeutic range to provide optimal therapy for PCP.

We thank Ms Z Latief for processing blood specimens, and the children and their caregivers for participating. The study was funded by a 'Secure the Future Grant' from Bristol Myers Squibb.

1. Chintu C, Mudenda V, Lucas S, *et al*. Lung disease at necropsy in African children dying from respiratory illnesses: a descriptive necropsy study. *Lancet* 2002; **360:** 985-990.
2. Zar HJ, Dechaboon A, Hanslo D, Apolles P, Magnus K, Hussey G. *Pneumocystis carinii* pneumonia in HIV-infected children in South Africa. *Pediatr Infect Dis J* 2000; **19:** 603-607.
3. Graham SM, Mtitimila EI, Kamanga HS, Walsh AL, Hart CA, Molyneux ME. Clinical presentation and outcome of *Pneumocystis carinii* pneumonia in Malawian children. *Lancet* 2000; **355:** 369-373.
4. Ruffini DD, Madhi SA. The high burden of *Pneumocystis carinii* pneumonia in African HIV-1-infected children hospitalised for severe pneumonia. *AIDS* 2002; **16:** 105-112.
5. Hughes WT. *Pneumocystis carinii* pneumonia: new approaches to diagnosis, treatment and prevention. *Pediatr Infect Dis J* 1991; **10:** 391-399.
6. Lau WK, Young LS. Trimethoprim-sulphamethoxazole treatment of *Pneumocystis carinii* pneumonia in adults. *N Engl J Med* 1976; **295:** 716-718.
7. Hughes WT, Feldman S, Chaudhary SC, *et al*. Comparison of pentamidine isethionate and trimethoprim-sulphamethoxazole in the treatment of *Pneumocystis carinii* pneumonia. *J Pediatr* 1980; **92:** 285-291.
8. Siber GR, Smith AL. Pharmacokinetics of intravenous trimethoprim-sulphamethoxazole in children and adults with normal and impaired renal function. *Rev Infect Dis* 1982; **4:** 566-578.
9. Laizure SC, Holden CL, Stevens RC. Ion-paired high-performance liquid chromatographic separation of trimethoprim, sulfamethoxazole and N4-acetylsulfamethoxazole with solid-phase extraction. *J Chromatogr* 1990; **528:** 235-242.
10. Chinn WFT, Vandenbroucke A, Fong IW. Pharmacokinetics of trimethoprim-sulphamethoxazole in critically ill and non-critically ill AIDS patients. *Antimicrob Agents Chemother* 1995; **39:** 28-33.
11. Stevens RC, Laizure SC, Williams CL, Stein DS. Pharmacokinetics and adverse effects of 20-mg/kg/day trimethoprim and 100-mg/kg/day sulfamethoxazole in healthy adult subjects. *Antimicrob Agents Chemother* 1991; **35:** 1884-1890.
12. Addo-Yobo E, Chisaka N, Hassan M, *et al*. Oral amoxicillin versus injectable penicillin for severe pneumonia in children aged 3 to 59 months: a randomised multicentre equivalency study. *Lancet* 2004; **364:** 1141-1148.
13. Dray-Spira R, Lepage P, Dabis F. Prevention of infectious complications of paediatric HIV infection in Africa. *AIDS* 2000; **14:** 1091-1099.
14. Lipshultz SE, Easley KA, Orav EJ, *et al*. Left ventricular structure and function in children infected with human immunodeficiency virus: the prospective P2C2 HIV Multicenter Study. Pediatric Pulmonary and Cardiac Complications of Vertically Transmitted HIV Infection (P2C2 HIV) Study Group. *Circulation* 1998; **97:** 1246-1256.
15. Sattler FR, Cown R, Nielsen DM, Ruskin J. Trimethoprim-sulphamethoxazole compared with pentamidine for the treatment of *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome: a prospective, non-crossover study. *Ann Intern Med* 1988; **109:** 280-287.

Accepted 27 February 2006.