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Pyrimethamine Alone as Prophylaxis for Cerebral Toxoplasmosis in Patients with Advanced HIV Infection

Summary: Prophylaxis for toxoplasma encephalitis was performed with pyrimethamine alone (50 mg daily) in 56 patients with advanced HIV infection. Thirty-eight patients were at high risk for toxoplasma encephalitis ($CD4^+$ counts $\leq 200/\mu l$, and presence of serum IgG antibodies to *Toxoplasma gondii*). The overall treatment period was 697 months (mean 12.5 ± 12.1). During prophylaxis, only one patient developed toxoplasma encephalitis, four patients discontinued treatment due to adverse reactions. Steady state pyrimethamine plasma concentrations were measured by gas chromatography. Mean plasma level was 1,887 ± 1,161 ng/ml, during liver enzyme-inducing comedication plasma levels were significantly (p = 0.0001) reduced (1,488 ± 884 ng/ml versus 1,978 ± 1,196 ng/ml without comedication). All patients received a folinic acid supplement of 7.5 mg daily. Serum folate levels ranged from 5.7–105 (43.7 ± 29.2) nmol/l; severe hematological side effects did not occur.

Introduction

Toxoplasma encephalitis is the most common opportunistic infection of the central nervous system in patients with the acquired immunodeficiency syndrome (AIDS). The incidence of toxoplasma encephalitis in HIV-infected patients depends on the prevalence of latent toxoplasma infection, which varies geographically. It is reported that about one third of the patients tested positive for serum IgG to *Toxoplasma gondii* will ultimately develop toxoplasma encephalitis [1–3]. Prognosis for toxoplasma encephalitis is poor. Early mortality is as high as 16%, and 40% to 50% of patients will have residual neurologic impairment [4]. Median survival is 4–8 months [5, 6]. There is therefore a critical need for primary and secondary prophylaxis of toxoplasma encephalitis.

In our present study, we investigated the efficacy and patient's tolerance for high-dose pyrimethamine alone as prophylaxis for toxoplasma encephalitis. Since it is known that pyrimethamine plasma levels can vary markedly [7], and in order to obtain valid data on patient's compliance and drug efficacy, steady-state pyrimethamine plasma concentrations were measured by gas chromatography. Results were compared with those published by other investigators [8–11].

Patients and Methods

From September 1989 to May 1995, 56 patients entered the study. All patients had advanced HIV infection with an absolute $CD4^+$ lymphocyte count of $\leq 200/\mu l$ or a history of an AIDS-defining opportunistic infection or neoplasm. Thirty-eight patients had a positive serologic test for IgG antibody to *T. gondii* by a standard commercially licensed laboratory method (Table 1). Nine patients had a previous period of toxoplasma encephalitis, 47 patients obtained pyrimethamine as primary prophylaxis.

Informed consent was obtained from all patients. Every patient had a Karnofsky performance state of ≥70 (except two patients with a history of severe toxoplasma encephalitis) and showed no sign of severe impairment of liver, kidney or the hematological system (total bilirubin ≤2 mg/dl, serum creatinine ≤2 mg/dl, hemoglobin ≥10 g/dl, absolute neutrophil count ≥1,000/µl, platelet count ≥100,000/µl).

Table 1: Prophylaxis for toxoplasma encephalitis with pyrimethamine containing drugs. Baseline characteristics of treated patients; efficacy and tolerance of treatment.

Pyrimethamine dosage/week (mg)	350
Patients (n)	56
Age (years)	36 ± 8
Sex	7 f; 49 m
Intravenous drug use (%)	27
$CD4^+$ cells/µl ± SD	88 ± 71
Patients (n) with IgG-antibodies to *Toxoplasma gondii*	38
Follow-up (months)	
Total	697
Mean ± SD	12.5 ± 12.1
Patients with severe side effects (n)	4
Failure of prophylaxis (n)	1

f = female; m = male

Prophylactic treatment was performed with oral pyrimethamine 50 mg daily. Oral folinic acid (7.5 mg/day) was added as Leucovorin® to prevent hematological side effects. All patients received pyrimethamine as a single morning dose.

Antiretroviral therapy was administered as zidovudine, dideoxyinosine or dideoxycytidine alone or in combination. Prophy-

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laxis for *P. carinii* infection was performed with aerosolized pentamidine every month. No patient was treated with any additional drug with potential activity against *T. gondii*. Eleven patients received an enzyme-inducing comedication such as rifampin, carbamazepine, phenobarbital or phenytoin. During prophylactic treatment with pyrimethamine, a total of 433 blood samples was drawn just before the next administration of pyrimethamine (24 h values = trough levels). After centrifugation, plasma samples were stored at −20°C until taken for analysis. Pyrimethamine plasma concentrations were determined by gas chromatography (Hewlett Packard 5880a with a nitrogen-phosphorus-selective detector, splitless injection and a 15 m DB (Dura Bond) 17 fused-silica column, 0.32 mm i.d.. Conditions were as follows: Injection port 250 °C, oven temperature 180 °C−280 °C, 10°/min, detector temperature 300 °C, carrier gas was helium with a flow rate of 2.85 ml/min).

Serum folate levels were measured in 19 patients receiving folinic acid supplementation. Folate levels were determined by a local commercial laboratory (normal range 3.4−44 nmol/l).

Prophylaxis with pyrimethamine was stopped in cases of severe side effects known to be associated with pyrimethamine, including nausea, vomiting, rash or myelosuppression (hemoglobin ≤7 g/dl, absolute neutrophil count ≤500/µl, platelet count ≤50,000/µl).

A presumptive diagnosis of toxoplasma encephalitis was made in patients with changes in neurologic function consistent with toxoplasma encephalitis, typical lesions on magnetic resonance imaging (MRI) or computed tomography (CT), and a clinical response to specific therapy with pyrimethamine at a curative dosage (150 mg/d) combined with sulfadiazine (6−8 g/d) over a 6-week period.

Statistical analysis was performed with Student's t-test. All values are given as mean ± SD and range. P values of ≤0.05 were considered significant.

Results

The mean duration of follow-up was 12.5 ± 12.1 (1−51) months. The total duration of follow-up was 697 months. Of the 56 patients receiving high-dose pyrimethamine alone, 52 (93%) tolerated a full dose during the observation period. Side effects that led to discontinuation of therapy were nausea, vomiting, sleeplessness and headache in one case. Severe hematologic toxicity did not occur during supplementation with folinic acid as performed in all patients. There was no correlation between side effects and pyrimethamine plasma levels. Three patients showed side effects during the first month of pyrimethamine therapy, one patient after 1 year of treatment.

Only one patient on primary prophylaxis with 50 mg pyrimethamine a day for 3 months developed toxoplasma encephalitis. Pyrimethamine plasma concentration at this time was 891 ng/ml.

Secondary prophylaxis for toxoplasma encephalitis was associated with a relatively long mean survival (13.7 months from initial maintenance therapy).

During prophylaxis for toxoplasma encephalitis with drugs containing pyrimethamine 568 steady-state pyrimethamine plasma concentrations could be determined by gas chromatography (Figure 1). Twenty-three further plasma levels from 12 patients had to be excluded from further analysis because of absence of pyrimethamine in plasma as an indication of non-compliance. As expected, pyrimethamine plasma levels showed a wide range from patient to patient. Mean pyrimethamine plasma concentration was 1,887 ± 1,161 (56−8,522) ng/ml. During treatment with drug metabolism inducing comedication, a tendency towards decreased pyrimethamine plasma concentrations was observed. Eighty plasma samples from 11 patients were determined in this group. Mean pyrimethamine plasma level was 1,488 ± 884 (56−5,796) ng/ml. In 45 patients without comedication (353 samples) mean pyrimethamine level was 1,978 ± 1,196 (70−8,522) ng/ml. Using the Student's t-test, we found a significant ($p = 0.0001$) difference in pyrimethamine plasma levels between these two groups.

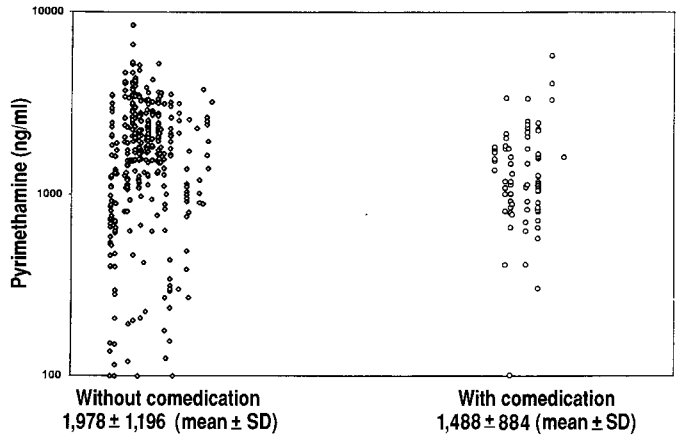

Figure 1: Pyrimethamine plasma concentrations with and without enzyme-inducing comedication during prophylaxis for toxoplasma encephalitis with pyrimethamine dosed 50 mg daily.

Serum folate levels ranged from 5.7−105 nmol/l with a mean value in the upper normal range (43.7 ± 29.2 nmol/l).

Discussion

Although the number of patients studied is relatively small, we found that pyrimethamine given alone at a dose of 50 mg daily could be highly effective and safe as prophylaxis against toxoplasma encephalitis in patients with advanced HIV infection. Of the 56 patients treated in our study, 38 were at high risk for infection with toxoplasma encephalitis [12, 13], having an absolute $CD4^+$ lymphocyte count of ≤200/µl and serum IgG antibodies to *T. gondii*. Only one (2.6%) of them developed toxoplasma encephalitis during the observation period.

Previous studies using pyrimethamine alone for prophylaxis of toxoplasma encephalitis showed similar results. *Bachmeyer* and associates [8] found that of 26 patients at risk receiving 50 mg pyrimethamine daily for primary prophylaxis for a median duration of 10 months, none

developed toxoplasma encephalitis. A secondary prophylaxis for toxoplasma encephalitis with 50 mg daily pyrimethamine alone was performed by *de Gans* et al. [10]. Only two relapses occurred during maintenance therapy; median survival was 36 weeks.

Only a few drug combinations have been shown to be effective as prophylaxis of toxoplasma encephalitis. Low-dose trimethoprim-sulfamethoxazole (TMP-SMX) was evaluated by several investigators [9, 14]. *Tocchetti* et al. [15] observed a trend towards greater effectiveness of cotrimoxazole (960 mg three times weekly) compared with 500 mg sulfamethopyrazine/25 mg PYR twice weekly or PYR 25 mg/dapsone 100 mg twice weekly. TMP-SMX is also useful as prophylaxis for *Pneumocystis carinii* pneumonia, but enthusiasm for this combination has been tempered by its recognized high incidence of toxicity in patients with AIDS. Toxicity is also the major problem in long-term treatment with the combination of pyrimethamine and sulfadiazine [5, 16, 17]. These especially allergic complications are mostly due to sulfonamides. In the present study, 93% of the patients receiving 50 mg pyrimethamine daily tolerated the full dose over 12.5 ± 12.1 months.

In our study, 18 patients with absence of serum IgG to *T. gondii* were treated before May 1991, when the importance of toxoplasma serology was not yet evident. Nevertheless, including those patients in our analysis may provide essential information concerning tolerance of long-term treatment with high-dose pyrimethamine and steady-state pyrimethamine plasma levels.

Hematological toxicity is a major dose-related side effect of treatment with pyrimethamine. As shown, these side effects may be prevented by the prophylactic use of folinic acid [8, 16]. We used a daily dose of 7.5 mg that produced mean folate plasma levels in the upper normal range.

Measuring steady-state pyrimethamine plasma levels, we confirmed the investigations of *Weiss* et al. [7]. Plasma concentrations varied widely during continuous treatment, and drug levels were also not reliably predictable in individual patients from the daily dose that was used. In addition, pyrimethamine plasma levels seem to be influenced by enzyme-inducing comedication, as shown in this study. For these reasons, and in order to identify patients with poor compliance, a pharmacological monitoring of patients on long-term treatment with pyrimethamine could be helpful. We suggest that drug levels of 1,000−3,000 ng/ml during prophylaxis should be adequate to suppress toxoplasma encephalitis in AIDS-patients at risk for it. During curative treatment of toxoplasma encephalitis, *Weiss* and co-workers [7] proposed pyrimethamine plasma levels >3,000 ng/ml.

In summary, the findings of this study indicate that prophylactic treatment with pyrimethamine alone, producing plasma levels of about 1,000 to 3,000 ng/ml, is effective and safe for a majority of patients. Severe side effects may be avoided by adding a small dose of folinic acid. However, the results of this study must be interpreted with caution. Further studies are needed. They should be prospective, double-blind and controlled, comparing patients receiving pyrimethamine alone with those receiving combinations as mentioned above.

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Zusammenfassung: Monotherapie mit Pyrimethamin als Prophylaxe der cerebralen Toxoplasmose bei Patienten mit fortgeschrittener HIV-Infektion. Bei 56 Patienten mit fortgeschrittener HIV-Infektion wurde eine Prophylaxe der cerebralen Toxoplasmose mit Pyrimethamin als Monotherapie in einer Dosierung von 50 mg täglich durchgeführt. 38 dieser Patienten wiesen ein hohes Risiko für die Entwicklung einer Toxoplasma-Encephalitis auf ($CD4^+$-Zellen ≤200/µl und Nachweis von IgG-Antikörpern gegen *Toxoplasma gondii*). Die gesamte Behandlungsdauer betrug 697 Monate (im Mittel 12,5 ± 12,1). Während der Prophylaxe entwickelte lediglich ein Patient eine cerebrale Toxoplasmose, vier Patienten brachen die Behandlung wegen Nebenwirkungen ab. Steady-state-Pyrimethamin-Plasmakonzentrationen wurden durch Gaschromatographie bestimmt. Der mittlere Plasmaspiegel betrug 1.887 ± 1.161 ng/ml, während einer Leberenzym-induzierenden Komedikation wurden signifikant (p = 0,0001) verminderte (1.488 ± 884 ng/ml vs. 1.978 ± 1.196 ng/ml ohne Komedikation) Plasmakonzentrationen gemessen. Alle Patienten erhielten additiv 7,5 mg Folinsäure pro Tag. Die gemessenen Serum-Folsäurespiegel schwankten zwischen 5,7 und 105 (43,7 ± 29,2) nmol/l, schwerwiegende hämatologische Nebenwirkungen traten hierunter nicht auf.

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Book Review

Y. Becker, G. Darai (eds.)
PCR: Protocols for Diagnosis of Human and Animal Virus Diseases
xvii, 596 pages, 27 tables, MS-DOS diskette enclosed
Springer-Verlag, Berlin, Heidelberg, New York 1995
Price: DM 168,–

This book is a supplement to *Diagnosis of Human Viruses by Polymerase Chain Reaction Technology*, which appeared as volume 1 in the "Frontiers of Virology" series in 1992. This volume is to provide PC users with basic information about the diagnosis of viral infections by means of computers. The book is divided into three main sections: the diagnosis of major virus diseases, animal virus diseases, and a PC technology section. This is a general work of reference which, however, must be supplemented by literature searches elsewhere for specific questions. The word "protocols" in the title is somewhat misleading, as the book is a collection of various articles about individual subject areas, not a list of PC instructions. The PC technology section is too brief as a whole and could have included references to data banks for sequence analysis (such as EMBL, Swissprot, etc.), Internet addresses and bibliographical references for further information. The enclosed diskette (why is it only in the MS-DOS format?) is not much of a help, as it is merely a copy of the book and, furthermore, lacks a "read me" introductory file.

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