Toxoplasmic encephalitis with hyperpigmentation and pancytopenia after treatment with fansidar: a case report and review of literature

RN. Peck[1], S Kalluvya[2], W Johnson[3], DW. Fitzgerald[4]

Abstract

Toxoplasmic encephalitis is a common opportunistic infection in HIV infected individuals in sub-Saharan Africa but is difficult to treat in settings where first line therapy is not available. Fansidar has been recommended as an alternative regimen in these settings. In this report we describe the case of a patient with toxoplasmic encephalitis who was treated with fansidar with good response but fatal side effects. This case illustrates the potential dangers of treating toxoplasmic encephalitis with fansidar. Accordingly, we also review the literature regarding alternative treatment regimens for toxoplasmic encephalitis that may be equally effective but less toxic than fansidar.

Keywords: toxoplasmic encephalitis, fansidar, pancytopenia, hyperpigmentation

Introduction

Toxoplasmic encephalitis is a common opportunistic infection in patients infected with HIV but is difficult to treat in resource-limited settings.

The first line therapy for toxoplasmic encephalitis is a combination of pyrimethamine and either sulfadiazine or clindamycin and 60% - 80% percent of patients will improve with this regimen [1]. Unfortunately, these medications are often not available in developing countries.

In places where first line therapy is not available, one of the medications used for treating toxoplasmosis is fansidar, a combination of pyrimethamine and sulfadoxine. Fansidar is widely available in sub-Saharan Africa where it is used as malaria prophylaxis in pregnant women. No clinical trials have yet been done to determine the best dosing regimen for fansidar for treatment of *Toxoplasma gondii*.

In this report we describe the case of a 25-year-old HIV infected female with toxoplasmic encephalitis that was treated with fansidar at high doses, improved clinically and radiographically but developed fatal side effects. We also discuss the growing evidence for alternative regimens that may be equally effective and less toxic than high-dose Fansidar.

Case Report

A 25-year-old female was admitted with fever and cough. Three days prior to her admission, she developed fever with chills and rigors and a cough productive of greenish sputum with streaks of blood. On the day of admission the patient developed worsening dyspnea and recurrent, non-bloody, non-bilious vomiting. A chest radiograph taken at admission revealed a dense, right lower lobe consolidation. The patient was diagnosed with pneumonia and treated with ceftriaxone 2 grams daily for 7 days. A malaria smear was negative. Sputum for AFB was negative twice. Liver function tests were normal. The white blood count was $5.0x10^9$/L with normal differential, hemoglobin 10.5g/L and a platelet count of $101x10^9$/L. A rapid test for HIV was positive and the patient's CD4 count was 74 cells/ml.

The patient's symptoms improved on antibiotic therapy but on 4th day of admission, she started complaining of generalized weakness and pain "all over the body." On hospital day 6, the patient developed left sided body weakness and on hospital day 10 she was noted to be confused. Examination revealed a complete left sided hemiplegia. A computed tomography (CT) scan with contrast showed multiple, ring-enhancing lesions in the right parietal lobe compatible with toxoplasmic encephalitis.

On the following day the patient's family requested discharge against medical advice. She returned to the ward 6 days later with persistent hemiplegia. On re-admission, the patient was started on a regimen of pyrimethamine 75mg and sulfadoxine 1500mg three times daily orally (3 tablets of Fansidar 3 times daily) and folinic acid 5mg per day.

On day 10 of treatment she was able to walk with assistance. Her power at that time was noted to be grade 2/5 in the upper extremity and grade 3/5 in the lower extremity. Physical examination also revealed a generalized hyperpigmentation, most prominent on the palms and soles.

On day 16 of treatment the patient developed persistent epistaxis and hematemasis. Nasal packing was performed and she was transfused one unit of blood. The patient was transferred to the intensive care unit where she was found to be pancytopenic with a white blood count of $1.1x10^9$/L, hemoglobin 5.7g/L and a platelet count $4x10^9$/L. Fansidar was discontinued and the patient was started on folic acid 10mg intravenous daily. She was treated with aggressive transfusion of whole blood and the bleeding stopped within 24 hours.

A repeat CT scan at this time, 22 days after initiation of treatment, revealed complete resolution of the ring enhancing lesions seen on the prior CT. However, he patient's clinical status continued to deteriorate and on ICU day 5, a repeat full blood picture showed a white blood cell count of 1.1, hemoglobin of 2.3 and a platelet count of 1.

The patient died the following morning. An autopsy was requested but the family refused. The immediate cause of death remained unknown.

Corresponding to: : R Peck, P. O. Box 1370, Bugando Medical Centre, Mwanza, Tanzania, Fax Number: +255282500799, E-mail: rnp2002@gmail.com

[1]Bugando Medical Centre, [2]Bugando University College of Health Sciences, [3]Weill Cornell Medical College

Table 1: Alternative Regimens for Treating Toxoplasma Encephalitis in Resource Limited Settings.

Drug	Regimen	Design	Population	Endpoint	Results
TMP/SMX	10/50 mg/kg/day PO or IV divided Q12H x 4 weeks	Randomized trial comparing TMP/SMX with P+S*	77 cases in Italy	1) clinical response at 2 weeks, 2) adverse effects	1) 70% vs 70% (P+S) 2) 12% vs 20% (P+S) [8]
TMP/SMX	10/50 mg/kg/day PO or IV divided Q12H x 4 weeks	Case Series	25 cases in South Africa	1) full recovery, disability or death, 2) adverse effects	1) 44%, 40%, 16% 2) 4% [9]
Fansidar	4 tabs PO OD x 2 days then 1 tab PO OD x 4 weeks	Case Series	323 cases in Ethiopia	1) clinical response at 2 weeks, 2) severe adverse effects	1) 78% 2) 20% [2]

* P+S = Pyrimethamine and Sulfadiazine

Discussion:

Toxoplasmic encephalitis is common in sub Saharan Africa, where estimates of toxoplasma serology positivity range from 80%-90%.[1] Patients with HIV and CD4 T cell count less than 100 cells/mL who are toxoplasma serology positive have a 30% probability of developing toxoplasmic encephalitis in the absence of prophylaxis.[(1)] Despite this high prevalence, effective treatment regimens are not available at many health care centers in the region.

Toxoplasmic encephalitis typically presents with a combination of headache, fever, altered mental status, focal neurologic deficits and seizures. The diagnosis can be confirmed by CT scan, with multiple or single ring enhancing lesions. In the absence of a CT scan, the diagnosis can be made with clinical findings and response to treatment.

The first line regimen for treatment of toxoplasma enphalitis is a combination of pyrimethamine and either sulfadiazine or clindamycin. There is no second-line regimen described in our national guidelines.[(1)]

In some developing countries fansidar, a combination of pyrimethamine 25mg and sulfadoxine 500mg, is used for the treatment of toxoplasmic encephalitis. In the absence of clinical trials, recommendations for dosing regimens vary widely from 1 tab orally per day to 3 tabs orally 3 times per day. [2] We chose a regimen of Fansidar 3 tabs 3 times daily based on the local experience of one of the authors. (Dr. S Kalluvya, personal communication)

Pancytopenia is a common and dangerous side effect of long-term fansidar treatment. It typically presents 3-4 weeks after initiation of therapy and is due to bone marrow suppression.[(1)]. Even fansidar 1 tablet daily given to patients with toxoplasmic encephalitis can cause severe cytopenias in nearly 20% of patients. [(2)]

Hyperpigmentation has also been reported in patients treated with pyrimethamine.[(1)] In our patient, hyperpigmentation developed after 4 weeks of treatment and shortly before she developed pancytopenia. This progression suggests that hyperpigmentation could be a warning sign for pancytopenia in patients treated with pyrimethamine.

The severe side effects seen in this case point to the need for a less toxic alternative regimen. Table 1 summarizes studies of trimethoprim-sulfamethoxazole (TMP/SMX) and lower doses of fansidar for the treatment of toxoplasmic encephalitis.[(2, 3)]

Given the current evidence, TMP/SMX (also known as Co-trimoxazole) is probably the best regimen for treating toxoplasmic encephalitis in places where 1st line regimens are not available. A Cochrane Review article concluded that TMP/SMX is not inferior to 1st line regimens in the treatment of toxoplasmic encephalitis and that it may be a suitable choice for resource limited settings. In South Africa, TMP/SMX is already recommended as 1st line therapy .[(1)]

The best time to initiate antiretroviral therapy in the setting of acute opportunist infections like toxoplasmosis is not known. In this case we opted to treat the patient's toxoplasmosis and to defer antiretroviral therapy for 2 weeks out of concern for overlapping drug toxicities and immune reconstitution as well as to allow time for intensive adherence counseling. Consideration should be given to earlier initiation of antiretroviral therapy in patients with toxoplasmosis.

In summary, we have presented a case of a 25-year-old female with AIDS and toxoplasmic encephalitis who was treated with fansidar. She improved clinically and radiographically, but developed severe pancytopenia. This case suggests that high dose fansidar may be a dangerous treatment regimen. We recommend that TMP/SMX given at a dosage of 10/50 mg/kg/day divided in twice daily doses and given for 4 weeks would be a good alternative for treating toxoplasmic encephalitis in places where pyrimethamine and sulfadiazine are not available.

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References

1. Porter SB, Sande MA. Toxoplasmosis of the central nervous system in the acquired immunodeficiency syndrome. N Engl J Med 1992;327:1643.
2. Amogne W, Teshager G, Zenebe G. Central nervous system toxoplasmosis in adult Ethiopians. Ethiop Med J 2006;44:113-120.
3. The United Republic of Tanzania, Ministry of Health. National Guidelines for the Clinical Management of HIV and AIDS. Second Edition, April 2005.
4. WHO. TB/HIV: A clinical manual. Second edition. 2004.
5. Kachel L, Krawczyk-Kulis M, Holowiecki J. Panctypopenia as a complication of treatment of toxoplasmosis. Pol Tyg Lek 1992;47:136-7.
6. Ozturk R, Engin A, Ozaras R, Mert A, Tabak F, Aktug Y. Hyperpigmentation due to pyrimethamine use. The Journal of Dermatology 2002;29:443-445.
7. Torre D, Casari S, Speranza F, Donisi A, Gregis G, Poggio A et. al. Randomized trial of trimethoprim-sulfamethoxazole versus pyrimethamine-sulfadiazine for therapy of toxoplasmic encephalitis in patients with AIDS. Itallian Collaborative Study Group. Antimicrobial Agents and Chemotherapy 1998;42(2):1346-1349.
8. Arens J, Barnes K, Crowley N, Maartens G. Treating AIDS-associated cerebral toxoplasmosis – pyrimethamine plus sulfadiazine compared with co-trimoxazole, and outcome with adjunctive glucocorticoids. South African Medical Journal 2007;97(10):956-958.
9. Dedicoat M, Livesley N. Management of toxoplasmic encephalitis in HIV-infected adults (with an emphasis on resource-poor settings). Cochrane Database Syst Rev 2006;3:CD005420.
10. Standard Treatment Guidelines and Essential Drugs List. Pretoria, South Africa: The National Department for Health, 2003.