

The patient did not receive any medication known to alter the pharmacokinetics of levofloxacin. During levofloxacin treatment, renal function improved (creatinine clearance=102.3 mL/min) and glucose levels were unchanged. No electrocardiographic abnormalities or any adverse effect related to levofloxacin administration were found. The patient received this dose of intravenous levofloxacin for a total of 6 days, followed by oral levofloxacin at 500 mg/12 h for an additional 4 days. Clinical cure of the respiratory infection was rapidly achieved and the patient was discharged.

Written informed consent was obtained from the patient to use this treatment regimen and to obtain blood samples.

Very few studies have examined fluoroquinolone pharmacokinetics in obese patients,^{2,3} and, to our knowledge, this is the first pharmacokinetic evaluation of levofloxacin in a patient with severe morbid obesity. Levofloxacin was administered at an actual body weight-adjusted dose of 4 mg/kg/12 h based on a ciprofloxacin dosage recommendation for obese patients.² With this regimen, the values of C_{max} and CL were similar to those obtained in non-obese healthy volunteers receiving a dose of 750 mg/24 h,⁵ the dose recommended for the treatment of community-acquired pneumonia in adults,⁴ but the AUC_{0-24} was double (143.27 mg h/L, twice the value of the $AUC_{0-\tau}$ because levofloxacin was administered twice daily). It has also been previously recommended that the dose of quinolones should be based on a weight correction factor of 45% of excess body weight.³ This dose was administered to a morbidly obese patient who reached a therapeutic peak plasma concentration, but no other pharmacokinetic parameters were reported.⁶ It has been suggested that this lower adjusted dosing could result in low interstitial levofloxacin levels due to impaired levofloxacin penetration in the tissues of obese patients.² In our patient, levofloxacin had larger absolute V_{ss} and $t_{1/2}$ compared with those described in non-obese patients, which may be explained by a significant distribution of levofloxacin into excess weight.¹

Regarding pharmacodynamic parameters, an AUC_{0-24}/MIC ratio of 143.27 was achieved, a value that exceeds the optimal ratio for favourable outcomes in patients with *S. pneumoniae* infections.⁷

In conclusion, an intravenous levofloxacin dose of 750 mg/12 h (4 mg/kg/12 h) in our patient with morbid obesity achieved double the adult exposure following a standard dose of 750 mg per day to non-obese healthy volunteers. Consequently, it could be queried whether it is necessary to administer higher body weight-adjusted doses of levofloxacin in this population.

Additionally, the observed longer $t_{1/2}$, resulting from an increase in V , suggests that it would be suitable to administer an initial loading dose to achieve the steady state rapidly, but followed by the administration of doses given less frequently than 12 hourly in order to avoid further drug accumulation. Nevertheless, these findings should be confirmed with further pharmacokinetic studies including a higher number of patients to ensure efficacy and avoid dose-related toxicity.

Funding

This study was carried out as part of our routine work. M. V. is supported by FIS through grant CP04/00121 from the Spanish Health Department in

collaboration with the research institute of the Hospital de la Santa Creu i Sant Pau, Barcelona, and is a member of the CIBERSAM Network.

Transparency declarations

None to declare.

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J Antimicrob Chemother 2011

doi:10.1093/jac/dkr147

Advance Access publication 1 April 2011

Failure of conventional treatment with pyrimethamine and sulfadiazine for secondary prophylaxis of cerebral toxoplasmosis in a patient with AIDS

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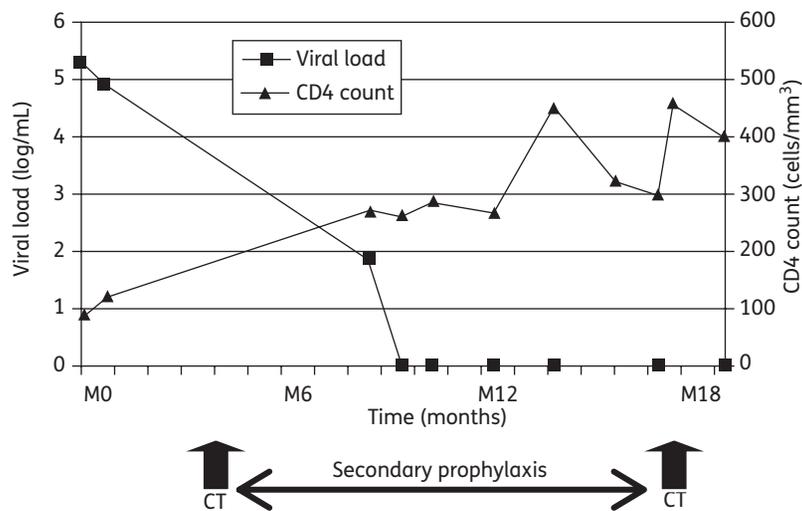


Figure 1. Occurrence of cerebral toxoplasmosis (CT) and evolution of CD4+ T cell count and viral load.

Keywords: immunodeficiency, *Toxoplasma gondii*, case management, treatment failure

Sir,

Cerebral toxoplasmosis remains one of the AIDS-defining events associated with the highest mortality.¹ The disease remains challenging despite the striking decrease in its incidence associated with the advent of highly active antiretroviral therapy (HAART).² We report a case of relapse of cerebral toxoplasmosis despite conventional secondary prophylaxis, which relies on half-dose pyrimethamine and sulfadiazine until immune status has been restored for 6 months.³ A slight decrease in CD4+ T cell proportion was the only announcing event, whereas initial *Toxoplasma* strain typing (type II) and ongoing virological response were reassuring. This report should raise awareness of the possible failure of the conventional strategy, and of the importance of all available parameters in assessing residual risk.

An adult patient was diagnosed with asymptomatic HIV infection in early 2009. Antiretroviral treatment with tenofovir, emtricitabine and boosted darunavir was initiated because of low CD4 count (91 cells/mm³). Four months later, the patient presented with headache, asthenia, behaviour changes and weight loss. Cerebral toxoplasmosis was diagnosed because of characteristic lesions on cerebral MRI examination, severe immunodeficiency (CD4 count 120 cells/mm³), bad observance of co-trimoxazole prophylaxis and good response to pyrimethamine (100 mg on the first day then 75 mg/day), folinic acid (25 mg/day) and sulfadiazine (6 g/day) for 6 weeks. *Toxoplasma* serology showed a high titre of anti-*Toxoplasma* specific IgG antibodies (6043 IU/mL) and no specific IgM antibodies. Secondary prophylaxis of pyrimethamine (25 mg/day, associated with folinic acid) and sulfadiazine (2 g/day) was administered thereafter. No other opportunistic infection was diagnosed.

Under HAART, CD4 count rose above 200 cells/mm³ (22% of T cells) and viral load became undetectable from the end of 2009 (Figure 1). Consequently, secondary prophylaxis was stopped after 7 months. Four weeks after this interruption, the patient presented again with headache, asthenia and aphasia. Viral load was still undetectable, and CD4 count was 324 cells/mm³

(18% of T cells). The titre of anti-*Toxoplasma* IgG antibodies was high, though lower than 1 year earlier (1622 IU/mL). Unfortunately, no serology had been performed in the meantime. Low titres of IgA specific antibodies were detected, suggesting parasitic reactivation. Cerebral MRI examination showed new lesions characteristic of cerebral toxoplasmosis. Because of the good immune status, stereotaxic biopsy was performed. Real-time PCR detected a high load of *Toxoplasma gondii* DNA in the cerebral biopsy. Microsatellite typing identified a type II strain. Pathological examination showed a polymorphic inflammatory infiltrate. There was no infiltration with CD8+ T lymphocytes evocative of immune reconstitution inflammatory syndrome, and no tumoral proliferation. The patient was treated again with full-dose pyrimethamine and sulfadiazine, and quickly presented clinical and radiological improvement.

Cerebral toxoplasmosis has been commonly described in patients suffering from AIDS, especially before the introduction of HAART.^{2,3} Clinical disease is rare among patients with CD4 count >200 cells/mm³, and the greatest risk occurs among patients with a CD4 count of <50 cells/mm³.³ Though rare cases have been reported in patients with up to 408 CD4+ T cells/mm³, they were mostly diagnosed only by clinical and radiological criteria.^{4,5} To our knowledge, we report the first case of parasitological documentation of cerebral toxoplasmosis in a patient with >300 CD4+ T cells/mm³.

More interestingly, failure of conventional secondary prophylaxis for cerebral toxoplasmosis in patients with AIDS has been reported only a few times before. Previous reports relied on presumptive diagnoses, and were associated with a decrease in CD4+ T lymphocyte count or percentage below thresholds of prophylaxis discontinuation.⁵ International guidelines indeed recommend maintaining treatment with half-dose pyrimethamine and sulfadiazine until CD4 count is >200 cells/mm³ (and 15% of total lymphocytes) for 6 months.³ This strategy was not able to prevent relapse in this case. This failure did not appear to be related to specific parasitic features, as microsatellite typing established a type II *Toxoplasma* strain, which is predominant in Europe, and not one of the more virulent types that are more common in other parts of the world. Additionally,

no evidence suggested decreased parasitic susceptibility to the drugs used for secondary prophylaxis, as curative treatment using the same drugs proved effective. It is noteworthy that neither viral response nor CD4 count heralded the relapse. The only preceding event was the diminution of CD4+ T cell proportion to <20%.

Restoration of a *T. gondii*-specific T cell response (such as *in vitro* lymphocyte proliferative response and interferon- γ production in response to *T. gondii* soluble antigen extract) was shown in patients increasing their CD4 counts under HAART after cerebral toxoplasmosis.⁶ However, the time necessary to restore specific immunity has not been established. Indeed, some studies suggested that this may occur after 12–18 months of successful HAART.^{6,7} Thus, stopping prophylaxis earlier might result in toxoplasmosis relapse in specific patients. However, this seems to be very uncommon, so the recommended strategy appears safe overall. Interestingly, high titres of anti-*T. gondii* IgG antibodies might not be associated with lymphocyte proliferative response to soluble antigen extract.⁷

Acknowledgements

We thank Dr Ajzenberg (Limoges Hospital) for strain typing.

Funding

This study was carried out as part of our routine work.

Transparency declarations

None to declare.

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J Antimicrob Chemother 2011

doi:10.1093/jac/dkr134

Advance Access publication 14 April 2011

Economic incentives for the (over-)prescription of broad-spectrum antimicrobials in German ambulatory care

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Keywords: antibiotics, fluoroquinolones, price elasticity

Sir,

Jensen *et al.*¹ recently described the relationship between decreasing prices and increasing demand for ciprofloxacin. This relationship was shown for the ambulatory setting in Denmark, a country where patients receive a relatively low reimbursement for outpatient medication (until 1999: fixed percentage of 50%; since 2000: 50%–85% after the patient has spent the deductible of about €67 for outpatient medication within the calendar year).

In Germany, outpatient medication is provided as benefits-in-kind to patients covered by statutory health insurance (SHI; nearly 90% of the German population). In the ambulatory sector, patients only have to make a small co-payment (between €5 and €10) for every prescription. However, following the introduction of generics into the German pharmaceuticals market (Figure 1), we noted a similar increase in demand for broad-spectrum antimicrobials.

Interestingly, in Germany, the increase in consumption of broad-spectrum antimicrobials is not due to the fact that respective antimicrobial agents have become affordable for a larger proportion of the population, as pointed out by Jensen *et al.*¹ as a possible reason for the increase in consumption in Denmark. Rather, the increase may possibly be related to the fact that in Germany a physician's decision to prescribe an antibiotic is probably guided by financial incentives. In Germany, ambulatory care physicians are generally self-employed, and the SHI reimburses fixed budgets for pharmaceuticals, the size of which depends on the number of patients and their ages.² According to this reimbursement system and the