

TOXIC UVEITIS CAUSED BY PHARMACODYNAMIC INTERACTIONS OF RIFABUTIN AND PROTEASE INHIBITORS: A CASE REPORT

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RÉSUMÉ:

Il faudrait toujours tenir compte des réactions toxiques (uvéïte, arthrite et leucopénie) de la Rifabutine à doses normales à cause des interactions pharmacocinétiques avec d'autres médicaments (par ex. les inhibiteurs de la protéase).

Ce cas montre que ce genre d'uvéïte est cliniquement significatif. Le diagnostic d'uvéïte, particulièrement une uvéïte avec hypopyon, chez un malade immunodéprimé rend généralement nécessaire une évaluation systémique exhaustive ainsi qu'une thérapie ophtalmique et systémique intensive.

SUMMARY:

Toxic reactions (uveitis, arthritis and leucopenia) of Rifabutin at normal doses should always be considered because of pharmacokinetic interactions with other drugs (e.g. the protease inhibitors).

This case demonstrates that this kind of uveitis is clinically significant as the diagnosis of uveitis, particularly hypopyon uveitis, in an immunocompromised patient generally mandates extensive systemic diagnostic evaluation, as well as intensive ophthalmic and systemic monitoring and therapy.

SAMENVATTING:

Het is belangrijk de toxische reacties (uveïtis, arthritï en leucopenie) ten gevolge van het gebruik van rifabutine in het achterhoofd te houden. Zelfs bij het gebruik van normale dosissen moet men alert zijn door de farmacocinetische interacties met andere medicatie (bv. protease inhibitors).

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received: 01.09.06

accepted: 14.11.06

Deze casus toont aan dat dit soort uveïtis klinisch significant is. De diagnose van uveïtis, en in het bijzonder een hypopyon uveïtis, bij een immunogecompromiteerde patiënt vereist meestal een intensieve diagnostische evaluatie, alsook een intensieve oftalmologische en systemische controle en behandeling.

MOTS-CLÉS:

Rifabutine - uvéïte - interactions pharmacocinétiques - SIDA

KEY WORDS:

Rifabutin - uveitis - pharmacokinetic interactions - AIDS

INTRODUCTION:

Anterior uveitis in a patient presenting the acquired immunodeficiency syndrome (AIDS) remains a diagnostic and therapeutic challenge. In the aqueous humor of these uveitis eyes several organisms can be found: herpes zoster ophthalmicus, *Toxoplasma gondii*, syphilis, fungi, cytomegalovirus and occasionally the human immunodeficiency virus (HIV) (5,8,12). A hypopyon is not characteristic of any of these uveitis syndromes. Particularly in AIDS-patients treated with Mycobutin, the Rifabutin dose related uveitis syndrome (14) (causing an anterior uveitis with or without a hypopyon or even a panuveitis (4,13)) must be considered.

This kind of uveitis has also been described in immunocompetent patients treated for *Mycobacterium avium* complex pulmonary infection with rifabutin (1, 9).

CASE REPORT:

A 40-year old woman with acquired immunodeficiency syndrome (AIDS) and a total CD 4 cell count of 191 cells/mm³ complained of a red and painful right eye (RE), associated with pain in several joints, most markedly in the right knee. She also complained of a decreased vision in the RE. Systemic medications included Saquinavir 1000 mg/day, Ritonavir 200 mg/day, Lamivudine 300 mg/day, Tenofovir 245 mg/day, Abacavir 600 mg/day, Atovaquon 10 cc/day, Omeprazol 20 mg/day, Rifabutin 300 mg/day, Isoniazide 300 mg/day and Pyridoxine 250 mg/day. Rifabutin was started 8 months earlier as prophylaxis against *Mycobacterium avium* complex (MAC). The ophthalmologic examination revealed a visual acuity of light perception in her RE. The left eye appeared normal. Slit lamp examination of the RE showed small endothelial precipitates on the corneal endothelium, an anterior chamber reaction with fibrin in the pupil and conjunctival hyperemia. Since fundoscopic examination was impossible, B-scan ultrasound was performed, showing a normal vitreum and an attached retina (figure 1).

The diagnosis of anterior uveitis was made and a treatment was started with topical antibiotics (Ofloxacin drops once every hour and an ointment at night), mydriatics (Homatropine-



Figure 1: (21/12/05: anteroposteriorly directed B scan image)



Figure 2: (22/12/05: inferiorly directed B scan image)

hydrobromide 3 times a day) and corticosteroids (Prednisolon acetate 2 times a day). The next day visual acuity remained unchanged, but on slitlamp examination a hypopyon of less than 1 mm was noted. The ultrasound of the posterior segment was repeated and showed condensations in the vitreous (figure 2). The patient underwent an anterior chamber tap. Fungi test, aerobic test and PCR for CMV and toxoplasmosis were all negative. Toxoplasma antibodies, CMV antibodies and syphilis serology were also found negative. No active infection could be demonstrated. It was decided to stop the Rifabutin and to administer topically a high dose of steroids (Prednisolon acetate every hour during the day and every two hours at night). The next day the patient was able to see hand movements and at slitlamp the hypopyon had disappeared. Fibrin was still present in the pu-

pil and on echo-B there were still vitreous condensations (figure 3). The same treatment was maintained in the following days. Vision improved up to 7/10 eight days later. The anterior chamber remained inflamed and yellow-whitish opacities were found inferiorly in the vitreous cavity. The local treatment was slowly tapered during the next 3 months. The second week we administered a drop of Prednisolon acetate every two hours during the day and at night a Prednisolon acetate ointment. We tapered the medication of one drop a week during the day and finally we stopped the ointment at night. The Rifabutin was suppressed but the rest of the systemic treatment was maintained. About 9 months after the first exam vision was 10/10, the anterior chamber was quiet and the retina looked normal. Some vitreal pigmented and non-pigmented inflammatory cells were present as well as the yellow-whitish opacities in the inferior and posterior vitreous. The echo B-scan confirmed the presence of vitreous condensations (figure 4).

DISCUSSION:

Therapeutic and prophylactic regimens directed specifically against MAC are increasingly used in patients infected with the human immunodeficiency virus (HIV). Several drugs used in the management of MAC have been associated with significant drug interactions involving the cytochrome P450 (CYP enzyme). This enzyme is highly influenced by other drugs used in the management of HIV patients; in particular protease inhibitors, as shown in this case (10).

Rifabutin is an inducer of CYP, while Ritonavir is a potent inhibitor of CYP and has been shown to substantially increase Rifabutin concentrations (2). Because of the increased risk of Rifabutin toxicity, especially in patients presenting uveitis of which the clinical appearance may vary from anterior uveitis with or without hypopyon to panuveitis and arthralgia (15), the dosage of Rifabutin should be reduced by at least 75% when associated with Ritonavir (11). The centers for Disease Control and Prevention issued that coadministration of Ritonavir and Rifabutin is probably well tolerated if the dosage of Rifabutin is reduced to 150 mg given 2 to 3 times a week (3,7).



Figure 3: (23/12/05 inferiorly directed B scan image)

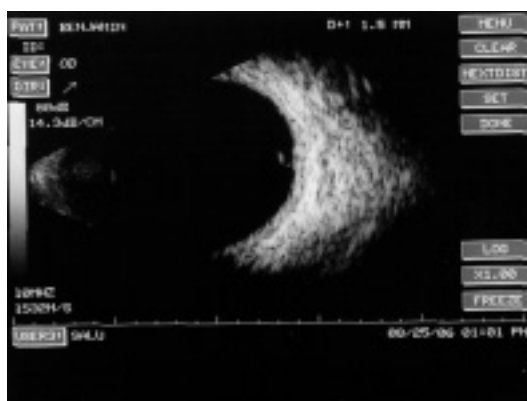


Figure 4: (25/08/06 inferiorly directed B scan image)

This uveitis is remarkable in that respect that it reacts promptly to topical administration of corticosteroids and elimination of the causative systemic Rifabutin (6,7).

CONCLUSION:

In the differential diagnosis of uveitis in an immunocompromised patient complaining of arthralgia, the dose related Rifabutin-uveitis syndrome should be taken into account. Even when the dosages seem to be correct, pharmacokinetic interactions between different drugs, and thus the possible toxic effects of those drugs, must be excluded.

REFERENCES:

- (1) BHAGAT N., READ R.W., RAO N.A., SMITH R.E., CHONG L.P. – Hypopyon uveitis in immunocompetent patients treated for Mycobac-

- terium avium complex pulmonary infection with rifabutin. *Ophthalmology*. 2001;108:750-2
- (2) CATO A., CAVANAUGH J., SHI H., HSU H., LEONARD J., GRANNEMAN R. – The effect of multiple doses of ritonavir on the pharmacokinetics of rifabutin. *Clin Pharmacol Ther* 1998;63:414-21
 - (3) CENTERS FOR DISEASE AND CONTROL PREVENTION. Updated guidelines of rifabutin or rifampicin for the treatment and prevention of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleotide reverse transcriptase inhibitors. *MMWR Morb Mortal Wkly rep* 2000;49:185-9
 - (4) CHAKNIS M.J., BROOKS S.E., MITCHELL K.T., MARCUS D.M. – Inflammatory opacities of the vitreous in rifabutin-associated uveitis. *Am J Ophthalmol*. 1996;122:580-2
 - (5) FARRELL P.L., HEINEMANN M.H., ROBERTS C.W., POLSKY B., GOLD J.W.M., MAMELOK A. – Response of human immunodeficiency virus-associated to zidovudine. *Am J Ophthalmol* 1988;106:7-10
 - (6) FRAUNFELDER F.W., ROSENBAUM J.T. – Drug-induced uveitis. Incidence, prevention and treatment. *Drug Staf* 1997;17:197-207
 - (7) GALLICANO K., KHALIQ Y., CANIGNAN G., TSENG A., WALMSLEY S., CAMERON D.W. – A pharmacokinetic (PK) study of intermittent rifabutin (RB) dosing with a combination of ritonavir (RT) and saquinavir (SQ) in HIV patients (abstract no.91). 7th conference on Retroviruses and Opportunistic Infections; 2000 Jan 30-Feb 2 San Francisco
 - (8) JACOBS D.S., PILIERO P.J., KUPERWASER M.G., SMITH J.A., HARRIS S.D., FLANIGAN T.P., GOLDBERG J.H., IVES D.V. – Acute uveitis associated with rifabutin use in patients with human immunodeficiency virus infection. *Am J Ophthalmol*. 1994;118:716-22
 - (9) KHAN M.A., SINGH J., DHILLON B. – Rifabutin-induced uveitis with inflammatory vitreous infiltrate. *Eye* 2000;14:344-6
 - (10) KUPER J.J., D'APRILE M. – Drug-drug interactions of clinical significance in treatment of patients with *Mycobacterium avium* complex disease. *Clin Pharmacokinet*. 2000;39:203-14.
 - (11) NORVIR PACKAGE INSERT. Chicago (IL): Abbott Laboratories, Inc., 2006:12
 - (12) SHULER J.D., ENGSTROM R.E., HOLLAND G.N. – Eternal ocular disease and anterior segment disorders associated with AIDS. *Int Ophthalmol Clin*. 1989;29:98-104
 - (13) SKOLIK S., WILLERMAIN F., CASPERS L.E. – Rifabutin-associated panuveitis with retinal vasculitis in pulmonary tuberculosis. *Ocul Immunol Inflamm*. 2005;13:483-5
 - (14) SKINNER M.H., BLASCHKE T.F. – Clinical pharmacokinetics of rifabutin. *Clin. Pharmacokinet*. 1995;28:115-25
 - (15) SUN E., HEATH-CHIOZZI M., CAMERON D.W., HSU A., GRANNEMAN R.G., MAURATH C.J.; LEONARD J.M. – Concurrent ritonavir and rifabutin increases the risk of rifabutin-associated adverse events (Abstract no. Mo.B171). XI International Conference on AIDS; 1996 Jul 7-12; Vancouver
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