

fectively induces, once the refractory period has ended, a return to the previous hypersensitivity state.

References

1. Prieto L. Antiinflamatorios no esteroideos y patología respiratoria. En: Comité de aditivos de la SEAIC (ed). Aditivos. Patología alérgica. SANED 1994; 201-247.
2. Stevenson DD, Simon RA. Sensitivity to aspirin and nonsteroidal antiinflammatory drugs. En: Middleton E, Reed CE, Ellis EF, Adkinson NF, Yunginger JW, Busse WW (ed). Allergy: principles and practice. Ed 5 th, vol. 2. St. Louis: 1998; Mosby, 1.225-1.234.
3. Szczeklik A. Aspirin-induced asthma: pathogenesis and clinical presentation. Allergy Proc 1992; 13:163-173.
4. Phillips GD, Foord R, Holgate ST. Inhaled lysine-aspirin as a bronchoprovocation procedure with aspirin in aspirin sensitive asthma. J Allergy Clin Immunol 1989; 84:232-241.
5. Dahlen B, Zetterstrom O. Comparison of bronchial and per oral provocation with aspirin in aspirin-sensitive asthmatics. Eur Respir J 1990; 3:527-534.
6. Stevenson DD, Simon RA, Mathison DA. Aspirin-sensitive asthma: tolerance to aspirin after positive oral aspirin challenges. J Allergy Clin Immunol 1980; 66:82-88.

DRUG HYPERSENSITIVITY REACTIONS IN HIV-INFECTED PATIENTS. INDUCTION OF COTRIMOXAZOLE TOLERANCE

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Adverse drug reactions are frequent in patients with HIV infection. Toxic-infective exanthemas may be indicative of an immunopathogenic effect of HIV or of other viruses. The products resulting from the metabolism of the administered drugs may act favouring the hypersensitivity response. T lymphocytes are important in these reactions. The increased frequency of reactions in patients with CD4⁺ counts ranging between 50 and 350 cells/ μ l might be due to a coincidence with the acme of the derangement of metabolic and immunologic mechanisms described in this paper and acquired in the course of HIV infection. It has been suggested that the side effects occurring during treatment with trimethoprim/sulfamethoxazole (cotrimoxazole) might be explained through the

formation of toxic hydroxylamines. Formation of these metabolites occurs preferently in the cytochrome P-450-induced hepatic microsomal metabolic pathways. Slow acetylation is more common in HIV-infected patients, who are moreover frequently polymedicated; this may lead to an accumulation of toxic metabolites such as hydroxylamines, which may in turn influence hypersensitivity. Glutathione is an antioxidant co-factor in the acetylation pathway that is decreased in HIV patients, and the cytotoxicity of hydroxylamines is increased in glutathione-depleted lymphocytes. Furthermore, hydroxylamines may act as haptens and be covalently bound to proteins, inducing the generation of toxic free radicals or the release of cell mediators. Cotrimoxazole represents a particular problem in this context, as about 50% of the patients require a change in their therapy after a reaction. Many patients may be treated with an alternative drug; for the remainder, the options are continuation of cotrimoxazole therapy with treatment of the reaction, reintroduction of the drug after withdrawal, and desensitisation. Success in desensitisation protocols (tolerance induction) appears to be more likely with protocols lasting for five or more days in patients with low CD4⁺ counts. In our study, the patients were to be entered into a desensitisation protocol or into slow reintroduction, according to their previous symptoms. The desensitisation protocol lasted six days and was carried out in-hospital. Forty-three patients were studied; 12 underwent controlled reintroduction of the drug, and 10 of them tolerated such reintroduction. Thirty-three patients were then selected (31 of them directly, plus the two who reacted upon reintroduction) for administration of the slow reintroduction (desensitisation) protocol. Overall, 32 of these 33 patients tolerated the drug. In the light of the results of our study and of other previous ones, it is very important to carry out an allergologic assessment in order to select the most adequate procedure. Even so, a "best and most effective" desensitisation procedure has not yet been established. Desensitisation or reintroduction of tuberculostatics is required when there is no effective alternative treatment available. Desensitisation protocols with other drugs have been sporadically reported in the case of HIV patients.

Key words: Drug reactions. Reintroduction. Desensitisation. Cotrimoxazole. HIV.

REACCIONES DE HIPERSENSIBILIDAD A FÁRMACOS EN PACIENTES INFECTADOS POR EL VIRUS DE LA INMUNODEFICIENCIA HUMANA. INDUCCIÓN DE TOLERANCIA A COTRIMOXAZOL

Las reacciones adversas a fármacos son frecuentes en pacientes con infección por el virus de la inmunodeficiencia humana (VIH). Los exantemas tóxico-infecciosos pueden indicar un efecto inmunopatogénico del VIH o de otros virus. Los productos del metabolismo de los fármacos administrados pueden actuar favoreciendo la respuesta de hipersensibilidad. Los linfocitos T son importantes en las reacciones. El aumento de frecuencia de reacciones en pacientes con CD4 entre 50 y 350/ μ l podría deberse a su coincidencia con el punto culminante de la alteración de los sistemas metabólicos e inmunológicos que se describen en este artículo y que se adquieren durante el curso de la infección por VIH. Se ha postulado que los efectos colaterales que ocurren durante el tratamiento con trimetoprima + sulfametoxazol (cotrimoxazol) pueden explicarse por la formación de hidroxilaminas tóxicas. La formación de estos metabolitos sucede predominantemente en vías metabólicas de los microsomas hepáticos inducidas por el citocromo P-450. La acetilación lenta es más común en pacientes infectados por VIH, que están, a menudo, polimedicados; esto conduce a la acumulación de metabolitos tóxicos como las hidroxilaminas, que pueden influir en la hipersensibilidad. El glutatión es un cofactor antioxidante de la vía de la acetilación que en pacientes con VIH está reducido. La toxicidad de las hidroxilaminas es mayor contra linfocitos deplecionados de glutatión. Por otro lado, las hidroxilaminas pueden ser hapténizadas y ser covalentemente unidas a proteínas, inducir radicales tóxicos o liberar mediadores celulares. El cotrimoxazol es un problema especial dado que un 50% de los pacientes requieren modificación de su tratamiento tras una reacción. Muchos pueden tratarse con un fármaco alternativo; para el resto las opciones son la continuación del fármaco mediante el tratamiento de la reacción, la provocación con el fármaco tras su suspensión, y la desensibilización. El éxito en las pautas de desensibilización (inducción de tolerancia) parece más probable en regímenes de cinco o más días, en pacientes con CD4 bajos. En

nuestro estudio los pacientes se incluirían en un protocolo de "desensibilización" o reintroducción lenta, o de provocación según la sintomatología previa. El protocolo de desensibilización duraba seis días y se realizaba en el hospital. Se evaluaron 43 pacientes; 12 de ellos se sometieron a reprovocación controlada con el fármaco, y 10 de estos 12 pacientes toleraron la provocación. Se seleccionaron 33 pacientes (31 de ellos directamente, y los 2 que reaccionaron a la reprovocación) para someterse al protocolo de reintroducción lenta. En total, 32 de estos 33 toleraron el fármaco. De acuerdo con los resultados de nuestro estudio y de los restantes estudios previos, es muy importante realizar una evaluación alergológica para elegir el procedimiento más adecuado. Sin embargo, el mejor y más eficaz método de desensibilización no se ha determinado todavía. La desensibilización o la provocación con fármacos tuberculostáticos son necesarias cuando no se puede utilizar un tratamiento alternativo eficaz. Se han descrito protocolos de desensibilización esporádicos en pacientes con VIH con otros fármacos.

Palabras clave: Reacciones medicamentosas. Reintroducción. Desensibilización. Cotrimoxazol. VIH.

Adverse drug reactions are quite more common among patients with human immune deficiency virus (HIV) infection and full-blown AIDS than among other persons. Hypersensitivity to cotrimoxazole (trimetoprim + sulfametoxazole) in the context of therapy or prophylaxis of *Pneumocystis carinii* pneumonia is the most frequent adverse drug reaction in the context of HIV infection. The most usual signs include morbilliform exanthema with or without fever occurring seven to ten days after the institution of therapy. Severe cutaneous reactions may also occur occasionally, such as the Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatitis and/or interstitial pneumonitis. IgE-mediated reactions are an exception. Other drugs may also trigger adverse drug reactions in HIV-positive patients; among those that frequently induce adverse reactions are the sulfamides, aminopenicillins, isoniazide, rifampicin, clindamycin and dapsone. Other drugs have also been implicated in adverse drug reactions (e. g. phenytoin, pentamidine, valproate, phenobarbital, didanosine, 5-fluoro-cytosine, thiacetone, reverse transcriptase inhibitors and protease inhibitors)^{1,2}.

Pathogenesis of drug hypersensitivity in HIV-infected patients

*Immunologic factors*¹⁻³

The observation that HIV-infected patients can and do develop fever and skin reactions to chemically unrelated drugs might suggest that the pathogenesis of those reactions is not drug-dependent, but dependent on the underlying disease. The observed exanthemata show a considerable similitude to those seen with amoxycillin in Epstein-Bar virus (EBV) infection, suggesting an immunopathogenic effect of HIV or of other viruses such as cytomegalovirus (CMV) or EBV itself. Changes have been reported in the pharmacokinetics of a given drug in HIV+ patients; furthermore, increased drug- and drug metabolite-related toxicity has been observed in virus-infected cells. The basophils from HIV-positive patients show increased IgE-mediated histamine release. And still, no correlation has been found between these observations and drug hypersensitivity reactions. A Th-1 - Th-2 switch may be seen, which changes the cytokine release pattern, in HIV-positive patients. T-lymphocytes may be important in these patients: as the frequency of hypersensitivity reactions decreases as the disease progresses, the T-cells may indeed participate in adverse drug reactions, and their sensitivity might decrease with the progression of the disease. The increased frequency of hypersensitivity reactions among patients with CD4+ counts ranging between 50 and 350 cells/ μ l might be due to a number of metabolic and immunologic factors acquired in the course of HIV infection.

*Toxic and metabolic factors*¹⁻⁵

It has been put forward that the side effects occurring during therapy with cotrimoxazole and also with other drugs might be explained through the generation of toxic hydroxylamines. These metabolites are mainly generated in cytochrome P-450-induced hepatic microsomes, but they can also be produced in the monocytes and neutrophils through the action of the myeloperoxidase enzyme pathway. The cytochrome P-450 pathway is a complementary one in the metabolism of a number of drugs, and acetylation is quantitatively more important. Slow acetylators predominantly use the cytochrome P-450 pathway, and this leads to the accumulation of toxic metabolites such as hydroxylamines. Slow acetylation is more common among HIV-infected patients in whom demethylation is reduced while 8-

hydroxylation is increased. HIV-infected patients often receive polychemotherapy, and the coincident intake of enzyme-inducing drugs or of drugs that are metabolised through the cytochrome P-450 pathway may have an influence in hypersensitivity reactions.

Glutathione is an antioxidant co-factor in the acetylation pathway. The glutathione synthetase levels are reduced in HIV-infected patients, and the glutathione concentrations are consequently decreased³⁻⁵. Hydroxylamine cytotoxicity is more marked against glutathione-depleted lymphocytes than against cells with normal glutathione levels; furthermore, hydroxylamines may become haptenated and be covalently bound to proteins, then inducing toxic free radicals or the release of cell mediators.

Sulfamides are the drugs most frequently involved in adverse drug reactions in HIV-infected patients, in whom up to 80% levels of such reactions have been reported as compared to less than 5% among non-HIV+ patients³. Sulfamethoxazole (SMZ) is metabolised through acetylation to the stable metabolite N4-acetyl-SMZ (50-70%), and through the cytochrome P-450 pathway to 5-hydroxy-SMZ or to a reactive hydroxylamine. The acetylation phenotype, the glutathione deposits and the cytochrome P-450 may all influence the relative importance of these metabolic pathways in a given individual³. This might explain the peculiar characteristics of these reactions, which appear to be dose-dependent and sometimes do not appear upon challenge with the drug.

The cotrimoxazole problem

Cotrimoxazole is the drug of first choice for the therapy and prophylaxis of *Pneumocystis carinii* pneumonia and of cerebral toxoplasmosis⁶. Up to 50% of the patients who develop reactions with cotrimoxazole may be treated with an equally effective alternative drug that does not induce such a reaction. For the remainder of the cases, the available options are^{7,8-17}: (a) continuation of the drug ("treating through"), managing the reaction with corticosteroids and/or antihistamines, (b) challenge with the drug, and (c) desensitisation.

According to the results reported up to now, sulfamide hypersensitivity has been managed through these procedures with success rates ranging between 68% and 100%^{8,17}. This leads us not to be excessively conservative and to institute an allergologic intervention in these hypersensitivity reactions.

Success with the desensitisation protocols appears to be more likely with protocols extending over five or more

days in patients with low CD4⁺ counts. Cooperation with the Internal Medicine and Infectious Diseases specialists is important in achieving adequate patient selection and in establishing adequate approaches. The studies reported up to now evidence considerable differences in the inclusion and exclusion criteria and in the procedures applied (challenge or desensitisation, duration of the desensitisation protocol, interval between doses, etc.).

Most authors consider desensitisation to be better than the challenge procedures, because of the risk inherent in the latter and also because it is often not necessary to establish a certainty diagnosis through controlled drug challenge, as the symptoms are quite clear and repetitive. However, drug re-challenge might have an application in patients with very mild symptoms, with low CD4⁺ levels or with no clear relationship between the reaction and the intake of cotrimoxazole^{14,17}.

Both short and long desensitisation protocols have been described. The short ones appear to be better in the aspect of compliance, while the long ones are safer and more successful⁸⁻¹⁷. The choice of a short protocol should not be based only on the compliance aspect, but also on the need for rapid therapy of *P. carinii* pneumonia, while a long protocol should be chosen when prophylaxis is required.

In our own experience¹⁷, the inclusion criteria encompass those HIV⁺ patients with an adverse reaction to cotrimoxazole that mandates discontinuation of therapy, in the two following cases: (a) formal indication of cotrimoxazole therapy according to the current accepted guidelines for prevention of opportunistic infections in AIDS, and (b) patients referred for allergologic study and intervention by their Internal Medicine and/or Infectious Diseases specialists. Patients with the Stevens-Johnson syndrome or with severe visceral reactions were excluded. Based on the nature of the reactions as reported in the clinical files, the patients were included in a desensitisation protocol or in a re-challenge one.

All drugs that might negatively influence the protocol tolerance should be discontinued or substituted (drugs with hydroxylamine metabolites). The cases with the more severe reactions may be managed with premedication (patients with clear and severe reactions). This may also increase the success rate.

We have applied a 6-day protocol when *P. carinii* pneumonia prophylaxis was required, and a short one when immediate therapy was needed. As in the case of other reported protocols⁸⁻¹⁶, we also have achieved high success rates.

Our six-day protocol was as follows (based on the sulfamethoxazole dose): on the 1st day, 0.2 mg, 0.8 mg, 2.0 mg and 4.0 mg, with 45-minute intervals between successive doses; on the 2nd day, 8 mg and 12 mg, with a one-hour interval; on the 3rd day, 40 mg and 80 mg, with a one-hour interval; on the 4th day, 160 and 240 mg, also with a one-hour interval; on the 5th day, a single dose of 400 mg, and on the 6th day, a single dose of 800 mg. This last daily dose was then maintained. The protocol was administered on an in-hospital basis, with a 6-hour post-dosing control and observation period.

Up to now, 14 patients have undergone controlled challenge, and 12 of them have tolerated this. Those who did not, plus a further 33 patients, eventually tolerated the drug with a desensitisation protocol. One patient experienced a hypersensitivity reaction one week after the end of the desensitisation protocol. A short protocol was successfully applied in two cases.

According to the results achieved both in our own series and in other reported studies, it is very important to carry out an allergologic assessment in order to choose the most adequate procedure; the "safest and most effective" desensitisation protocol, however, still remains to be defined. Studies such as the one here presented, with large patient populations, increase the experience and the confidence in the results.

Sulfadiazine hypersensitivity has also been assessed and desensitisation, mainly in short protocols, has also been used, though less frequently than in the case of cotrimoxazole. The success of the desensitisation protocols¹⁷ depends on the chosen procedure, the selection of patients for premedication and for drug re-challenge, the withdrawal of possibly interfering drugs, a good clinical condition of the patient, and a close cooperation with the internists and infectologists, the latter being a *sine qua non* precondition.

Cotrimoxazole desensitisation allows us to avoid or circumvent the obstacles represented by hypersensitivity reactions in the prophylaxis and therapy of *Pneumocystis carinii* pneumonia.

The problem of tuberculostatic drugs

Desensitisation or re-challenge with these drugs becomes necessary when no effective alternative therapy is available. Rifampicin and isoniazide are the two drugs most often involved, and a number of successful desensitisation protocols have been reported.

References

1. Coopman SA, Johnson RA, Platt R, Stern RS. Cutaneous disease and drug reactions in HIV infection. *N Engl J Med* 1993; 328: 1670-1674.
2. Bayard PJ, Berger TG, Jacobson MA. Drug hypersensitivity reactions and human immunodeficiency virus disease. *J AIDS* 1992; 5: 1237-1257.
3. Koopmans, van der Ven AJAM, Vree TB, van der Meer JWM. Pathogenesis of hypersensitivity reactions to drugs in patients with HIV infection: allergic or toxic? *AIDS* 1995; 9: 217-222.
4. Carr A, Gross AS, Hoskins JM, Penny R, Cooper DA. Acetylation phenotype and cutaneous hypersensitivity to trimethoprim-sulfamethoxazole in HIV infected patients. *AIDS* 1994; 8: 333-337.
5. Staal FJT, Ella SW, Roeder M, Anderson MT, Herzenberg LA. Glutathione deficiency and human immunodeficiency virus infection. *Lancet* 1992; 339: 909-912.
6. USPHS/IDSA. Prevention of opportunistic infections working group. 1997 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. *MMWR* 1997; 46 (RR-12): 1-46.
7. Carr A. Role of desensitization of drug hypersensitivity in patients with HIV infection. *Drug Saf* 1997; 17: 119-126.
8. White MV, Haddad ZH, Brunner E, Sainz C. Desensitization to trimethoprim-sulfamethoxazole in patients with acquired immunodeficiency syndrome and *Pneumocystis carinii* pneumonia. *Ann Allergy* 1989; 62: 177-179.
9. Absar N, Daneshvar H, Beall G. Desensitization to trimethoprim-sulfamethoxazole in HIV-infected patients. *J Allergy Clin Immunol* 1994; 93: 1001-1005.
10. Gluckstein D, Ruskin J. Rapid oral desensitization to trimethoprim-sulfamethoxazole (TMP-SMZ): use in prophylaxis for *Pneumocystis carinii* pneumonia in patients with AIDS who were previously intolerant to TMP-SMZ. *Clin Infect Dis* 1995; 20: 849-853.
11. Kalanadhabhatta V, Muppidi D, Sahni H, Robles MD, Kramer M. Successful oral desensitization to trimethoprim-sulfamethoxazole in acquired immune deficiency syndrome. *Ann Allergy Asthma Immunol* 1996; 77: 394-400.
12. Nguyen MT, Weiss PJ, Wallace MR. Two day oral desensitization to trimethoprim sulfamethoxazole in HIV infected patients. *AIDS* 1995; 9: 573-575.
13. Belchí-Hernández J, Espinosa-Parra F. Management of adverse reactions to prophylactic trimethoprim-sulfamethoxazole in patients with human immunodeficiency virus infection. *Ann Allergy Asthma Immunol* 1996; 76: 355-358.
14. Moreno-Ancillo A, Cabañas R, Barranco P, Caballero MT, Muñoz ML, Martín Barroso JA, López Serrano MC. Allergic evaluation of adverse reactions to trimethoprim-sulfamethoxazole in patients with HIV (abstract). *Allergy* 1997; 52 (Suppl.37): 94.
15. Caumes E, Guernonprez G, Lecomte C, Katlama C, Bricaire F. Efficacy and safety of desensitization with sulfamethoxazole and trimethoprim in 48 previously hypersensitive patients infected with human immunodeficiency virus. *Arch Dermatol* 133: 465-469.
16. Demoly P, Messaad D, Sahla H, Fabre J, Faucherre V, André P, et al. Six hour trimethoprim sulfamethoxazole graded challenge in HIV infected patients. *J Allergy Clin Immunol* 1998; 102: 1033-1036.
17. Moreno-Ancillo A, López Serrano MC. Hypersensitivity reactions to drugs in HIV infected patients. Allergic evaluation and desensitization. *Clin Exp Allergy* 1998; 28 (Suppl 4): 57-60.