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BRIEF REPORT

Approach to establishing and evaluating clinical relevance of drugs interactions in HIV patients: 2009 update

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KEYWORDS
Drug interactions;
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Abstract
Objective: To update information on drug interactions in patients with HIV/AIDS.
Method: PubMed was used to review English and Spanish articles published between 1 July 2007 and 30 April 2009 on antiretroviral drug interactions in humans. The search included a review of interactions between commonly-used medications in patients with HIV/AIDS and references from articles considered to be relevant.
Results: Fifty two new interactions were identified having to do with CYP3A4 metabolism and competition for intestinal absorption. New pharmacokinetic interactions were identified for medications that were already on the market, and we report interactions for drugs that were recently introduced: Tipranavir, Fosamprenavir, Darunavir, Raltegravir, Maraviroc and Etravirine.
Conclusions: There is evidence of 52 new interactions between medications using metabolic routes in the CYP450 enzymatic system, and an explanation is given for others in the intestinal absorption process.

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PALABRAS CLAVE
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VIH/sida;
Interacciones farmacocinéticas

Aproximación para establecer y evaluar la relevancia clínica de las interacciones medicamentosas en pacientes infectados con virus de la inmunodeficiencia humana: actualización 2009

Resumen

Objetivo: Actualizar información sobre interacciones medicamentosas en pacientes con VIH/sida.

Método: Se realizó una revisión en PubMed de artículos publicados en inglés y español entre el 1 de julio de 2007 y el 30 de abril de 2009 sobre interacciones de antirretrovirales en humanos. La búsqueda fue complementada con la revisión de interacciones de medicamentos utilizados frecuentemente en pacientes con VIH/sida y de referencias de artículos considerados relevantes.

Resultados: Se encontraron 52 nuevas interacciones relacionadas con el metabolismo por el CYP3A4 y la competencia por la absorción intestinal, también se encontraron nuevas interacciones de tipo farmacocinético para medicamentos que ya estaban en el mercado, y se reportaron interacciones para medicamentos recientemente comercializados: tipranavir, fosamprenavir, darunavir, raltegravir, maraviroc y etravirina.

Conclusiones: Hay evidencia de 52 nuevas interacciones, encontrándose medicamentos que utilizan vías metabólicas en el sistema enzimático CYP450, y se aclaran otras del proceso de absorción intestinal.

Introduction

Because the use of highly active antiretroviral (ARV) therapy includes 3 or more ARV drugs, it is associated with a greater likelihood of drug interactions (DI), which can lead to safety and effectiveness problems. In the last two years 6 new ARV agents have been commercialised which are part of the second or third line of treatment or rescue schemes. Due to the pharmacokinetic properties of ARV drugs, their therapeutic use could be thought to be accompanied by unidentified or unreported DI.[1] In 2007 a review was published about DI with ARV drugs which had been identified in Pubmed between January 1996 and June 2007, and in which it was possible to access the complete text of 296 articles. In the case of clinically relevant pharmacokinetic interactions, nearly 80%were related to changes in systemic clearance (due to the systemic inhibition or induction of the metabolic activity of the CYP3A4 isoform), approximately 15%to changes in bioavailability (changes in gastrointestinal pH and presystemic clearance [mediated by intestinal CYP3A4]) or in P-glycoprotein activity.[1] To classify the clinical relevance of the DI, a proposed classification was used based on the severity and probability of their occurrence.[2]

Since most DI with ARV drugs are clinically relevant, it was considered appropriate to update this review with a new search until April 2009, using the same search strategy. In this respect, the aim of this work was to update the previously systematised information about DI in patients with HIV/AIDS, verifying how the proposal worked to define and evaluate the clinical relevance of the interactions stated previously by the authors.

Method

A search of PubMed was performed for articles about ARV drug interactions in humans published in English and Spanish between 1 July 2007 and 30 April 2009. The search strategy was that the title and abstract had to include "drug interactions and antiretroviral agents". The search was complemented with a review, over the same period, of the clinically relevant DI in patients with HIV/AIDS defined in the updated treatment guidelines for adult and teenage patients,[3] and of the references in the articles which were considered relevant. The study followed the classification proposed by the authors[2] in 2007 to define and assess the clinical relevance of DI based on the severity and probability of their occurrence.

Results

Among the 46 new DI due to enzyme inhibition by protease inhibitors (PI), 41.3%were at level 2 (high risk) of clinical relevance, and were mainly (42.1%) related to atazanavir, ritonavir and lopinavir (Table 1). Table 2 shows the DI related to the use of nucleoside and non-nucleoside analogue transcriptase inhibitors.

In the case of drug-disease interactions, new information was found regarding the higher likelihood of the appearance of insulin resistance syndrome associated with the use of PI and non-nucleoside analogue reverse transcriptase inhibitors (relevance level 2: high). This is attributed to an increase in lipidaemia, visceral adiposity and hypertriglyceridaemia. Thus, it is recommended that

Table 1 New interactions due to enzyme inhibition by protease inhibitors

Pharmacological group or drugs affected	Drug interaction	Clinical relevance: level of risk	Comments, suggestions
Simvastatin[4]	ATV	2: high	CYP3A4 inhibition by ATV drug, increase in levels and toxicity of simvastatin, increasing risk of rhabdomyolysis and acute kidney failure Recommendation: change dose
Efavirenz, paclitaxel, losartan, dyclophenac, phenytoin, amitryptyline, omeprazon, fluoxetine, warfarin, ibuprofen, glibenclamide[5]	Ritonavir, nelfinavir	3: medium	Increase in metabolism of drugs metabolised by CYP2B6, CYP2C8, ICYP2C9, CYP2C19. Recommendation: change dose
Tenofovir[6]	ATV, LPV, DRV, SQV, FPV	2: high	Coadministration of TDF with ATV, LPV, DRV and SQV increases Cp of tenofovir, while FPV decreases it. Recommendation: change the treatment guidelines according to combination
Warfarin sodium[7]	LPV/r	3: medium	LPV/r can increase the metabolism of S enantiomer of warfarin by CYP2C9; likewise, the R enantiomer by stimulating CYP1A2. Recommendation: monitor INR and change the dose of anticoagulant
Minocicline[8]	ATV	3: medium	Reduction in levels and effect of ATV drugs, interference in enterohepatic recirculation through alterations in bacterial flora Recommendation: monitor and adjust dose
Etravirine[9]	ATV/r	1: very high	Cp of ATV drugs is reduced 38% Avoid joint administration
	Tipranavir	1: very high	Cp of etravirine is reduced 75% Avoid joint administration
	FPV/r	1: very high	Cp of FPV is reduced 77% Avoid joint administration
	LPV/r	2: high	Cp of etravarine can increase by 85%en HIV patients Recommendation: be careful with coadministration
	DRV/r	3: medium	Cp of etravirine is reduced 50% Recommendation: can be given together without change in dose
Raltegravir[9]	Tipranavir	2: high	Cp of raltegravir is reduced when used together with Tipranivir
	ATV	2: high	Cp of raltegravir increased when administered together with ATV drugs
Maraviroc[9]	All PI	2: high	PI increase the plasma levels of maraviroc. Recommendation: reduce the dose of maraviroc by up to 50%

ATV indicates atazanavir; Cp, concentration in plasma; DRV, darunavir; FPV, fosamprenavir; INR, international normalised ratio; LPV, lopinavir; PI, protease inhibitors; r, ritonavir; SQV, saquinavir; TDF, tenofovir; HIV, human immunodeficiency virus.

Table 2 New interactions due to the use of nucleoside and non-nucleoside analogue transcriptase inhibitors

Pharmacological group or drugs affected	Drug interaction	Clinical relevance risk	Comments, suggestions
Leflunomide, methotrexate, aminopterin, pirimetamin trimetoprim[10]	Stavudine	1: very high	It inhibits hepatocyte mitochondrial DNA and produces liver damage. Avoid association and supplement with uridine derivatives
Lamivudine[11]	Apricitabine	2: high	It inhibits cell activation of apricitabine and other deoxycytidine analogues. Avoid this association
Raltegravir[9]	Efavirenz	2: high	Cp of raltegravir is reduced when coadministered with efavirenz

Cp indicates concentration in plasma; DNA, deoxyribonucleic acid.

monitoring is carried out every 6 months of the lipid profile of patients who start or are undergoing treatment with these drugs.[12]

Discussion

With the increased use of ARV drugs, in particular PI and reverse transcriptase inhibitors, and the arrival of new ARV drugs it is becoming more evident that they are metabolised via common pathways of the CYP450 enzyme complex, which leads to an increased probability of new interactions due to the inhibition or stimulation of its isoforms, with different levels of risk and clinical relevance.

More original studies were found about pharmacokinetic DI which go more deeply into the P-glycoprotein transporter and efflux pumps activated by enzymes, which can be blocked or stimulated by ARV agents such as atazanavir, which reduces their plasma levels with the concomitant use of minocycline due to interfering with enterohepatic recirculation. New studies have appeared which investigate DI in models of cellular permeability ($CaCO_2$ cells).[6]

Atazanavir increases the effective plasma concentrations of other ARV drugs, such as tenofovir, raltegravir and araviroc, while etravirine produces a decrease. The probability of clinically-relevant high risk DI is also increased when atazanavir is combined with simvastatin, so knowing this can avoid phenomena as severe as acute kidney failure secondary to rhabdomyolysis.

The authors recommend ongoing reviews of the appearance of new interactions with ARV drugs, evaluating the scientific evidence and classifying their level of clinical relevance because ARV therapy is one of the most dynamic in terms of launching new products onto the market.[3]

Conflict of interest

The authors affirm that they have no conflicts of interest.

References

1. Amariles P, Giraldo NA, Faus MJ. Interacciones medicamentosas en pacientes infectados con el VIH: aproximación para establecer y evaluar su relevancia clínica. Farm Hosp. 2007;31:283-302.
2. Amariles P, Giraldo NA, Faus MJ. Interacciones medicamentosas: aspectos generales y aproximación para establecer y utilizar su relevancia clínica. Med Clin (Barc). 2007;129:27-35.
3. Panel on Antiretroviral Guidelines for Adult and Adolescents. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Department of Health and Human Services. November 3, 2008; 1-146 [accessed 3/15/2009]. Available from: http://www.aidsinfo.nih.gov/Content-Files/AdultandAdolescentsGL.pdf
4. Schmidt GA, Hoehns JD, Purcell JL, Friedman RL, Elhawi Y. Severe rhabdomyolysis and acute renal failure secondary to concomitant use of simvastatin, amiodarone, and atazanavir. J Am Board Fam Med. 2007;20:411-6.
5. Dixit V, Hariparsad N, Li F, Desai P, Thummel KE, Unadkat JD. Cytochrome P450 enzymes and transporters induced by anti-human immunodeficiency virus protease inhibitors in human hepatocytes: Implications for predicting clinical drug interactions. Drug Metab Dispos. 2007;35:1853-9.
6. Tong L, Phan TK, Robinson KL, Babusis D, Strab R, Bhoopathy S, et al. Effects of human immunodeficiency virus protease inhibitors on the intestinal absorption of tenofovir disoproxil fumarate in vitro. Antimicrob Agents Chemother. 2007;51:3498-504.
7. Hughes CA, Freitas A, Miedzinski LJ. Interaction between lopinavir/ritonavir and warfarin. CMAJ. 2007;177:357-9.
8. DiCenzo R, Peterson DR, Cruttenden K, Mariuz P, Rezk NL, Hochreiter J, et al. Effects of minocycline and valproic acid coadministration on atazanavir plasma concentrations in human immunodeficiency virus-infected adults receiving atazanavir-ritonavir. Antimicrob Agents Chemother. 2008;52:3035-9.
9. Aberg JA. Drug-drug interactions with newer antiretroviral agents. Top HIV Med. 2008;16:146-50.
10. Setzer B, Lebrecht D, Walker UA. Pyrimidine nucleoside depletion sensitizes to the mitochondrial hepatotoxicity of the reverse transcriptase inhibitor stavudine. Am J Pathol. 2008;172:681-90.
11. Holdich T, Shiveley LA, Sawyer J. Effect of Lamivudine on the plasma and intracellular pharmacokinetics of apricitabine, a novel nucleoside reverse transcriptase inhibitor, in healthy volunteers. Antimicrob Agents Chemother. 2007;51:2943-7.
12. Grunfeld C. Insulin resistance in HIV infection: drugs, host responses, or restoration to health? Top HIV Med. 2008;16:89-93.