# Carbamazepine–Indinavir Interaction Causes Antiretroviral Therapy Failure

Patricia WH Hugen, David M Burger, Kees Brinkman, Hadewych JM ter Hofstede, Rob Schuurman, Peter P Koopmans, and Yechiel A Hekster

**OBJECTIVE:** To report a case of antiretroviral therapy failure caused by an interaction between carbamazepine and indinavir.

**CASE SUMMARY:** A 48-year-old HIV-positive white man was treated with antiretroviral triple therapy, consisting of indinavir, zidovudine, and lamivudine. His HIV-RNA (viral load) became undetectable (<400 copies/mL) less than two months after this therapy was started; this was confirmed one month later. Shortly after the start of antiretroviral therapy, the patient developed herpes zoster, which was treated with famciclovir. Tramadol was initially prescribed for postherpetic neuralgia; however, this was substituted with carbamazepine due to insufficient analgesic effect. Indinavir plasma concentrations decreased substantially during carbamazepine therapy. Carbamazepine was stopped after 2.5 months and, two weeks later, the HIV-RNA was detectable ($6 \times 10^3$ copies/mL). Resistance for lamivudine was observed in that blood sample; resistance for zidovudine might have been present, and resistance to indinavir was not detected. A few months later, a further increase of the HIV-RNA occurred ($300 \times 10^3$ copies/mL), after which the therapy was switched to a new antiretroviral regimen containing nevirapine, didanosine, and stavudine.

**DISCUSSION:** Physicians may prescribe carbamazepine for HIV-infected patients to treat seizures or postherpetic neuralgia, which are complications of opportunistic infections such as herpes zoster or toxoplasmosis. Carbamazepine is a potent enzyme inducer, predominantly of the CYP3A enzyme system, while HIV-protease inhibitors such as indinavir are substrates for and inhibitors of CYP3A. Therefore, an interaction between these drugs could be expected. A low dose of carbamazepine (200 mg/d) and the usual dose of indinavir (800 mg q8h) in our patient resulted in carbamazepine concentrations within the therapeutic range for epilepsy treatment; indinavir concentrations dropped substantially. The virologic, resistance, and plasma drug concentration data, as well as the chronology of events, are highly indicative of antiretroviral treatment failure due to the interaction between carbamazepine and indinavir.

**CONCLUSIONS:** Concomitant use of carbamazepine and indinavir may cause failure of antiretroviral therapy due to insufficient indinavir plasma concentrations. Drugs other than carbamazepine should be considered to prevent this interaction. Amitriptyline or gabapentin are alternatives for postherpetic neuralgia; valproic acid or lamotrigine are alternatives for seizures. When alternate drug therapy is not possible, dosage adjustments, therapeutic drug monitoring, and careful clinical observation may help reduce adverse clinical consequences.

**KEY WORDS:** antiretroviral therapy, indinavir, carbamazepine, cytochrome P450 enzymes.

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Indinavir is one of the HIV-protease inhibitors that are metabolized by the hepatic CYP3A4 enzyme system. Concomitant use of indinavir with strong inducers of CYP3A, such as carbamazepine or rifampin, may lower indinavir plasma concentrations. Low indinavir concentrations are associated with failure of antiretroviral therapy.[1] Therefore, close monitoring of the efficacy of the antiretroviral regimen that includes indinavir or substituting the interacting drug with another drug within the same therapeutic group is warranted. Protease inhibitors inhibit CYP3A4 and can cause toxicity by increasing the plasma concentrations of CYP3A4 substrates.[1,2]

Although the introduction of protease inhibitors has provided substantial antiretroviral potency in the treatment of HIV, it also has increased the potential for drug–drug interactions. In practice, interacting drugs are often combined because HIV-infected patients need prophylaxis or treatment for a wide range of opportunistic infections[3,4] or for complications such as adverse effects of antiretroviral treatment. We report a case of antiretroviral therapy failure in a patient who received interacting drugs during his HIV treatment.

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## CASE REPORT

A 48-year-old white man (90 kg) tested HIV-positive in April 1997. At that time, he had an HIV-RNA (viral load) of $100 \times 10^3$ copies/mL and a CD4+ cell count of $300 \times 10^6$/L. Figure 1 shows all relevant data, in chronological ordered, of what happened thereafter. The patient started triple therapy consisting of indinavir 800 mg q8h, lamivudine 150 mg bid, and zidovudine 200 mg tid in May (HIV-RNA $200 \times 10^3$ copies/mL). After one month, the HIV-RNA had dropped from $200 \times 10^3$ to $2 \times 10^3$ copies/mL. Three weeks later, he stopped therapy because of personal reasons and did not resume antiretroviral therapy for five months. At the end of November, he restarted the same triple combination. At that time, the HIV-RNA was $70 \times 10^3$ copies/mL with a CD4+ cell count of $190 \times 10^6$/L. After two months of therapy, the HIV-RNA was undetectable (<400 copies/mL), which was confirmed one month later. The CD4+ cell counts at these times were 340 and $400 \times 10^6$/L, respectively. In the first week of April 1998, the HIV-RNA was detectable again ($6 \times 10^3$ copies/mL), with a further increase to $300 \times 10^3$ copies/mL in July. The CD4+ cell count had decreased to $200 \times 10^6$/L at that time. In August, a new regimen was started containing nevirapine, didanosine, and stavudine, which produced satisfactory response; after one month, the HIV-RNA was $3 \times 10^3$ copies/mL and the CD4+ cell count was $420 \times 10^6$/L.

During the second period of triple therapy (December 1997), the patient developed herpes zoster. He was first treated with famciclovir; tramadol was added to treat the postherpetic neuralgia. Tramadol was discontinued because the patient did not experience adequate analgesia; carbamazepine 200 mg/d was started in mid-January 1998. Carbamazepine was discontinued at the end of March; tramadol was restarted due to insufficient clinical response to carbamazepine and complaints of drowsiness.

Indinavir plasma concentrations are monitored routinely in patients treated in our hospital. Concentrations are determined by a validated RP-HPLC method,[5] after which the concentration ratio is calculated by dividing each patient's indinavir plasma concentration by the average value in a reference population at the same time point after ingestion (reference population, n = 14, $AUC_{0\text{-}8h}$ 19.3 mg/L•h, maximum concentration 8.6 mg/L, minimum concentration 0.14 mg/L).[1] Before carbamazepine was started, the indinavir concentrations were slightly below the lower limit of the mean population curve ± 2 SEM. The two samples drawn during carbamazepine therapy were much lower (25% and 4% of the mean population values). Carbamazepine concentrations, measured by fluorescence polarization immunoassay technology (Abbott, Chicago, IL), were within the therapeutic window for epilepsy treatment, which is probably higher than expected for the low dose given to our patient. Approximately two weeks after carbamazepine was discontinued, the indinavir concentration was higher than the mean; just before the indinavir triple combination was stopped, the plasma concentration was again at the lower limit of the mean curve ± 2 SEM. Looking at the actual plasma concentrations, the following comparison can be made: in the sample in 1997, which was taken 4.5 hours after ingestion, the indinavir concentration was 0.45 mg/L (reference population 0.88 mg/L). No comparison with other samples at this time point can be made. Two samples were drawn at ±2.75 hours after ingestion: the first, before carbamazepine was started, was 2.0 mg/L (reference population 3.3 mg/L), the second, during carbamazepine therapy (3 wk), was 0.9 mg/L. Three samples were drawn at ±3.75 hours after ingestion (2.2 times lower than before carbamazepine). The concentration before carbamazepine was 1.1 mg/L (reference population 1.6 mg/L), the one during carbamazepine (7 wk) was 0.07 mg/L (16 times lower), and the third, shortly after withdrawal of carbamazepine, was 2.6 mg/L (2.4 times higher than the concentration before carbamazepine). These data show that comparing plasma data at similar intervals after ingestion results in lower plasma concentrations (up to 16 times lower) when carbamazepine is administered. Even though the community pharmacist notified the physician of the possible interaction between carbamazepine and indinavir and the indi-

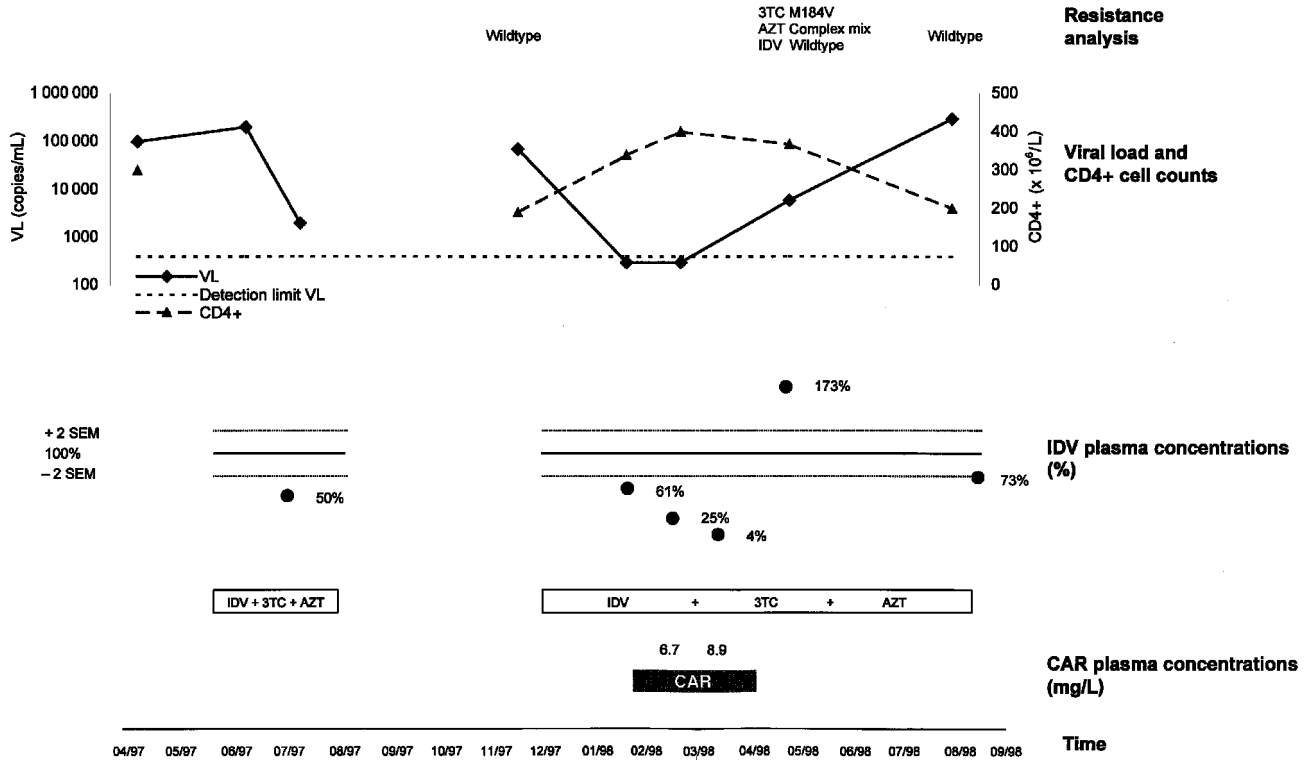


**Figure 1.** Chronologic overview of HIV-RNA (viral load), CD4+ cell counts, resistance data, drug use, indinavir plasma concentrations compared with mean population data (n = 14), and carbamazepine plasma concentrations. 3TC = lamivudine; AZT = zidovudine; CAR = carbamazepine; IDV = indinavir; VL = viral load (HIV-RNA).

navir concentrations were low during carbamazepine therapy, no dosage adjustment of indinavir was made.

Based on the low indinavir concentrations and the consecutive increase in HIV-RNA under triple therapy pressure, resistance was expected. Genotypic resistance analysis was performed using an automated sequencer (ABI 377, PE Biosystems, Foster City, CA) and Big-Dye-terminator chemistry (PE Biosystems). Population sequencing of the entire protease gene and of the RT gene from amino acid 1 to approximately 300 was performed using polymerase chain reaction amplified genome fragments derived from plasma virus RNA.[6] The baseline serum samples (November 1997), as well as those obtained in April 1998 (HIV-RNA $6 \times 10^3$ copies/mL) and July 1998 (HIV-RNA $300 \times 10^3$ copies/mL), were analyzed.

The virus was completely wildtype for lamivudine, zidovudine, and indinavir in November 1997. However, in April 1998 the lamivudine resistance mutation (M184V) was detected as a mixture with the wildtype, and for zidovudine a complex heterogenic genotype was observed at codon 215, among which the resistance mutation might have been present. No resistance mutations of indinavir were detected. In July 1998, no resistance mutations of lamivudine, zidovudine, or indinavir were detected.

During the use of indinavir, our patient was using other medications; however, he was receiving only oxazepam and carbamazepine when the indinavir plasma concentrations were very low (February and March 1998). Oxazepam was used the whole time the patient was taking indinavir except August 1998; oxazepam is not expected to lower indinavir concentrations. Other drugs that were used concomitantly with indinavir were an amitriptyline analog (June 1997), temazepam (June 1997, April and August 1998), and tramadol (January and April 1998). None of these drugs lower indinavir concentrations, which is reflected in the concentration ratios.[2]

In addition to the insufficient indinavir plasma concentrations during carbamazepine therapy, poor compliance could be an explanation for the treatment failure. For that reason, a detailed analysis on compliance was performed: the AIDS-specialist nurse estimated that the patient was compliant after an extensive interview; the physician believed the patient was compliant; pharmacy records in combination with prescription data and the interview with the patient did not suggest noncompliance; no specific notes about noncompliance were found in the medical record; plasma concentrations of indinavir were detectable; and ingestion times documented on the plasma sample collection forms showed differences in ingestion times over the follow-up period, indicating that the patient reported real ingestion times. Based on these data, there was no reason for us to doubt the patient's compliance, except for missing a dose approximately once a month.

The interaction was probable according to the Naranjo[7] scale; however, four of the 10 items on the scale were not applicable to this case report.

## Discussion

Carbamazepine is associated with numerous interactions when given concomitantly with other drugs[8]; however, carbamazepine concentrations often are the only ones closely monitored.

Carbamazepine is predominantly metabolized by CYP3A4; CYP2C9 and CYP1A2 play a less important role. The CYP3A4 route is responsible for the production of the active metabolite carbamazepine-10,11-epoxide.

Inhibition of CYP3A4 by drugs such as ketoconazole, cimetidine, macrolide antibiotics, and HIV-protease inhibitors may increase carbamazepine concentrations into the toxic range. We suspected this in our patient when he reported drowsiness and when his carbamazepine concentrations were in the upper half of the therapeutic range for epilepsy, although a low dose of carbamazepine had been prescribed.

Carbamazepine can have a strong effect on plasma concentrations of certain drugs due to induction of CYP3A and possibly other cytochrome P450 subtypes. Concentrations of indinavir in our patient were decreased to 25% and 4% of the population values at two consecutive measurements; without carbamazepine, these ratios were approximately within the normal range or higher. HIV-protease inhibitors are predominantly metabolized by CYP3A4; CYP2D6 and CYP2C9 contribute to the metabolism as well.[9] Inducers of these enzymes, such as carbamazepine, may therefore produce subtherapeutic protease inhibitor concentrations.

When indinavir concentrations were decreased in our patient, only two-drug therapy was given, which appeared to be insufficient to fully suppress the virus, allowing lamivudine resistance to develop. It has been reported[10-12] that with a rise in the HIV-RNA resistance for reverse transcriptase inhibitors occurs earlier than it does for protease inhibitors. This may be due to the large selective benefit that occurs with the lamivudine M184V mutation compared with resistance mutations observed with protease inhibitors. Once the M184V mutation appears, the mutated virus has a 1000-fold selective benefit compared with the wildtype virus, while for indinavir, single or double mutations do not appear to result in a measurable reduction in susceptibility.[13]

Our patient developed herpes zoster shortly after starting highly active antiretroviral therapy, which has been previosuly described.[3] After the acute treatment of the infection, the HIV-RNA was undetectable; therefore, the herpes infection does not explain the increased HIV-RNA that developed a few months later.

If we assume that the patient complied with the antiretroviral regimen, significantly lower indinavir concentrations, caused by the interaction between carbamazepine and indinavir, is the most likely explanation for the increased HIV-RNA and the development of lamivudine resistance. The question here is what would be the optimal treatment for postherpetic neuralgia for a patient on combination antiretroviral therapy containing protease inhibitors. The same question applies for HIV-infected patients who have seizures due to, for example, toxoplasmosis infection. Carbamazepine therapy is often considered an option but, based on what occurred in our patient, that may not be the best choice. Based on the data presented in this case report and taking into account what can be expected when carbamazepine is given with protease inhibitors, the combination of these drugs should be avoided. Pharmacokinetic studies are needed to establish whether it is feasible to overcome subtherapeutic indinavir concentrations by starting with higher indinavir and lower carbamazepine dosages, and to make further dosage adjustments based on therapeutic drug monitoring. However, clinicians should first choose alternatives for carbamazepine. Table 1 lists several treatment options for postherpetic neuralgia and

epilepsy and the possible interactions of these agents with protease inhibitors. Based on the data in this table, amitriptyline or gabapentin can be used for postherpetic neuralgia, and valproic acid or lamotrigine can be used as anticonvulsants; therapy should be monitored for toxicity of amitriptyline and efficacy of valproic acid or lamotrigine. There are a few other options (e.g., nortriptyline or aspirin for postherpetic neuralgia or gabapentin for epilepsy), but clinical experience and proof of efficacy are limited or the risk of interaction is unclear.

**Table 1.** Carbamazepine and Alternatives for Treatment of Postherpetic Neuralgia or Epilepsy in HIV-Infected Patients Receiving HIV-Protease Inhibitors

| Drug | Interaction with Protease Inhibitors | Responsible System | Management | Efficacy PHN | Reference |
|---|---|---|---|---|---|
| Postherpetic neuralgia | | | | | |
| carbamazepine | ritonavir, saquinavir, nelfinavir, indinavir | induction of CYP3A4 by carbamazepine, inhibition of CYP3A4 by protease inhibitors | consider substitution for carbamazepine, monitor protease inhibitor efficacy, monitor carbamazepine toxicity | inconclusive | 2,14-17 |
| amitriptyline | ritonavir | inhibition of CYP2D6 by ritonavir | monitor amitriptyline toxicity, consider dose reduction of amitriptyline | good | 2,16-20 |
| nortriptyline | ritonavir | inhibition of CYP2D6 by ritonavir | monitor nortriptyline toxicity, consider dose reduction of nortriptyline | good | 2,16 |
| capsaicin | no | topical application | no specific requirements | moderate | 18,21,22 |
| acetylsalicylic acid | no | topical application | no specific requirements | good | 23,24 |
| gabapentin | no | excreted unchanged in urine | no specific requirements | good | 8,20,25 |
| tramadol | ritonavir | inhibition of CYP2D6 by ritonavir | monitor tramadol toxicity and efficacy | inconclusive | 2,20,26,27 |
| oxycodone | ritonavir | inhibition of CYP2D6 and 3A by ritonavir | monitor oxycodone toxicity | good | 16,28-30 |
| vincristine (iontophorese) | ritonavir, saquinavir, indinavir, nelfinavir | inhibition of CYP3A by protease inhibitors | monitor vincristine toxicity | inconclusive | 2,22,27 |
| clomipramine | ritonavir | inhibition of CYP2D6 by ritonavir, inhibition of CYP2D6 by clomipramine | monitor clomipramine toxicity, monitor ritonavir toxicity | moderate | 2,26,30 |
| Epilepsy | | | | | |
| carbamazepine | ritonavir, saquinavir, nelfinavir, indinavir | induction of CYP3A4 by carbamazepine, inhibition of CYP3A4 by protease inhibitors | consider substitution for carbamazepine, monitor protease inhibitor efficacy, monitor carbamazepine toxicity | | 2,31 |
| valproic acid | ritonavir | induction of glucuronyl transferase by ritonavir | monitor valproic acid efficacy | | 2,32 |
| lamotrigine | ritonavir | induction of glucuronyl transferase by ritonavir | monitor lamotrigine efficacy | | 2,27,32 |
| phenytoin | ritonavir, saquinavir, indinavir, nelfinavir | induction of CYP3A and 2D6 by phenytoin, inhibition of CYP2C by ritonavir | monitor protease inhibitor efficacy, monitor phenytoin toxicity, consider substitution for phenytoin | | 2,30,31 |
| phenobarbital | ritonavir, saquinavir, indinavir, nelfinavir | induction of CYP3A by phenobarbital | monitor protease inhibitor efficacy, consider substitution for phenobarbital | | 2 |
| primidone | ritonavir, saquinavir, indinavir, nelfinavir | primidone → phenobarbital induction of CYP3A by primidone/phenobarbital | monitor protease inhibitor efficacy, consider substitution for primidone | | 30,31 |
| ethosuximide | ritonavir | inhibition of CYP3A and 2C by ritonavir | monitor ethosuximide toxicity, consider dose reduction of ethosuximide | | 27,30,31 |
| felbamate | ritonavir, saquinavir, indinavir, nelfinavir | induction of CYP3A by felbamate | monitor efficacy of protease inhibitors | | 31 |
| clonazepam | ritonavir, saquinavir, indinavir, nelfinavir | inhibition of CYP3A by protease inhibitors | monitor clonazepam toxicity | | 2 |
| diazepam | ritonavir, saquinavir, indinavir, nelfinavir | inhibition of CYP2C and 3A by ritonavir, inhibition of CYP3A | contraindicated, monitor diazepam toxicity, consider substitution for diazepam | | 2,32 |
| topiramate | ritonavir | inhibition of CYP2C19 by ritonavir? | monitor topiramate toxicity | | 30,31 |
| tiagabine | ritonavir, saquinavir, indinavir, nelfinavir | inhibition of CYP3A by protease inhibitors | monitor tiagabine toxicity | | 31 |
| gabapentin | no | excreted unchanged in urine | no specific requirements | | 8,31 |
| vigabatrine | no | excreted unchanged in urine | no specific requirements | | 8,31 |

## Summary

The interaction between carbamazepine and indinavir in our patient significantly lowered indinavir plasma concentrations, which are assumed to be subtherapeutic. This interaction apparently caused insufficient viral suppression, resulting in an increase in HIV-RNA and the development of lamivudine resistance. When carbamazepine was discontinued and indinavir concentrations returned to normal, the HIV-RNA still increased. These results show that carbamazepine and indinavir should not be combined. This, theoretically, also applies for the other HIV-protease inhibitors.

Pharmacokinetic studies are needed to establish whether it is feasible to overcome subtherapeutic indinavir concentrations in this combination therapy by starting with a higher indinavir dosage and a lower carbamazepine dosage, and to make further dosage adjustments based on therapeutic drug monitoring. However, replacing the interacting drug with a drug that has a lower interaction risk is preferred. Carbamazepine might be substituted for gabapentin or amitriptyline in the treatment of postherpetic neuralgia; valproic acid or lamotrigine are alternatives for carbamazepine if an anticonvulsant is needed.

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EXTRACTO

**OBJETIVO:** Informar el caso de fracaso de terapia antiretroviral causada por la interacción entre carbamazepina y el inhibitor de proteasa indinavir.

**RESUMEN DEL CASO:** Un hombre de 48 años de edad infectado con el VIH, estaba recibiendo tratamiento antiretroviral triple que consistía de zidovudina, lamivudina, e indinavir. Con este régimen, la carga viral se hizo no-detectable (<400 copias/mL) en menos de dos meses de tratamiento. Poco después de haber comenzado la terapia antiretroviral el paciente desarrolló infección por herpes zoster, la cual fue tratada con famciclovir. Luego de este episodio, recibió tramadol para neuralgia post-herpética, pero fue sustituída por carbamazepina debido a una respuesta analgésica inadecuada. Durante el período que el paciente recibió carbamazepina, la concentración de indinavir disminnuyó sustancialmente. Luego de 2.5 meses de tratamiento, la carbamazepina fue descontinuada, y dos semanas más tarde la carga viral (VIH-RNA) era detectable ($6 \times 10^3$ copias/mL). Se detectó resistencia a lamivudina, mientras que resistencia a indinavir no fue detectada. Unos meses más tarde se observó un aumento adicional en la carga viral ($300 \times 10^3$ copias/mL), y el paciente fue comenzado en otro régimen antiretroviral.

**DISCUSIÓN:** Es posible que pacientes infectados con el VIH desarrollen neuralgia post-herpética como una complicación asociada a infección por los virus de herpes zoster o toxoplasma, infecciones oportunistas comunes en estos pacientes. También pueden recibir carbamazepina debido a que padecen de desórdenes convulsivos. La carbamazepina es un inductor potente de enzimas hepáticas, en particular del sistema CYP3A. El indinavir es a su vez sustrato para el metabolismo por este sistema, a la vez que posee la capacidad de inhibir el CYP3A4. Es de esperarse que una interación entre estos medicamentos pueda ocurrir. En el caso descrito, una dosis baja de carbamazepina (200 mg po qd) y la dosis usual de indinavir (800 mg po q8h), resultó en unas concentraciones antiepilépticas adecuadas para carbamazepina, mientras que las concentraciones de indinavir disminuyeron sustancialmente. En este caso, la resistencia viral, los datos de concentraciones plasmáticas de los medicamentos, y la cronología de los eventos son altamente indicativos de un fracaso de la terapia antiretroviral debido a la interacción entre indinavir y carbamazepina.

**CONCLUSIONES:** El uso concomitante de indinavir y carbamazepina puede causar que la terapia antiretroviral no sea efectiva, debido a la disminución en la concentración plasmática de indinavir. Para evitar que esto ocurra, se debe considerar el no utilizar carbamazepina. Se sugieren amitriptilina y gabapentin como alternativas para el tratamiento de neuralgia post-herpética, y el uso de ácido valpróico o lamotrigine para desórdenes convulsivos. Si utilizar estas alternativas no es posible, entonces el seguimiento terapéutico de las concentraciones y ajustes en dosis correspondientes son recomendados para disminuir la posibilidad de efectos no deseables y sus consecuencias.

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RÉSUMÉ

**OBJECTIF:** Signaler le cas d'un échec à la thérapie antirétrovirale causé par une interaction entre la carbamazépine et l'indinavir, un inhibiteur de la protéase du VIH.

**RÉSUMÉ DU CAS:** Un homme séropositif âgé de 48 ans a été traité avec une triple thérapie antirétrovirale composée d'indinavir, de zidovudine, et de lamivudine; avec cette thérapie, la charge virale du patient est devenue non discernable (<400 copies/mL) en moins de deux mois. Ceci a été confirmé un mois plus tard. Peu de temps après le début de la thérapie antirétrovirale, le patient a développé une infection à l'herpes zoster qui a été traitée avec du famciclovir. Dans un premier temps, le tramadol a été prescrit pour la névralgie postherpétique; cependant, il a été remplacé subséquemment par de la carbamazépine dû à un effet analgésique insuffisant. Durant le traitement avec la carbamazépine, les concentrations plasmatiques d'indinavir ont diminué de façon substantielle. La carbamazépine a été utilisée pendant deux mois et demi; deux semaines après son arrêt, la charge virale est devenue détectable ($6 \times 10^3$ copies). Dans ce prélèvement, une résistance à la lamivudine a été observée, alors que la résistance à la zidovudine puisse être présente et que celle à l'indinavir n'ait pas été détectée. Quelques mois plus tard, une nouvelle augmentation de la charge virale a été observée ($300 \times 10^3$ copies/mL); un nouveau traitement antirétroviral a été initié chez le patient.

**DISCUSSION:** Les médecins peuvent prescrire la carbamazépine chez les individus infectés par le VIH pour traiter des convulsions ou de la névralgie postherpétique, lesquelles sont des complications des infections opportunistes tels l'herpes zoster ou la toxoplasmose. La carbamazépine est un inducteur enzymatique puissant, principalement du système enzymatique du CYP3A, alors que les inhibiteurs de la protéase du VIH tel l'indinavir sont des substrats et des inhibiteurs de ce même système enzymatique. Dès lors, on pourrait s'attendre à une interaction entre ces deux médicaments. Dans le cas décrit ci-haut, une faible dose de carbamazépine (200 mg par jour) et une dose habituelle d'indinavir (800 mg aux 8 heures) ont permis d'obtenir des concentration de carbamazépine à l'intérieur de l'écart thérapeutique pour le traitement de l'épilepsie, alors que les concentrations d'indinavir ont chuté de façon substantielle. Dans ce cas, la résistance virale, les concentrations plasmatiques des médicaments, et la séquence des évènements sont des indicatifs d'un échec de la thérapie antirétrovirale dû à l'interaction entre la carbamazépine et l'indinavir.

**CONCLUSIONS:** L'utilisation concomitante de carbamazépine et d'indinavir peut causer un échec de la thérapie antirétrovirale, dû à des concentrations plasmatiques insuffisantes d'indinavir. Pour prévenir cette interaction, des médicaments autres que la carbamazépine devraient être considérés. Par exemple, l'amitriptyline et la gabapentine sont des alternatives pour traiter la névralgie postherpétique, alors que l'acide valproïque et la lamotrigine sont des alternatives pour le traitement des convulsions. S'il n'est pas possible de prescrire une alternative, des ajustements de doses, le suivi des concentrations plasmatiques des médicaments, et une observation clinique attentive peuvent aider à réduire les conséquences cliniques indésirables.

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