Differenti effetti di carbamazepina/oxcarbazepina sull'esposizione ai farmaci antiretrovirali nella pratica clinica.

Different effects of carbamazepine/oxcarbazepine on antiretrovirals exposure in real life settings.

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Riassunto

Carbamazepina e oxcarbazepina sono forti induttori degli enzimi metabolici sia di fase I sia di fase II; per questo motivo, nella pratica clinica potrebbero verificarsi interazioni farmacologiche (DDI) tra queste due molecole e i farmaci antiretrovirali.

In questo lavoro abbiamo valutato la rilevanza di tale DDI in un contesto clinico reale, approfittando di un servizio specifico (Ambulatorio GAP - Gestione Ambulatoriale delle Politerapie) che si occupa di gestire la polifarmacia nei pazienti con infezione da HIV. Sono stati arruolati nello studio i pazienti trattati in concomitanza con carbamazepina o oxcarbazepina e farmaci antiretrovirali controindicati per almeno tre mesi. Di questi pazienti sono stati anche raccolti i risultati disponibili delle concentrazioni basali sia dei farmaci antiepilettici sia di quelli antiretrovirali.

Nel database dell'ambulatorio GAP sono stati identificati dieci pazienti sieropositivi trattati con carbamazepina o oxcarbazepina (7 uomini, 3 donne, età media 51±7 anni). Tutte le valutazioni delle concentrazioni basali di carbamazepina e oxcarbazepina sono risultate entro i limiti terapeutici. Anche le concentrazioni basali di tenofovir e darunavir misurate in questi pazienti erano comparabili con i valori solitamente misurati nei pazienti con infezione da HIV regolarmente seguiti nel nostro ospedale. Al contrario, le concentrazioni basali di atazanavir e dolutegravir sono risultate significativamente inferiori rispetto ai valori solitamente misurati nei pazienti con infezione da HIV non trattati con i due farmaci antiepilettici (190±91 vs. 546±380 ng/mL; p<0.001; 191±78 vs. 1096±510 ng/mL; p<0.001, rispettivamente).

In conclusione, la co-somministrazione di carbamazepina o oxcarbazepina con atazanavir o dolutegravir dovrebbe essere evitata; qualora non fossero disponibili altre opzioni terapeutiche, l'utilizzo del dosaggio terapeutico del farmaco (TDM) per questi due antiretrovirali è fortemente raccomandato. Da valutare anche la possibilità di aumento delle dosi.

Abstract

Carbamazepine and oxcarbazepine are strong inducers of both phase I and phase II metabolic enzymes. For this reason, potential drug-drug interactions (DDIs) may take place between these two drugs and antiretrovirals. Here, we aimed to assess the relevance of these DDIs in real life clinical settings, taking advantage from an out-patient clinical service set-up in our hospital with the aim of managing of polypharmacy in HIV. Patients treated concomitantly with carbamazepine or oxcarbazepine and contraindictated antiretrovirals for at least three months were considered. Data on therapeutic drug monitoring (TDM) of both antiepileptic and antiretrovirals trough concentrations were collected.

Ten HIV-positive patients given carbamazepine or oxcarbazepine were identified (7 men, 3 women, mean age 51±7 years). All the TDM evaluations for carbamazepine and oxcarbazepine resulted within the therapeutic ranges. TDM results of tenofovir and darunavir measured in these patients were comparable with values usually measured in the overall population of HIV-infected patients routinely followed in our hospital. Conversely, the trough concentrations of atazanavir and dolutegravir resulted significantly lower compared with values usually measured in HIV-infected patients not treated with antiepileptic drugs (190±91 vs. 546±380 ng/mL; p<0.001; 191±78 vs. 1096±510 ng/mL; p<0.001, respectively).

Coadministration of carbamazepine or oxcarbazepine with atazanavir or dolutegravir should be avoided; if no other therapeutic options are available, the adoption of TDM for these antiretrovirals is strongly advisable, eventually combined with increased antiretroviral doses.

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Potenziali conflitti di interesse:
nessuno.

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Introduction

Carbamazepine and oxcarbazepine are two structurally related compounds mainly used as anti-epileptic drugs [1-3]. Beside their action

as monotherapy or adjunctive therapy for the treatment of partial and generalized tonic-clonic seizures, these drugs are well-known inducers of both phase I and phase II metabolic enzymes [4-6]. In particular, both carbamazepine and oxcarbazepine are strong inducers of cytochrome 3A (CYP3A), the family of enzymes involved in the metabolism of most antiretrovirals [7]. For this reason, the majority of the combinations between antiretrovirals and carbazepine or oxcarbazepine are scored as "red" (do not coadminister) or "orange" (use with caution) flags by the HIV drug-interaction website from the University of Liverpool (available at www.hiv-druginteractions.org). It must be considered, however, that the quality of evidence for these drug-drug interactions (DDIs) is low or very low: in most cases, in fact, coadministrations of these drugs have not be formally studied and the DDIs are indirectly predicted taking into account both the inducing potential of the two antiepileptic drugs and the metabolic pathways of each antiretroviral.

Here, we aimed to assess the relevance of potential DDIs between carbamazepine or oxcarbazepine and antiretroviral drugs in real life clinical settings, taking advantage from the out-patient clinical service (*Gestione Ambulatoriale Politerapie*, GAP) set-up in September 2016 in our hospital with the aim of managing of polypharmacy in HIV-infected patients [7].

Methods

Subject population and study design

The database of our GAP outpatients' clinics (with nearly 900 HIV-infected patients on active follow-up) was investigated in search for HIV-infected patients treated with carbamazepine or oxcarbazepine for at least three months and antiretrovirals potentially interacting with these two antiepileptic drugs (red or orange flags according to the Liverpool website). Demographical and clinical information were also collected, together with data on therapeutic drug monitoring (TDM) of both antiepileptic and antiretrovirals trough concentrations (all the TDM available in the database of the laboratory before the GAP visit were considered). Data on TDM of antiretrovirals measured in the patients given carbamazepine or oxcarbazepine were compared with mean drug concentrations collected from our laboratory in the 10-year experience with the routine TDM of antiretrovirals (nearly 800-1000 TDM requests per year).

Statistical analyses

The frequency distribution data are expressed as percentages; all of the other measures are expressed as mean values ± standard deviation. The chi-squared test was used to compare the frequency counts between the groups. The comparison in the continuous numerical variables were performed using unpaired t-test. All statistical analyses were performed by MEDCALC, Software (Mariakerke, Belgium). A P value of less than 0.05 was considered as statistically significant.

Ethics statement

This retrospective study was conducted using data collected for clinical purposes, all of which had been previously made anonymous in accordance with the requirements of the Italian Personal Data Protection Code (Legislative Decree No. 196/2003) and the general authorizations issued by the Italian Data Protection Authority. Ethics Committee approval was considered unnecessary because under Italian law it is only required in the case of prospective clinical trials of medical products for clinical use (Arts. 6 and 9 of Legislative Decree No. 211/2003). All patients provided informed consent for the medical procedures used for routine treatment purposes.

Results

Ten HIV-positive patients given carbamazepine (n=6) or oxcarbazepine (n=4) were identified (7 men, 3 women, mean age 51±7 years). As shown in **Table 1**, at the time of the first GAP visit, these patients were given oxcarbazepine or carbamazepine for 3126±2267 days. Reasons for the treatment with one of the two antiepileptic drugs (eventually combined with levetiracetam or topiramate) were idiopathic epilepsy (n=5), post-infection (cerebral toxoplasmosis and viral encephalitis) epilepsy (n=3), post ischemic stroke epilepsy (n=1), and trigeminal neuralgia (n=1),

The results of TDM requests for antiepileptic (n=31) and antiretroviral (n=55) drugs are given in **Table 2**. All the TDM evaluations for carbamazepine and oxcarbazepine resulted within the therapeutic ranges, a task reached by wide distribution in the daily drug doses (from 200 to 900 mg for carbamazepine

Patients' Characteristics	Values
Age, years	51 ± 7
Women, n	3
Body weight, Kg	77 ± 4
Serum creatinine, mg/dL	0.8 ± 0.1
GGT, IU/L	70 ± 49
ALT, IU/L	38 ± 26
HCV/HBV co-infection, n	4 (all HCV)
CD4 cell count, cells/mm3	530 ± 293
Viral load >37 copies/mL, n	1 (22370 copies/mL)
Days of antiepileptic therapy^	3126 ± 2267
PI-based antiretroviral therapy, n*	8
NNRTI-based antiretroviral therapy, n*	1
Tenofovir-based antiretroviral therapy, n*	8
INI-based antiretroviral therapy, n*	4

PI: *protease inhibitor;*
NNRTI: *non-nucleoside reverse transcriptase inhibitor;*
INI: *integrase inhibitor;*
ALT: *alanine aminotransferase;*
GGT: *gamma-glutamyltransferase;*
HCV: *hepatitis C virus;*
HBV: *hepatitis B virus;*

^ At the time of the GAP visit

**Some patients received >1 antiretroviral regimen during the observational period.*

Table 1. Clinical and demographic characteristics of the 10 HIV-infected patients on maintenance carbamazepine or oxcarbazepine therapy

and from 600 to 4000 mg for oxcarbazepine). Tenofovir trough concentrations measured in the HIV-infected patients given concomitantly one of the two antiepileptics with tenofovir disoproxil fumarate (TDF) (49±13 vs. 109±62 ng/mL; p=0.115) or with tenofovir alafenamide (TAF) (11.4±3.5 ng/mL vs. 17.8±7.8; p=0.246) showed drug concentrations comparable with values usually measured in the overall population of HIV-infected patients routinely followed in our hospital. The same trend was found also for darunavir (2329±1274 vs. 2837±1937 ng/mL in patients given or not given concomitantly carbamazepine or oxcarbazepine; p=0.512) Conversely, the trough

Drug	Drug TDM (n)	Drug concentrations	Therapeutic range
Oxcarbazepine, mg/L	10	19.5 ± 4.3	10 – 35
Carbamazepine, mg/L	21	7.4 ± 1.8	4 – 12
Tenofovir (TDF), ng/mL	10	49 ± 13	40 – 180
Tenofovir (TAF), ng/mL	12	11.4 ± 3.5	Not established
Atazanavir, ng/mL	8	190 ± 91	150 – 800
Darunavir, ng/mL	8	2329 ± 1274	>500
Dolutegravir, ng/mL	7	191 ± 78	>100
Raltegravir, ng/mL	6	472 ± 698	>40
Rilpivirine, ng/mL	2	<20, 35	>25
Elvitegravir, ng/mL	2	<25, 160	>45

TDF: *tenofovir diproxil fumarate;*
TAF: *tenofovir alafenamide;*
s *therapeutic drug monitoring.*

Table 2. Antiepileptic and antiretroviral drug trough concentrations measured in the 10 HIV-infected patients on maintenance carbamazepine or oxcarbazepine therapy (all the TDM available in database of the laboratory before the GAP visit were considered).

concentrations of atazanavir (190±91 vs. 546±380 ng/mL; p<0.001) and dolutegravir (191±78 vs. 1096±510 ng/mL; p<0.001) resulted significantly lower compared with values usually measured in HIV-infected patients not treated with antiepileptic drugs. Only two TDM assessments were available for elvitegravir and rilpivirine, respectively: one TDM for each drug resulted below the lower limit of quantification (LOQ) of the assay (Table 2). As expected, great variability in the raltegravir trough concentrations was observed, with an interindividual coefficient of variation >100% [8,9]. It must be underlined, however, that in the only patient experiencing virologic failure with resistance mutations to integrase inhibitors (G140S and Q148H) while on oxcarbazepine, we measured trough raltegravir concentrations below the LOQ.
After the GAP visits the therapy with carbamazepine or oxcarbazepine was modified in six out of the eight HIV-infected patients: five patients were shifted to other antiepileptic drugs (topiramate, levetiracetam or lacosamide) and one was shifted to steroid treatment for the worsening of pain symptoms caused by trigeminal neuralgia

(with concurrent discontinuation of darunavir treatment).
In the remaining two patients, both treated with darunavir, the therapy was not modified.

Discussion

To the best of our knowledge, this is the first report on the use of carbamazepine or oxcarbazepine in HIV-infected patients with TDM data for both antiepileptic and antiretroviral drugs in real life settings. In agreement with the Liverpool website, no significant impact of the two antiepileptic drugs on tenofovir plasma trough concentrations was observed in patients treated with TDF (this coadministration is scored as "green": TDF results were included in the present study just because the drug was given in combination with other antiretrovirals potentially interacting with carbazepine or oxcarbazepine). Unexpectedly, the same trend was observed also for TAF (the DDI between carbamazepine or oxcarbazepine and TAF is scored as "red flag"), eventually challenging findings from DDI studies carried out in healthy volunteers [10]. It must be considered, however, that a therapeutic range for tenofovir concentrations has not be established yet for TAF. Therefore, the clinical relevance of this DDI cannot be firmly established.
In our small cohort of patients, we observed a highly significant effect of carbamazepine/oxcarbazepine on dolutegravir exposure, with drug trough concentrations resulting 3- to 5-fold lower compared with values usually measured in HIV-infected patients. This is an expected finding: in fact, the DDIs between dolutegravir and carbamazepine or oxcarbazepine are scored, respectively, as "orange" or "red flag" combinations for the well-known inducing effects of the two antiepileptic drugs on both enzymes involved in dolutegravir metabolism (namely, uridine diphosphate glucuronosyl transferase 1A1 and CYP3A). It should be noted, however, that no dolutegravir concentrations below 100 ng/mL (set as the minimum effective drug concentrations) were measured in our patients, eventually arguing against a potential clinical relevance of these DDIs.
The most relevant finding from our study is the observed opposite effect of carbamazepine or oxcarbazepine on the HIV protease inhibitors, namely atazanavir and darunavir. Indeed, we found that this concomitant administration resulted in very low trough concentrations of atazanavir, with 2- to 3-fold lower levels compared with values usually measured in HIV-infected patients and with some patients experiencing franck underexposure (that is a concentration below 150 ng/mL [11]). Conversely, no significant reduction in the darunavir trough concentrations were observed in patients concomitantly treated with carbazepine or oxcarbazepine. The mechanisms for this unexpected finding is presently unknown. We can only speculate that the opposite effect of the two antiepileptic drugs on darunavir and atazanavir might be eventually driven by: a) a different affinity of the two protease inhibitors for CYP3A4 versus CYP3A5 enzymes matched with a different degree of induction of carbamazepine or oxcarbazepine on the two CYP3A isoforms and/or b) differences in the systemic exposure of the two protease inhibitors; in fact, atazanavir circulates in the plasma at concentrations that are usually 4- to 6-fold lower compared with darunavir [12]. As a result, azatanavir, being present at lower plasma concentrations, is likely to be the favorite victim for the inducting effects of the antiepileptic drugs compared with darunavir. Irrespective from the mechanism, the clinical implications of our findings is that coadministration of carbamazepine or oxcarbazepine with atazanavir or dolutegravir should be avoided; if no other therapeutic option are available, the adoption of TDM for these antiretrovirals is strongly advisable, eventually combined with increased antiretroviral doses as suggested also by the Liverpool website.
Given its retrospective design, involving a limited number of patients, the present study is not powered to formally assess the clinical relevance of the described DDIs. It should be mentioned, however, that only one out of the ten patients treated with carbazepine or oxcarbazepine experienced virologic failure with resistance mutations to raltegravir.
As final comment, we would like to bring the attention to the fact that the eight patients indentified from our database were being treated for more than 3000 days with drug combinations of antiretrovirals and antiepileptics that were potentially contraindicated, suggesting that some important DDIs may be missed in everyday clinical practice. This highlights, in our mind, the importance to set up an ad hoc, multidisciplinary service for the optimal management of polypharmacy in HIV-infected patients, as the GAP service is attempting to do in our hospital [7].

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