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The impact of enzyme-inducing antiepileptic drugs on antiretroviral drug levels: A case-control study☆

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Summary
Purpose: To evaluate the impact of enzyme-inducing antiepileptic drugs (EI-AEDs) on serum antiretroviral (ARV) levels in patients with HIV.
Methods: Data from the U.S. Military HIV Natural History Study were screened to identify participants taking ARVs with EI-AEDs and controls taking ARVs with non enzyme-inducing AEDs (NEI-AEDs). The proportion of serum ARV levels below the recommended minimum concentrations (C_{min}) was compared between these groups.
Results: ARV levels were available for 10 individuals exposed to 16 intervals on combined ARVs/EI-AEDs (phenytoin and carbamazepine) and for 25 controls exposed to 30 overlap intervals on combined ARVs/NEI-AEDs. The percentage of overlap intervals with ≥1 ARV levels below C_{min} was higher in the EI-AED group than in controls (37.5% vs. 23.3%; $p = 0.124$). After excluding intervals associated with serum levels of EI-AEDs below the reference range ($n = 6$), the proportion of intervals with ≥1 ARV level below C_{min} was significantly greater among EI-AED recipients (60%) compared to controls (23.3%; $p = 0.008$).

☆ Statistical analysis completed by Greg Grandits.

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Conclusions: ARV levels below C_{min} were more common in participants receiving EI-AEDs, the difference being statistically significant for intervals associated with EI-AED levels within the reference range. These data suggest that, in agreement with current guidelines, EI-AEDs should be avoided in patients receiving ARV therapy.

Introduction

Antiepileptic drugs (AEDs) are commonly used in patients with HIV for associated seizure disorders and painful peripheral neuropathies. The occurrence of seizure disorders is increased among HIV-infected patients, with an incidence of up to 11% (Kellinghaus et al., 2008, Holtzman et al., 1989, Wong et al., 1990). A distal sensory polyneuropathy can also occur in up to 57% of patients with HIV (Cornblath and Mcarthur, 1988; Ellis et al., 2010; McArthur et al., 2005). AEDs are also used to treat other conditions, including migraine and mood disorders (Liedtke et al., 2004).

Evidence-based guidelines for AED selection for people with HIV/AIDS (Birbeck et al., 2012b, 2012c) indicate that clinically significant drug interactions can occur when antiretroviral (ARV) agents are combined with enzyme-inducing AEDs (EI-AEDs), including carbamazepine, phenytoin, and phenobarbital. These interactions can have bi-directional effects, resulting in altered serum levels of both EI-AEDs and ARVs. Lower EI-AED levels may lead to reduced efficacy including breakthrough seizures and neuropathic pain. Conversely, a reduction in ARV levels can lead to loss of virologic control, CD4 decline, acquired immune deficiency syndrome (AIDS), and ultimately death. Additionally, reduced efficacy of ARVs can facilitate the development of resistance mutations and increase the risk of transmitting drug-resistant virus.

We previously reported that combined use of ARVs and EI-AEDs led to higher rates of HIV treatment failure compared to use of ARVs in combination with AEDs that are not enzyme-inducing (NEI-AEDs) (Okulicz et al., 2011). To further evaluate and quantify this interaction, we used stored samples from the U.S. Military HIV Natural History Study (NHS) to measure serum levels of ARVs in patients on concurrent therapy with EI-AEDs and in a control group with co-administered NEI-AEDs.

Methods

Participants were identified from a database of over 5300 military members, retirees, and beneficiaries 18 years or older with HIV infection enrolled in the NHS since 1986 (Weintrob et al., 2008; Marconi et al., 2010). In this IRB-approved study, consented individuals are evaluated at participating United States military treatment facilities approximately every 6 months. Data including demographic characteristics, laboratory data, medication use, and clinical events with medical record confirmation are systematically collected.

As previously described (Okulicz et al., 2011), the NHS database was searched for individuals taking the EI-AEDs phenytoin, carbamazepine, or phenobarbital concurrently with a non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI)-based ARV regimen. To be included, participants were required to be taking the ARV regimen for $\geq$6 months and the EI-AED for $\geq$28 consecutive days during that period. This identified 19 participants with 53 EI-AED/ARV overlap periods, which were the focus of the previous study (Okulicz et al., 2011). For the purpose of the current study, we selected overlap periods for which frozen sera were available for drug level determination of the prescribed NNRTIs (either efavirenz or nevirapine) or PIs (lopinavir/ritonavir, atazanavir, or darunavir), and the prescribed EI-AED. Participants with EI-AED or ARV levels below the limit of detection were excluded, due to presumed non-adherence. This identified 16 overlap periods in 10 subjects for the current study, including 5 overlap periods for efavirenz, 3 for nevirapine, and 8 for lopinavir.

For the control group, we applied the same algorithm to select individuals prescribed NEI-AEDs (lamotrigine, zonisamide, levetiracetam, topiramate, gabapentin, tiagabine, or pregabalin) in combination with an NNRTI- or PI-based ARV regimen used by the EI-AED case group. Participants taking valproic acid, an enzyme inhibitor, and oxcarbazepine, a weak enzyme inducer, were excluded. Approximately two controls (as available) were randomly selected per case, within each ARV drug strata (efavirenz, nevirapine, or lopinavir/ritonavir). After exclusion of overlap periods with $\geq$1 ARV level below detection, a total of 30 overlap periods in 25 subjects were selected, including 12 overlap periods for efavirenz, 3 for nevirapine, and 15 for lopinavir.

To ensure sufficient time for drug-drug interactions to take effect, only serum specimens after 7 days of ARV/AED overlap were eligible. Two specimens from the overlap period were selected for both cases and controls when available, otherwise one specimen was selected. Two specimens were available for the majority of subjects, including 11 of 16 (69%) case periods and 21 of 30 (70%) control periods. All participants were prescribed standard daily doses of ARVs, specifically efavirenz (600 mg), nevirapine (400 mg), and lopinavir/ritonavir (800 mg/200 mg). EI-AED doses varied and were captured from the clinical database and chart review when available.

EI-AED and ARV serum level testing

Serum levels of EI-AEDs and ARVs were measured in repository samples stored at −80 °F. For EI-AEDs, only carbamazepine and phenytoin were prescribed in cases meeting eligibility criteria, and their levels were measured by the CEDIA Carbamazepine II assay and the ONLINE TDM Phenytoin assay (Roche Diagnostics, Indianapolis, IN). The laboratory reference ranges were 4.0—12.0 mcg/mL for carbamazepine and 10.0—20.0 mcg/mL for phenytoin. The