
Case report

A case of a potential drug interaction between clobazam and etravirine-based antiretroviral therapy

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The cytochrome P450 isoforms primarily involved in clobazam metabolism are CYP3A4 and 2C19. Drugs that modulate these enzymes would then be expected to alter the exposure of clobazam and its major metabolites. Etravirine, a second-generation non-nucleoside reverse transcriptase inhibitor has been shown to induce CYP3A4, while inhibiting CYP2C9 and CYP2C19. We report a case in which a potential drug interaction between clobazam and etravirine may have led to increased concentrations of clobazam and its pharmacologically active metabolite, N-desmethylclobazam, causing neurotoxic symptoms.

Case report

In January 2007, a 44-year-old HIV-positive male, who remained off antiretroviral therapy for the previous 15 years, presented with dysarthria and progressive right-sided weakness affecting the face, arm and leg. Investigations including an MRI of the head revealed multiple lesions in the right mesial temporal lobe, bilateral occipital lobes and left thalamic area. His cerebral spinal fluid was negative for bacteria, cryptococcus, herpes simplex virus types 1 and 2, Epstein–Barr virus, cytomegalovirus, human herpes virus 8 and JC virus, and his syphilis serology was non-reactive. He was started on high-dose sulfamethoxazole/trimethoprim for presumed toxoplasma encephalitis and subsequently displayed significant clinical and radiological improvement over the following weeks. Most recent CD4+ T-cell count and viral load at that time were 90 cells/mm³ and >500,000 copies/ml, respectively. The patient was started on combination antiretroviral therapy with zidovudine/lamivudine, tenofovir and efavirenz.

In June 2007, he had two episodes of generalized seizures. A repeat MRI showed persistence, but improvement, of the brain lesions. Seizure prophylaxis was initiated with valproic acid 1,500 mg/day. He experienced two more episodes of seizures by November 2007, resulting in an increase to his valproic acid dose, followed by another seizure 2 months later, which led to the addition of clobazam (CLB) 10 mg daily and a further increase of his valproic acid to 2,500 mg/day. In October 2008, he was readmitted to hospital after experiencing four additional seizures and his CLB dose was increased to 10 mg twice daily. Finally, he remained seizure-free and at his May 2010 neurology visit, it was reported that he had no evidence of cognitive impairment.

A change was made to his antiretroviral regimen in June 2010, switching him from lamivudine/zidovudine, tenofovir, raltegravir and lopinavir/ritonavir to tenofovir/emtricitabine, raltegravir, lopinavir/ritonavir and etravirine, due to drug resistance. After 1 month, the patient reported that he began experiencing unsteady gait, weakness and slurred speech. He denied any headaches, nausea, vomiting, seizures or auras but noted excessive daytime somnolence, sleeping up to 16 h/day. Speech was fluent, but slow, and repetition and comprehension was preserved. The rest of his neurological exam was unremarkable. An MRI completed in June 2010 revealed stable findings. Antiepileptic serum concentrations were frequently measured by CML Healthcare (Mississauga, ON, Canada) throughout his treatment (Table 1) given the refractoriness of his seizure disorder. Suspecting that some of his symptoms were related to his elevated anticonvulsant concentrations, both his valproic acid and CLB doses were reduced to 2,000 mg/day and 10 mg/day, respectively. Within 2 weeks of the de-escalation of antiepileptic doses, there was substantial improvement in his neurological exam,
specifically improved speech and motor performance. With resolution of his dysarthria, weakness and ataxia, together with his stable MRI findings, it was concluded that the aetiology of his psychomotor impairment was likely pharmacological in origin.

Discussion

Collectively, with the sequence of events, corresponding drug concentrations, and the absence of drug changes over 18 months except for the addition of etravirine, we suspect a drug interaction occurred between etravirine and CLB, causing the onset of new neurological symptoms in our patient.

Etravirine is a second-generation non-nucleoside reverse transcriptase inhibitor, specifically designed for treatment-experienced HIV-positive patients. This agent is primarily metabolized by the CYP450 system, specifically CYP3A4, CYP2C9 and CYP2C19. Additionally, etravirine has been demonstrated to be an inducer of CYP3A4, while inhibiting CYP2C9 and CYP2C19 [1]. When combined with maraviroc or sildenafil, primarily CYP3A4 substrates, their overall exposure was decreased by 53% and 57%, respectively [1]. By contrast, when etravirine was started in subjects receiving voriconazole, a 2C19 (major) substrate also metabolized by 3A4 and 2C9, voriconazole minimum plasma concentration and area under the curve increased by 23% and 14%, respectively [2].

Clobazam, a 1,5-benzodiazepine with antiepileptic properties, is primarily used as an adjunct for treatment refractory seizure disorders. It is frequently prescribed to HIV-positive patients who require adjuvant therapy because the traditional anticonvulsants, such as phenytoin and carbamazepine, have been associated with troublesome drug interactions with antiretrovirals [3,4]. CLB has not been observed to induce the cytochrome P450 system, which would risk subtherapeutic antiretroviral concentrations. Its biotransformation, however, is through this system and the specific isoforms involved have been characterized by Giraud et al. [5]. CLB is metabolized to both an active metabolite N-desmethylclobazam (NCLB) and to an inactive one, 4-hydroxy-clobazam. Isoenzymes 3A4, 2C19 and 2B6 mediate the formation of the active metabolite, while 2C19 and 2C18 mediate formation of CLB’s inactive metabolite and catalyse the hydroxylation of NCLB (Figure 1) [5]. The active metabolite NCLB has been demonstrated to have a much longer half-life than the parent drug, that is, 42 h versus 18 h, respectively [6]. In addition, NCLB has been estimated to retain 20–40% of the pharmacological activity of the parent drug [7]. Clinical studies have suggested that modulation of specific P450 enzymes can alter the clearance of CLB. For example, concomitant use of inducers of the CYP3A isoform, such as phenytoin and carbamazepine, has led to the accumulation of the N-desmethyl metabolite [8]. Additionally, subjects that carried the defective CYP2C19*2 allele developed markedly increased NCLB plasma concentrations and demonstrated symptoms consistent with CLB toxicity [9].

To date, there have been no published reports of interaction between CLB and any antiretroviral agent. Our patient developed symptoms consistent with neurological toxicity to CLB within weeks of changing his antiretroviral medications to include etravirine.

Table 1. Therapeutic drug monitoring of valproic acid and clobazam

<table>
<thead>
<tr>
<th>Date</th>
<th>Antiretroviral regimen</th>
<th>VPA dose, mg/day</th>
<th>VPA plasma concentration, µmol/l</th>
<th>CLB dose, mg/day</th>
<th>CLB plasma concentration, µmol/l</th>
<th>NCLB plasma concentration, µmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan 2007</td>
<td>AZT, 3TC, TDF, EFV</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Jun 2007</td>
<td>AZT, 3TC, TDF, EFV</td>
<td>1,500</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Oct 2007</td>
<td>AZT, 3TC, TDF, RAL, LPV/r</td>
<td>1,500</td>
<td>576</td>
<td>10</td>
<td>0.22</td>
<td>&lt;0.8</td>
</tr>
<tr>
<td>Jun 2008</td>
<td>AZT, 3TC, TDF, RAL, LPV/r</td>
<td>2,500</td>
<td>648</td>
<td>10</td>
<td>0.22</td>
<td>&lt;0.8</td>
</tr>
<tr>
<td>Aug 2008</td>
<td>AZT, 3TC, TDF, RAL, LPV/r</td>
<td>2,500</td>
<td>745</td>
<td>10</td>
<td>0.22</td>
<td>&lt;0.8</td>
</tr>
<tr>
<td>Oct 2008</td>
<td>AZT, 3TC, TDF, RAL, LPV/r</td>
<td>2,500</td>
<td>638</td>
<td>20</td>
<td>0.58</td>
<td>&lt;0.8</td>
</tr>
<tr>
<td>Sep 2009</td>
<td>AZT, 3TC, TDF, RAL, LPV/r</td>
<td>2,500</td>
<td>912</td>
<td>20</td>
<td>0.51</td>
<td>&lt;0.8</td>
</tr>
<tr>
<td>May 2010</td>
<td>AZT, 3TC, TDF, RAL, LPV/r</td>
<td>2,500</td>
<td>683</td>
<td>20</td>
<td>0.55</td>
<td>&lt;0.8</td>
</tr>
<tr>
<td>Jun 2010</td>
<td>ETR, FTC, TDF, RAL, LPV/r</td>
<td>2,500</td>
<td>-</td>
<td>20</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Jul 2010</td>
<td>ETR, FTC, TDF, RAL, LPV/r</td>
<td>2,500</td>
<td>-</td>
<td>20</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Aug 2010</td>
<td>ETR, FTC, TDF, RAL, LPV/r</td>
<td>2,500</td>
<td>763</td>
<td>20</td>
<td>1.08</td>
<td>7.33</td>
</tr>
<tr>
<td>Oct 2010</td>
<td>ETR, FTC, TDF, RAL, LPV/r</td>
<td>2,500</td>
<td>865</td>
<td>20</td>
<td>1.27</td>
<td>9.46</td>
</tr>
<tr>
<td>Dec 2010</td>
<td>ETR, FTC, TDF, RAL, LPV/r</td>
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<td>563</td>
<td>10</td>
<td>1.13</td>
<td>4.39</td>
</tr>
<tr>
<td>Feb 2011</td>
<td>ETR, FTC, TDF, RAL, LPV/r</td>
<td>2,000</td>
<td>753</td>
<td>10</td>
<td>0.7</td>
<td>2.38</td>
</tr>
</tbody>
</table>

*Reference range 347–693 µmol/l. 
*Reference range 0.33–1 µmol/l. 
*Reference range not established [7]. 
*Dechallenge of clobazam (CLB) and valproic acid (VPA) was initiated following observed values in October 2010. AZT, zidovudine; EFV, efavirenz; ETR, etravirine; FTC, emtricitabine; LPV/r, lopinavir/ritonavir; NCLB, N-desmethylclobazam; RAL, raltegravir; TDF, tenofovir; 3TC, lamivudine.
Additionally, the serum concentration of the active metabolite NCLB significantly increased over the following 4 months after adding etravirine (Table 1). Prior to the addition of etravirine, the serum concentration of NCLB was virtually undetectable, possibly secondary to the propensity of ritonavir to inhibit 3A4 and induce 2C9/19 [10]. Conversely, through the induction of 3A4 and inhibition of 2C19, we postulate that adding etravirine resulted in the accumulation of NCLB as supported by the significant increase in serum concentrations, and led to the clinical symptoms of gait instability and dysarthria. These findings are consistent with CLB toxicity reported in the literature. Approximately 40% of patients are reported to experience the following side effects to CLB in a dose-related fashion: sedation, drowsiness, dizziness, ataxia, muscle weakness and drooling [11,12].

Clobazam-induced adverse reactions have been reported in cases with CYP2C19 defective alleles [9]. In one study of 110 patients, Seo et al. [13] demonstrated that NCLB serum concentrations significantly increased in those with CYP2C19 deficient alleles. In addition, response to treatment was observed to be greater in these CYP2C19 deficient patients and, although not statistically significant, adverse effects occurred more frequently [13]. However, we do not think that our patient carried a defective CYP2C19 allele that led to elevated NCLB concentrations, since he previously tolerated CLB and had low NCLB concentrations for 2 years prior to the antiretroviral change. Importantly, high levels of CLB and NCLB are clinically relevant as described in the fatal case reported by Pok et al. [14]. The authors report that at autopsy serum concentrations of CLB and NCLB were 0.72 μg/ml (2.4 μmol/l) and 36 μg/ml (125.6 μmol/l), respectively, while no other drug compound was detected at supratherapeutic levels [14]. When the sum of CLB and NCLB exceeds 10 μg/ml (34 μmol/l) it is associated with serious toxicity [14], and early identification and dose titration may have avoided such toxicity in our case.

When applying the Drug Interaction Probability Scale proposed by Horn et al. [15] to evaluate drug interaction cases, there are sufficient data in the present case to support a probable drug–drug interaction. We do note that the concurrent dosage reduction of the antiepileptic drug valproic acid, in addition to CLB, introduced a confounder to this case. As seen in Table 1, serum concentrations of valproic acid were elevated following the addition of etravirine, and suggest that this possibly had a minor contributing role via 2C9 inhibition. CYP2C9 has been demonstrated as the primary P450 isoform responsible for the oxidation of valproic acid [16]; however, only 10% of valproic acid metabolism occurs through the P450 oxidation system [17]. Additionally, we do not believe that the elevated valproic acid concentration contributed to his new neurological symptoms as he had previously been asymptomatic at higher valproate concentrations. Bowden et al. [18] demonstrated in 65 patients receiving valproic acid, that the dose-related side effects (nausea, vomiting and sedation) were all more frequent at valproic acid trough levels >125 mg/l (862 μmol/l), and our patient had consecutive valproate levels below this threshold during the period of neurological symptoms.

Conclusions
The use of anticonvulsants in HIV-positive patients receiving antiretrovirals is often challenging and we present a case of neurotoxicity associated with the use of CLB. To our knowledge, this is the first published report of a potential drug interaction between CLB and etravirine. Therefore, we would suggest close clinical and therapeutic drug monitoring of patients when these two agents are used together, in order that dose adjustments can be made to minimize drug toxicity.

Disclosure statement
The authors declare no competing interests.

References

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