CLINICAL PHARMACOLOGY

THERAPEUTIC CHALLENGES: INTERACTIONS BETWEEN ANTICONVULSANTS AND ANTIRETROVIRALS

Case report

A 36-year-old HIV-infected woman presents for assessment for antiretroviral therapy. As her current CD4+ count is 92 cells/mm^3, she needs to commence antiretroviral therapy. She has a history of epilepsy since childhood, for which she receives treatment with carbamazepine. This case raises some important questions: Does this patient still require anticonvulsant therapy? What potential drug interactions could occur with antiretrovirals?

Where there is a known primary focus, stopping anticonvulsants has a high rate of relapse. In a patient with idiopathic epilepsy, who has had no seizures for at least 2 years, slow weaning from the anticonvulsants can be considered, with the patient's understanding and consent. Although her epilepsy is reasonably well controlled, she is not seizure free. Therefore she requires ongoing anticonvulsant therapy. Carbamazepine, together with most of the first-generation anticonvulsants, has significant drug interactions with antiretrovirals (ARVs). Therefore, valproic acid (VPA) (which does not have significant interactions with most ARVs – see Table I) was gradually introduced while carbamazepine was slowly weaned. Thereafter combination antiretroviral therapy (stavudine, lamivudine and nevirapine) was commenced.

Table I. **Anticonvulsants that can be used with NNRTIs and PIs**

Agent	Cautions/comments
Valproic acid	Minimal CYP450 metabolism Interaction with zidovudine, monitor for bone marrow toxicity Hepatic and mitochondrial toxicity
Lamotrigine	Minimal CYP450 metabolism Some lowering of lamotrigine levels with ritonavir
Levetiracetam	No significant interaction with ARVs noted
Gabapentin	No significant interaction with ARVs noted
Lorazepam	No significant interaction with ARVs noted
Oxazepam	No significant interaction with ARVs noted

This article reviews the interactions that exist between ARVs and anticonvulsants and makes some recommendations for clinical practice.

Anticonvulsant use in HIV infection

Anticonvulsants are frequently prescribed for patients with HIV. Seizures are more common in HIV-infected patients, occurring in approximately 10% of those with advanced disease.[1,2] There are multiple causes for seizures, including central nervous system opportunistic diseases (e.g. toxoplasmosis, cryptococcosis and tuberculosis), tumours (e.g. lymphoma), HIV encephalopathy and incidental causes (e.g. trauma and idiopathic epilepsy) which may predate the HIV infection. Anticonvulsants are also prescribed for other conditions, notably post-herpetic neuralgia and peripheral neuropathy, both of which are common in HIV. Anticonvulsants may also be used as mood stabilisers in psychiatric conditions such as depression and psychosis. With the rollout of ARVs, increasing numbers of people living with HIV have access to highly active antiretroviral therapy (HAART). In South Africa there are approximately 200 000 people on treatment (in both private and public sector), with many more qualifying for treatment (Osler M – personal communication). With increasing access to HIV treatment, there is increasing co-prescription of anticonvulsants and HAART. This creates a therapeutic dilemma, as the concurrent use of several of the ARVs and anticonvulsants results in drug-drug interactions which may render the drugs either unsafe or ineffective.[3]

Drug-drug interactions

Drug interactions can be described as either pharmacokinetic or pharmacodynamic. Pharmacokinetic effects refer to the effect of the body on the drug, which includes drug absorption, distribution, metabolism and excretion. Pharmacodynamic effects refer to the effect the drug has in the body (e.g. viral suppression with ARVs). This review focuses on the drug interactions that occur owing to drug metabolism.

In order for drugs to be eliminated from the body they must go through a process of metabolism. The cytochrome P450 (CYP450) enzyme system, located primarily in the liver and intestines, has evolved to convert lipophilic substances (such as drugs) to hydrophilic compounds that can be excreted by the kidneys. Cytochrome P450 is divided into 3 isoenzyme families, namely CYP1, CYP2 and CYP3. There are further subdivisions of this system, for example CYP3A4, which is involved in the majority of biotransformation processes.

Most of the commonly used first-generation anticonvulsants (phenytoin, carbamazepine and phenobarbitone) are metabolised by this system. The non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) are also substrates of CYP450. Not only are the anticonvulsants and ARVs substrates of this system, but they may also influence them by either inducing or inhibiting the hepatic enzyme activity (Tables II and III).

Induction of the CYP450 system results in increased enzyme expression, which in turn leads to increased biotransformation of the parent compound. This results in

Table II. **Anticonvulsants that interact with NNRTIs and PIs**

Agent	Metabolism	Cautions
Phenytoin	Substrate of CYP2C9, 2C19 Inducer of CYP3A	Decreased levels of PIs and NNRTIs Phenytoin levels reduced by PIs and NNRTIs Avoid combination
Carbamazepine	Substrate of CYP3A4 Inducer of CYP3A4	Decreased levels of NNRTIs and PIs Carbamazepine levels reduced by NNRTIs and increased by PIs Avoid combination
Phenobarbitone	CYP450 substrate Inducer of CYP2B6 & 3A4	Decreased levels of NNRTIs and PIs Phenobarbitone levels may be increased by PIs Avoid combination
Diazepam	Substrate of CYP3A4	Decreased levels when used with NNRTIs, increased levels when used with PIs
Clonazepam	Substrate of CYP3A4	Decreased levels when used with NNRTIs, increased levels when used with PIs

Table III. **Antiretrovirals and their metabolism**

Agent	Metabolism
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	
Nevirapine	Substrate of CYP3A4 Inducer of CYP3A4
Efavirenz	Substrate of CYP2B6 and 3A4 Inducer and inhibitor of CYP3A4
Nucleoside reverse transcriptase inhibitors (NRTIs)	
Zidovudine (AZT)	Glucuronidated; renally eliminated
Lamivudine (3TC) Didanosine (ddI) Stavudine (d4T)	Renally eliminated
Protease inhibitors (PIs)	
Lopinavir/ritonavir (Kaletra)	Substrate of CYP3A4 Inhibitor of CYP3A4 Inducer of CYP2C9, 2C19

lower effective drug levels, and ultimately in a decreased therapeutic effect. An example of this is the bi-directional interaction that occurs when carbamazepine and efavirenz are co-administered, resulting in lower levels of both drugs.[4] Both efavirenz and carbamazepine induce CYP3A4 (but efavirenz may also act as an inhibitor of CYP3A4). Lowered levels of carbamazepine may result in breakthrough seizures, and the decreased levels of efavirenz put the patient at risk of failing to suppress the HIV, and ultimately drug resistance.

Inhibition of the CYP450 system results in decreased enzyme expression. Therefore substrates requiring this system for their metabolism will be broken down more slowly. This will result in increased drug levels, putting the patient at risk of toxicity. The PIs (e.g. lopinavir/ritonavir (Kaletra)) are generally potent inhibitors of the CYP450 system, and carbamazepine levels can be raised into the toxic range when these drugs are used concurrently.[2,3] Conversely, phenytoin levels are reduced when co-administered with ritonavir, which induces CYP2C9 (phenytoin is a substrate of this isoenzyme). Therefore it is difficult to predict drug interactions without intimate knowledge of their metabolic pathways and inducing or inhibiting effects.

Therapeutic drug monitoring (TDM) is available to monitor the levels of first-line anticonvulsants. However, currently there is very limited access to TDM for AVRs. Combining CYP450-inducing drugs and ARVs is therefore not recommended.

Using anticonvulsants with ARVs

First-line anticonvulsants

The combination of phenytoin, carbamazepine or phenobarbitone with the NNRTIs and PIs may result in therapeutic failure or toxicity. Therefore, alternative anticonvulsants need to be identified for patients on ARVs.

VPA is a relatively affordable first-line anticonvulsant. It has not been reported to affect the metabolism of the NNRTIs or the PIs.[3] Metabolism of VPA occurs via glucuronidation, with negligible CYP450 metabolism.[5] It is therefore an appropriate alternative anticonvulsant agent for co-administration with the NNRTIs and PIs. There are three issues regarding VPA worth mentioning:

- VPA interacts with and increases the levels of one of the nucleoside reverse transcriptase inhibitors (NRTIs), i.e. zidovudine (AZT). Both drugs undergo glucuronidation, and VPA inhibits AZT metabolism via this mechanism, resulting in a two-fold increase in AZT levels.[3] Some clinicians recommend that the dose of AZT should be reduced. Increased monitoring for toxicity related to AZT (i.e. full blood count for bone marrow suppression) would be appropriate when these agents are co-administered.

- Concern has been raised that VPA increases HIV replication. The mechanism of this is related to VPA's ability to activate resting CD4+ cells. These latently infected cells are quiescent and consequently are not affected by ARVs, which can only act when HIV is actively replicating. More recently, the initial concern has been replaced by increased interest that this mechanism may in fact assist to clear the plasma of HIV by making the inaccessible HIV population in latently infected CD4+ cells amenable to treatment.[6]

- VPA can cause rises in liver transaminases, cholestasis and, rarely, fulminant hepatic failure. The mechanism is by inhibition of fatty acid β-oxidation, which results in microvesicular fat accumulation in hepatocytes and mitochondrial dysfunction. The NRTIs also cause fatty liver, therefore liver function should be closely monitored. Furthermore, all NRTIs may cause symptomatic hyperlactataemia and lactic acidosis. Co-administration of other drugs that affect mitochondrial function, including VPA, may increase the risk of this relatively uncommon, but potentially fatal, adverse drug reaction.[7]

Second-line anticonvulsants

Most of these agents have less potential for drug-interactions. However, there is still limited experience of their use with ARVs. Of these agents, the best options for co-prescription with either the NNRTIs or PIs would include lamotrigine (see below), topiramate, gabapentin and levetiracetam.[3,8] Unfortunately, their relatively high cost precludes widespread use.

Lamotrigine has recently come off patent and is likely to become increasingly affordable. Like valproate, it is metabolised by glucuronidation and not by the CYP450 system. However, lopinavir/ritonavir (Kaletra) induces glucuronidation of the lamotrigine, resulting in a significant decrease in its half-life and an increase in its clearance.[9] In a recent study, the dose of lamotrigine had to be doubled in order for its levels to remain in the therapeutic range. Therapeutic drug monitoring of lamotrigine is recommended when it is administered with ritonavir-boosted PIs.

Conclusion

There are significant drug interactions between ARVs and many first-line anticonvulsants. Because anticonvulsants are often used in HIV infection, clinicians need to be aware of potentially serious interactions. To illustrate this, a survey of drug interactions of South African private sector patients taking ARVs and other chronic medication found that anticonvulsants were among the most commonly prescribed interacting medications.[9] When an anticonvulsant is indicated, an agent that will not have clinically relevant interactions should be selected.

The knowledge of drug interactions is increasing constantly; in order to keep abreast of current important drug interactions clinicians should refer to one or more of the following sources (see box):

Medicines Information Centre, tel (021) 406-6829
www.mic.uct.ac.za (local database, including locally used medicines)
www.hopkins-aids.edu
www.hiv-druginteractions.org (Liverpool HIV Pharmacology Group)
www.tthivclinic.com/interactiontables (Toronto General Hospital)

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SINGLE SUTURE

BLAME YOUR OLDER BROTHERS

New research suggests that there is a prenatal origin to male homosexuality. Anthony Bogaert at Brock University, Canada, looked at a total of 944 homosexual and heterosexual men, including one group raised with non-biological male siblings. He reasoned that if simply being brought up with a lot of older brothers produced the effect, then it shouldn't matter if they shared their mother. But, it did matter. Only the number of biological older brothers was linked with sexual orientation. This was true even when the older brothers lived separately.

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