Managing psychotropic drugs with efavirenz

Rachel Therrien BPharm MSc

R Therrien. Managing psychotropic drugs with efavirenz. Can J Infect Dis Med Microbiol 2006;17(Suppl D):15D-16D.

Efavirenz is in the non-nucleoside reverse transcriptase inhibitor category of HIV antiretroviral medicines. It is an *in vivo* inducer of the CYP3A4 isoenzyme within the cytochrome P450 (CYP450) system, and an *in vitro* inhibitor of the system's CYP2C9/2C19, 3A4 and 2B6 isoenzymes; as a result, concentrations of psychotropic drugs can be increased or decreased depending on the specific enzyme pathway involved in their metabolism. CYP3A4 is responsible for metabolizing many benzodiazepines and other psychotropics, as well as selective serotonin reuptake inhibitors and tricyclic antidepressants. As an inducer of CYP3A4, efavirenz can increase the rate at which these agents are metabolized, resulting in administered psychotropic drug levels that are below their therapeutic thresholds. Conversely, efavirenz is an inhibitor of CYP2B6, which metabolizes agents such as bupropion; consequently, bupropion levels in the blood can increase. Given the existing conflicting data, the clinician may find it impractical to use an evidence-based approach when concomitantly prescribing efavirenz and psychotropic drugs to their HIV patients. Instead, it may be preferable to use a more pragmatic approach that applies knowledge of the most current pharmacological and pharmacokinetic data for psychotropics and non-nucleoside reverse transcriptase inhibitors, which may help better predict their potential interactions.

Key Words: Antiretrovirals; CYP450; Drug interactions; Efavirenz; Inducer; Inhibitor; Psychotropic drugs; Side effects

Efavirenz (Sustiva, Bristol-Myers Squibb Canada) is in the non-nucleoside reverse transcriptase inhibitor category of HIV antiretroviral medicines. It is an *in vivo* inducer of the CYP3A4 isoenzyme within the cytochrome P450 (CYP450) system, and an *in vitro* inhibitor of the system's CYP2C9/2C19, 3A4 and 2B6 isoenzymes (1,2). As a result, concentrations of psychotropic drugs can be increased or decreased depending on

Les psychotropes et l'efavirenz

L'efavirenz est un médicament antirétroviral, utilisé dans le traitement des infections à VIH, qui appartient à la catégorie des inhibiteurs non nucléosidiques de la transcriptase inverse. Il s'agit d'un inducteur *in vivo* de l'isoenzyme CYP3A4 présente dans le cytochrome P450 (CYP450) et d'un inhibiteur *in vitro* des isoenzymes CYP2C9/2C19, 3A4 et 2B6; ainsi, la concentration sanguine de médicaments psychotropes peut augmenter ou diminuer suivant la voie enzymatique empruntée pour leur métabolisme. La CYP3A4 intervient dans le métabolisme de nombreuses benzodiazépines et d'autres psychotropes ainsi que dans celui des inhibiteurs sélectifs du recaptage de la sérotonine et des antidépresseurs tricycliques. Comme l'efavirenz est un inducteur de la CYP3A4, il peut accroître la vitesse à laquelle ces médicaments sont métabolisés, d'où l'atteinte de concentrations sous-thérapeutiques de psychotropes. À l'inverse, comme l'efavirenz est un inhibiteur de la CYP2B6, qui métabolise des substances comme le bupropion, il peut entraîner une augmentation de la concentration sanguine de ce dernier médicament. Étant donné l'existence de données divergentes sur le sujet, les cliniciens peuvent trouver difficilement applicable l'approche fondée sur des preuves chez les patients porteurs du VIH, qui doivent à la fois prendre de l'efavirenz et des psychotropes. Dans ce cas, il peut être préférable de recourir à une approche plus pragmatique, qui s'appuie sur les données les plus récentes sur les propriétés pharmacologiques et pharmacocinétiques des psychotropes et des inhibiteurs non nucléosidiques de la transcriptase inverse, qui permettent de prévoir plus facilement les interactions éventuelles.

the specific enzyme pathway involved in their metabolism (3). Although efavirenz is actually a combined inhibitor/inducer of the CYP3A4 isoenzyme, it is known to be more of an inducer. The following table provides a useful overview of the potential interactions of efavirenz with benzodiazepines and other psychotropics, as well as selective serotonin reuptake inhibitors, tricyclic antidepressants and the agent bupropion.

TABLE 1
Potential drug interactions with efavirenz

Drug class	Notes
Benzodiazepines and hypnotics or anxiolytics metabolized by CYP3A4	
Alprazolam (Xanax*), bromazepam (Lectopam†), buspirone (Buspar‡), chlorthalidopoxide (Apo-Chlorthalidopoxide****), clonazepam (Rivotril†), clorazepate (Apo-Clorazepate****), diazepam (Valium†), flurazepam (Dalmane§), nitrazepam (Mogadon§), trazodone (Desyre†), zaleplon (Starnoc¶), zopiclone (Imovane**)	Possible decrease of benzodiazepine concentrations. Closely monitor for signs and symptoms of benzodiazepine withdrawal. Although an increase, rather than a decrease, in midazolam (Versed†) and triazolam (Halcion*) plasma concentration may be observed, these agents are contraindicated in the product monograph (2). However, a single dose of midazolam during a procedure would be acceptable. Safer alternatives to benzodiazepine conjugates include lorazepam (Ativan††), oxazepam (Apo-Oxazepam****) and temazepam (Restoril††).

continued on next page

Unités hospitalières de recherche, d'enseignement et de soins sur le sida (UHRESS)/Centre hospitalier de l'Université de Montréal (CHUM), Hôtel-Dieu, Montreal, Quebec

Correspondence: Ms Rachel Therrien, UHRESS-CHUM, 3840 rue St-Urbain, Montreal, Quebec H2W 1T8. Telephone 514-890-8148, fax 514-412-7234, e-mail rachel.therrien.chum@ssss.gouv.qc.ca

TABLE 1 (CONTINUED)
Potential drug-drug interactions

Drug class	Notes
Antidepressants metabolized by CYP3A4	
Amitriptyline (Apo-Amitriptyline ^{††††}), clomipramine (Anafranil ^{††}), doxepin (Sinequan ^{§§}), imipramine (Tofranil ^{¶¶}), sertraline (Zoloft [*]), trazodone (Desyrel [‡]), trimipramine (Apo-Trimip ^{††††})	Adjust according to patient response and to the onset of adverse effects. A 39% decrease in sertraline (Zoloft [*]) concentration was observed (4). Possible decrease in the concentration of antidepressants metabolized by CYP3A4. Monitor the clinical efficacy of these agents. A dosage adjustment may be necessary.
Citalopram (Celexa ^{***}), escitalopram (Cipralex ^{***}), mirtazapine (Remeron ^{†††}), venlafaxine (Effexor ^{††})	Also metabolized by CYP3A4, but due to their multiple metabolic pathways, are subject to fewer drug interactions.
Antidepressants metabolized by CYP2B6	
Bupropion (Wellbutrin ^{†††} , Zyban ^{†††})	Possible increase in bupropion concentration. Monitor for signs and symptoms of bupropion toxicity (2). One case series (10 patients) examined in vivo experience with the combination of bupropion and ritonavir, efavirenz or nelfinavir, and found no increase in the number of seizures (no seizures were reported) (5).
Antidepressants that are CYP3A4 inducers	
St John's Wort	Possible decrease in efavirenz concentration. Contraindicated with efavirenz (Sustiva [‡]).
Desipramine, fluoxetine (Prozac ^{§§§}), fluvoxamine (Luvox ^{¶¶¶}), maprotiline (Novo-Maprotiline ^{****}), nortriptyline (generic Apo- or Novo-Nortriptyline ^{****}), paroxetine (Paxil ^{††††})	No anticipated effects.
Antipsychotics metabolized by CYP3A4 or intense first-pass extraction	
Quetiapine (Seroquel ^{††††}), methotrimeprazine (Nozinan ^{**}), lozapine (Loxapac ^{§§§§})	Possible decrease in the concentration of these antipsychotics. Monitor clinical efficacy. A dosage adjustment may be necessary.
Pimozide (Orap ^{¶¶¶¶})	Although an increase, rather than a decrease, in pimozide (Orap ^{¶¶¶¶}) plasma concentration may be observed, it is contraindicated in the product monograph (1).
Chlorpromazine (Largactil ^{**}), clozapine (Clozaril ^{¶¶}), haloperidol (Apo-Haloperidol ^{††††}), olanzapine (Zyprexa ^{§§§}), perphenazine (Apo-Perphenazine ^{††††}), risperidone (Risperdal ^{*****})	No anticipated effects.
Mood stabilizers (CYP3A4 inducers)	
Carbamazepine (Tegretol ^{¶¶}), oxcarbazepine (Trileptal ^{¶¶})	Possible decrease of efavirenz and decrease of carbamazepine concentration. In one study, co-administration of efavirenz with carbamazepine led to a decrease in the area under the curve of efavirenz by 36% and a decrease in the area under the curve of carbamazepine by 27% (6). Avoid if possible, or closely monitor the efficacy of efavirenz. An efavirenz plasma concentration measurement may be indicated.
Valproic acid, lamotrigine (Lamictal ^{††††}), lithium (Carbolith [§])	No anticipated effects.
Psychostimulants	
Methylphenidate (Ritalin ^{¶¶}), modafinil (Alertec ^{††††})	Potentially metabolized by CYP3A4. Possible decrease in the concentration of methylphenidate and modafinil. Monitor clinical efficacy. A dosage adjustment may be necessary.

*Pfizer Canada Inc; †Hoffmann-La Roche Ltd; ‡Bristol-Myers Squibb Canada; §Valeant Canada Ltd; ¶Servier Canada Inc; **Sanofi-Aventis Canada Inc; ††Wyeth Canada; ‡‡Oryx Pharmaceuticals Inc; §§ERFA Canada Inc; ¶¶Novartis Pharmaceuticals Canada Inc; ***Lundbeck Canada Inc; †††Organon Canada Ltd; ‡‡‡Biovail Pharmaceuticals Canada; §§§Eli Lilly Canada Inc; ¶¶¶Solvay Pharma; ****Novopharm Ltd; ††††GlaxoSmithKline Inc; ‡‡‡AstraZeneca Canada Inc; §§§Sandoz Canada Inc; ¶¶¶¶Pharmel Inc; *****Janssen-Ortho Inc; †††††Shire BioChem; ‡‡‡‡Apotex Inc

CONCLUSION

The concomitant use of psychotropic drugs and an efavirenz therapy regimen requires close patient monitoring to quickly identify drug interactions and ensure clinical efficacy. However, having a thorough knowledge of the various drugs' pharmacokinetics may help the clinician predict which interactions can potentially occur and select therapeutic agents accordingly. Often a dosage adjustment may be all that is necessary to resolve an interaction issue. It is also important that clinicians refer to the most up-to-date pharmacokinetic information available when prescribing these agents because changes tend to occur rapidly in this area.

REFERENCES

1. Sustiva Product Monograph. Mississauga: DuPont Pharma Inc, 2001.
2. Hesse LM, von Moltke LL, Shader RI, Greenblatt DJ. Ritonavir, efavirenz, and nelfinavir inhibit CYP2B6 activity in vitro: Potential drug interactions with bupropion. *Drug Metab Dispos* 2001;29:100-2.
3. Thompson A, Silverman B, Dzeng L, Treisman G. Psychotropic medications and HIV. *Clin Infect Dis* 2006;42:1305-10.
4. Ruiz NM, Labriola DF, Fiske WD, et al. Efavirenz plasma levels are unaffected in patients receiving selective serotonin reuptake inhibitors. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, September 17 to 20, 2000. (Abst 1635)
5. Park-Wyllie LY, Antoniou T. Concurrent use of bupropion with CYP2B6 inhibitors, nelfinavir, ritonavir and efavirenz: A case series. *AIDS* 2003;17:638-40.
6. Kaul S, Ji P, Xie J, et al. A 2-way pharmacokinetic interaction between efavirenz and carbamazepine. 13th Conference on Retroviruses and Opportunistic Infections. Denver, February 5 to 8, 2006. (Abst 575a)