



Pharmacy

Ritonavir increases levels of erectile dysfunction agent 49 fold

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Within the past few weeks, there have been several requests from providers in our clinic and HIV-infected patients regarding the new drug being marketed as Levitra by Bayer Pharmaceuticals. Levitra (vardenafil) is a new selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 recently FDA-approved for the treatment of erectile dysfunction in adult males over the age of 18 years. The increase in the prevalence of erectile dysfunction has been associated with increased awareness on the part of the public and providers, much like the increase in the prevalence of obesity, disorders of lipid and glucose metabolism, smoking, hypogonadism (especially when associated with HIV infection and AIDS) as well as depression. It is therefore not surprising that patients with HIV infection may experience different levels of difficulties with erectile dysfunction during different stages of their HIV disease trajectory. Though only available by prescription the internet availability of vardenafil makes it attractive for all patients including those with HIV infection.

While recent pharmacological advances have generated increased public interest and demand for clinical services regarding erectile dysfunction, epidemiological data on sexual dysfunction across social groups are scant for both men and women.

In reviewing the highlights of this new agent, it became necessary to address some of the issues of drug-drug interaction associated with its use in the setting of HIV disease.

DRUG INTERACTIONS OF CLINICAL SIGNIFICANCE WITH VARDENAFIL (LEVITRA)

Protease inhibitors

Vardenafil is eliminated primarily through hepatic metabolism, mainly CYP3A1 and to a lesser extent by CYP2C isoforms. Concurrent use of drugs that inhibit the CYP3A system, such as ritonavir, indinavir, ketoconazole, itraconazole, as well as drugs with moderate CYP3a activity such as erythromycin, result in significant increases in plasma levels of vardenafil. In the case of ritonavir, 600mg in a twice daily dosing regimen was reported to increase levels of vardenafil 49-fold with a 13-fold increase in C_{max} of Levitra. This drug interaction is a consequence of the blocking of the hepatic metabolism vardenafil by ritonavir, a highly potent CYP3A4 inhibitor which also inhibits CYP2C9. Ritonavir significantly increased the half-life of vardenafil to 26 hours. The clinical implications of this are not yet completely understood but such high levels may precipitate problems of priapism even more. Data on the effect of vardenafil on efavirenz and other non-nucleoside reverse transcriptase inhibitors are expected. It is of interest to note that no pharmacokinetic interactions were observed when vardenafil was used with the other drugs used to treat the co-morbidities often associated with HIV disease, such as glyburide, ranitidine, antacids such as Maalox, warfarin and digoxin.

Nitrates and nitric oxide producing drugs

The blood pressure lowering effects of oral nitrates (0.4mg) taken 1 and 4 hours after vardenafil and increases in heart rate were

potentiated by a 20 mg dose of Levitra in healthy middle-aged adult subjects. These effects were not observed when Levitra was taken 24 hours before the nitroglycerin dose. Potentiation of the hypotensive effects of nitrates in patients with ischemic heart disease has not been evaluated in clinical studies and concomitant use of Levitra with such nitrates is contraindicated.

Alpha blockers

Levitra should not be used by patients on alpha blocker therapy either as part of their antihypertensive regimen or for the treatment of benign prostatic hypertrophy (BPH). This is because significant hypotension was observed to develop in a substantial number of subjects when given to healthy volunteers as 10mg or 20mg 6 hours after a 10mg dose of terazosin (Hytrin). Six of eight subjects experienced a standing systolic blood pressure of less than 85mm Hg.

Patients on antiretroviral agents, like the general public, are aware of the new developments in the management of erectile dysfunction and are fielding their questions to pharmacy and other providers. It is in recognition of these questions and issues that are being raised by clients and providers, that the above quick review of clinically-relevant drug-drug interactions is hereby offered. ♦

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