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Tipranavir

Updated: September 1, 2017.

OVERVIEW

Introduction

Tipranavir is an antiretroviral protease inhibitor used in the therapy and prevention of human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS). Tipranavir can cause transient and usually asymptomatic elevations in serum aminotransferase levels and is a rare cause of clinically apparent, acute liver injury. In coinfected patients, hepatic injury during highly active antiretroviral therapy including tipranavir may be a result of exacerbation of the underlying chronic hepatitis B or C, rather than a direct effect of the medication.

Background

Tipranavir (tye pran' a vir) a nonpeptidic antiretroviral protease inhibitor that acts by binding to the catalytic site of the HIV protease, thereby preventing the cleavage of viral polyprotein precursors into mature, functional proteins that are necessary for viral replication. Tipranavir was approved for use in the United States in adults in 2005 and for children in 2008 for the therapy of HIV infection in combination with other antiretroviral agents. Tipranavir is typically used in combination with low "booster" doses of ritonavir, which inhibits its hepatic metabolism and improves its pharmacokinetics. Tipranavir is available in capsules of 250 mg and as an oral solution (100 mg/mL) for pediatric use under the brand name Aptivus. The recommended dosage of tipranavir for adults is 500 mg in combination with ritonavir 200 mg, both taken twice daily. The dose in children is based upon body weight or body surface area. Common side effects include gastrointestinal upset, nausea, diarrhea, headache, fatigue and, with long term use, hyperlipidemia and lipodystrophy.

Hepatotoxicity

Some degree of serum aminotransferase elevations occur in a high proportion of patients taking tipranavir containing antiretroviral regimens. Moderate-to-severe elevations in serum aminotransferase levels (>5 times the upper limit of normal) are found in 3% to 10% of patients, although rates may be higher in patients with HIV-HCV coinfection. These elevations are usually asymptomatic and self-limited and can resolve even with continuation of the medication. Clinically apparent liver injury from tipranavir is rare, and the clinical pattern of liver injury, latency and recovery have not been well defined. Several protease inhibitors have been associated with acute liver injury arising 1 to 8 weeks after onset, with variable patterns of liver enzyme elevation, from hepatocellular to cholestatic. Immunoallergic features (rash, fever, eosinophilia) are uncommon, as is autoantibody formation. The acute liver injury due to tipranavir is usually self-limited, but it can be severe, and isolated cases of acute liver failure have been reported to the sponsor. In HBV or HCV coinfected patients, some instances appear to be due to exacerbation of the underlying chronic liver disease, perhaps as a result of sudden

immune reconstitution. Tipranavir therapy has not been clearly linked to lactic acidosis and acute fatty liver that is reported in association with several nucleoside analogue reverse transcriptase inhibitors. Thus, tipranavir is associated with a high rate of serum enzyme elevations which is generally higher than with other protease inhibitors, for which reason it is considered a second-line HIV protease inhibitor.

Likelihood score: E* (unproven but suspected cause of clinically apparent liver injury).

Mechanism of Injury

The cause of the clinical hepatotoxicity from tipranavir is not known. Tipranavir is extensively metabolized by the liver, largely by the cytochrome P450 system (CYP3A4), and toxic intermediates may be the cause of some liver injury. In patients with HIV infection who are coinfected with either HBV or HCV, initiation of potent antiretroviral therapy may be associated with flares of the underlying chronic hepatitis, which may be the result of reconstitution of the immune system, viral interactions or a direct effect of the drug.

Outcome and Management

The severity of the liver injury from tipranavir ranges from mild and transient enzyme elevations to more marked and symptomatic enzyme elevations and, rarely, to acute hepatitis which is usually self-limited, but can result in acute liver failure and death. For these reasons, routine monitoring with liver tests done before and at regular intervals is recommended for patients taking tipranavir. Improvements in serum aminotransferase elevations usually start within a few days of stopping therapy and recovery is usually rapid. Rechallenge may lead to recurrence and should be avoided. There is little evidence for cross reactivity to the hepatotoxicity of tipranavir with other protease inhibitors or antiretroviral agents. The exacerbation of hepatitis B or C that can occur with tipranavir based combination antiretroviral therapies can be severe and lead to acute liver failure or progressive, end stage liver disease. Patients with HCV or HBV coinfection should be monitored prospectively for viral and serum aminotransferase levels and appropriate therapy instituted if possible.

References to tipranavir are included with references to all the HIV protease inhibitors in the overview section of Protease Inhibitors (updated September 2017). Most of the HIV protease inhibitors in clinical use are proteinomimetic drugs and are structurally unrelated.

Drug Class: Antiviral Agents, Antiretroviral Agents

Other Drugs in the Subclass, Protease Inhibitors: Amprenavir, Atazanavir, Darunavir, Fosamprenavir, Indinavir, Lopinavir, Nelfinavir, Ritonavir, Saquinavir

CASE REPORT

Case 1. Serum enzyme elevations during tipranavir/ritonavir therapy.

[Modified from: Jülg B, Bogner JR, Goebel FD. Severe hepatotoxicity associated with the combination of enfuvirtide and tipranavir/ritonavir: case report. AIDS 2006; 20:1563. PubMed Citation]

A 52 year old man with long standing HIV-HBV coinfection and exposure to multiple antiretroviral agents developed serum aminotransferase elevations 2 weeks after having tipranavir/ritonavir added to a chronic regimen of zidovudine, lamivudine and enfuvirtide. Serum enzymes, which had been normal before therapy, included ALT 538 U/L and GGT 238 U/L. A liver biopsy was done that showed mild hepatitis and no steatosis. At the patient's request, enfuvirtide rather than tipranavir was stopped, and serum enzymes decreased by 50%. Serum GGT levels increased and, at this point, tipranavir was stopped, whereupon all liver tests returned to normal during the next 4 weeks. Serial levels of HBV DNA were not available, but at the height of the enzyme elevations, HBV DNA was 20,000 copies/mL.

Key Points

Medication:	Tipranavir/ritonavir
Pattern:	Hepatocellular (R=5.5, based upon GGT results)
Severity:	Mild (ALT elevations without jaundice)
Latency:	2 weeks
Recovery:	4 weeks
Other medications:	Ritonavir, zidovudine, lamivudine, enfuvirtide

Comment

A complex course in a patient with multidrug resistant HIV infection on five antiretroviral agents. Serum ALT levels rose after addition of tipranavir to his chronic antiviral regimen. Stopping enfuvirtide was followed by partial improvement in liver tests, but complete resolution came only with stopping tipranavir. Tipranavir with low dose ritonavir has been associated with prominent ALT elevations (at least 5 times the upper limit of the normal range) in up to 10% of patients. In this instance, the enzyme elevations did not resolve until tipranavir was stopped. In the absence of serial testing of serum enzymes, bilirubin, HIV levels, CD4 counts as well as HBV DNA (with HBeAg and anti-HBe testing), the role of an exacerbation of the underlying chronic hepatitis B caused by immune reconstitution cannot be excluded.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Tipranavir – Aptivus®

DRUG CLASS

Antiviral Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Tipranavir	174484-41-4	C31-H33-F3-N2-O5-S