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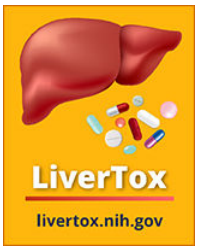

Saquinavir

Updated: September 1, 2017.

OVERVIEW

Introduction

Saquinavir is an antiretroviral protease inhibitor that is used in the therapy and prevention of human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS). Saquinavir can cause transient and usually asymptomatic elevations in serum aminotransferase levels and, rarely, can lead to clinically apparent acute liver injury. In HBV or HCV coinfected patients, highly active antiretroviral therapy with saquinavir may result of an exacerbation of the underlying chronic hepatitis B or C.

Background

Saquinavir (sa kwin' a vir) is an 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. Saquinavir was approved for use in the United States in 1995 and is still widely used in combination with other antiretroviral agents for the prevention and treatment of HIV infection in adults and children. Saquinavir is available under the brand name Invirase in 200 mg capsules and 500 mg tablets. It is usually used in combination with a low dose of ritonavir, which improves its pharmacokinetics and allows for twice daily dosing. The recommended dose of saquinavir is 1000 mg in combination with 100 mg of ritonavir, both taken twice daily. The most common side effects of HIV protease inhibitors include gastrointestinal upset, diarrhea, nausea, fatigue and, with long term use, hyperlipidemia and lipodystrophy.

Hepatotoxicity

Some degree of serum aminotransferase elevations occur in a high proportion of patients taking saquinavir 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 saquinavir is rare, and the clinical pattern of liver injury, latency and recovery have not been well defined. However, several other HIV protease inhibitors have been associated with symptomatic acute liver injury for which the clinical pattern has been defined. The injury usually arises 1 to 8 weeks after onset and has variable patterns of liver enzyme elevation, from hepatocellular to cholestatic. Immunoallergic features (rash, fever, eosinophilia) are uncommon, as is autoantibody formation. The injury is usually self-limited and resolves rapidly upon stopping the implicated protease inhibitor (Case 1).

Saquinavir has also been associated with a rapid onset (1 to 4 days) acute hepatic injury in patients who are taking rifampin and perhaps other agents that affect hepatic CYP 450 activity, such as phenobarbital (Case 1). This syndrome has the appearance of direct hepatotoxicity with acute hepatic necrosis. Jaundice is rare and the injury resolves rapidly once saquinavir is stopped. The cause of this rapid onset syndrome is unknown, but is probably caused by drug-drug interactions.

Finally, initiation of saquinavir based highly active antiretroviral therapy can lead to exacerbation of an underlying chronic hepatitis B or C in coinfected individuals, typically arising 2 to 12 months after starting therapy and associated with a hepatocellular pattern of serum enzyme elevations and concurrent increases in serum levels of hepatitis B virus (HBV) DNA or hepatitis C virus (HCV) RNA. These exacerbations of chronic viral hepatitis may represent immune reconstitution syndrome and can occur with initiation of any potent antiretroviral regimen. Saquinavir 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.

Likelihood score: D (Possible rare cause of clinically apparent liver injury).

Mechanism of Injury

The cause of liver enzyme elevations during saquinavir therapy is not known. Saquinavir is extensively metabolized by the liver via the cytochrome P450 system (CYP 3A4), and production of a toxic intermediate may underlie liver injury. Drugs that interact with the P450 system may predispose to hepatic injury from saquinavir. In patients with HCV or HBV coinfection, initiation of highly active 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 direct effects of the agents on the hepatitis virus.

Outcome and Management

The rare cases of clinically apparent liver injury attributed to saquinavir have been self-limited, and chronic hepatitis and vanishing bile duct syndrome have yet to be linked to saquinavir use. Rechallenge can lead to recurrence of liver injury and should be avoided. There is little evidence of cross reactivity among the various protease inhibitors which are typically proteinomimetic and structurally unrelated. In general, these other agents can be safely substituted. The exacerbation of hepatitis B or C that can occur with saquinavir based 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 saquinavir 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, Tipranavir

CASE REPORT

Case 1. Acute anicteric but symptomatic hepatic injury due to saquinavir.

[Modified from: Vandercam B, Moreau M, Horsmans C, Gala JL. Acute hepatitis in a patient treated with saquinavir and ritonavir: absence of cross-toxicity with indinavir. Infection 1998; 26:313. PubMed Citation]

A 46 year old man with HIV infection and idiopathic epilepsy developed nausea and vomiting a few hours after the first doses of an antiretroviral regimen of stavudine (40 mg), saquinavir (400 mg) and ritonavir (300 mg). He stopped the three medications and recovered rapidly. One week later, he restarted the medications and again developed nausea and vomiting within a few hours. He had no previous history of liver disease or exposure to viral hepatitis. He had been taking valproate, phenobarbital and primidone for epilepsy for many years and was on acyclovir as prophylaxis against herpes simplex for several months. Physical examination was normal and laboratory tests the day after the second single dose exposure showed ALT 1833 U/L, GGT 175 U/L without hyperbilirubinemia or eosinophilia. Tests for hepatitis A, B and C and other common viral infections that can affect the liver were negative. Serum levels of phenobarbital, valproate and primidone were in the normal range. The antiretroviral medications were stopped, symptoms resolved promptly, and serum enzyme abnormalities fell to normal within a few weeks. He was later restarted on stavudine in combination with lamivudine and indinavir without recurrence of symptoms or liver test abnormalities.

Key Points

Medication:	Saquinavir
Pattern:	Hepatocellular (R value=14.7 [using GGT instead of Alk P])
Severity:	Mild (serum aminotransferase elevations without jaundice)
Latency:	1 day upon reexposure
Recovery:	2 weeks
Other medications:	Valproate, phenobarbital, primidone, acyclovir, ritonavir, stavudine

Comment

While this case was considered "acute hepatitis", it actually represented gastrointestinal intolerance and marked serum aminotransferase elevations in response to a single dose of saquinavir (with ritonavir). Both the onset and the recovery from the hepatic injury were rapid and the patient remained anicteric. The coadministration of phenobarbital, valproate and/or primidone may have played a role in the hepatic injury, all being metabolized by the P450 system and causing major drug-drug interactions. In addition, one cannot say for sure whether it was saquinavir or ritonavir that was responsible for the reaction. Interesting, a similar pattern of abrupt ALT elevations and symptoms has been described in patients receiving saquinavir and ritonavir in combination with rifampin, another well-known CYP 3A4 inducer.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Saquinavir – Invirase®

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
Saquinavir	127779-20-8	C38-H50-N6-O5