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Zanamivir

Updated: January 4, 2015.

OVERVIEW

Introduction

Zanamivir is an inhibitor of the influenza neuramidase enzyme and is given by inhalation as therapy and prophylaxis against influenza A and B. Zanamivir has not been associated with clinically apparent liver injury, at least when given by inhalation.

Background

Zanamivir (za nam' i vir) is a sialic acid analogue and a potent inhibitor of the neuraminidase of influenza viruses. Inhibition of this enzyme causes a decrease in viral replication, probably as a result of interference with particle formation and release. Zanamivir is active against both influenza A and B viruses, but has no activity against other common upper respiratory tract viruses. In addition, resistance to zanamivir can develop rapidly. Zanamivir is indicated for therapy or post-exposure prevention of influenza A or B. Zanamivir was approved in the United States in 1999 and is frequently used during influenza outbreaks. Zanamivir is available as a powder for inhalation (5 mg/blister pack) under the brand name of Relenza. The recommended dose for therapy in adults is 2 oral inhalations of 5 mg each, twice daily for 5 days; the usual prophylactic regimen is 10 mg once daily for 10 days, starting within 2 days of close contact with an infected person or for 28 days in a community setting. Side effects are uncommon and include mild nausea, dizziness, headache, cough, nasal and throat irritation and bronchospasm.

Hepatotoxicity

In randomized controlled trials, 2% to 3% of zanamivir recipients developed ALT or AST elevations above twice the upper limit of the normal range, but a similar rate was found in placebo-treated patients. Despite widespread use, there is little evidence that zanamivir when used by inhalation causes liver injury, either in the form of asymptomatic serum enzyme elevations or clinically apparent liver disease. In pilot studies of intravenous zanamivir for severe influenza, serum enzyme elevations have been reported in ~10% of patients, occasionally with jaundice, but the role of zanamivir versus the underlying severe viral infection has not been defined.

Mechanism of Injury

Zanamivir has little hepatic metabolism and does not affect cytochrome P450 (CYP) activity. The typical course of zanamivir is for 5 to 10 days only, and the brief exposure and minimal hepatic metabolism may account for its absence of hepatotoxicity when given by inhalation.

Drug Class: Antiviral Agents

Other Drugs in the Class for Influenza: Amantadine, Baloxavir, Oseltamivir, Peramivir, Rimantadine

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Zanamivir – Relenza®

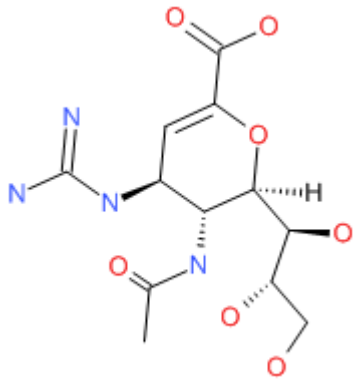
DRUG CLASS

Antiviral Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Zanamivir	139110-80-8	C12-H20-N4-O7	

ANNOTATED BIBLIOGRAPHY

References updated: 04 January 2015

Zimmerman HJ. Antiviral agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 621-3.

(Expert review of antiviral agents and liver injury published in 1999; amantadine and rimantadine have not caused "overt hepatic injury" and oseltamivir and zanamivir are not mentioned).

Núñez M. Influenza virus treatments. Hepatic toxicity of antiviral agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 513.

(Review of hepatotoxicity of antiviral agents; zanamivir is not discussed).

Acosta EP, Flexner C. Antiviral agents (nonretroviral). In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1593-1622. *(Textbook*

of pharmacology and therapeutics).

Hayden FG, Osterhaus AD, Treanor JJ, Fleming DM, Aoki FY, Nicholson KG, Bohnen AM, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza virus infections. GG167 Influenza Study Group. N Engl J Med 1997; 337: 874-80. PubMed PMID: 9302301.

(Two controlled trials of 5 day course of zanamivir or placebo in 417 adults with an influenza-like illness; "No drug-related effects on blood counts, blood chemical values, or urinalysis results were found").

Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. The MIST (Management of Influenza in the Southern Hemisphere Trialists) Study Group. Lancet 1998; 352: 1877-81. PubMed PMID: 9863784.

(Controlled trial of 5 day course of zanamivir vs placebo in 455 patients with influenza-like symptoms; "Laboratory results and vital signs did not differ between the two groups").

Freund B, Gravenstein S, Elliott M, Miller I. Zanamivir: a review of clinical safety. Drug Saf 1999; 21: 267-81. PubMed PMID: 10514019.

(Extensive review of safety and tolerance of zanamivir given by inhalation; ALT and AST elevations above twice the upper limit of normal occurred in 2-3% of zanamivir and 2% of placebo recipients; no mention of clinically apparent liver injury).

McNicholl IR, McNicholl JJ. Neuraminidase inhibitors: zanamivir and oseltamivir. Ann Pharmacother 2001; 35: 57-70. PubMed PMID: 11197587.

(Review of efficacy and safety of both zanamivir and oseltamivir; no mention of hepatotoxicity or ALT elevations).

Kaji M, Fukuda T, Tanaka M, Aizawa H. A side effect of neuraminidase inhibitor in a patient with liver cirrhosis. J Infect Chemother 2005; 11: 41-3. PubMed PMID: 15729487.

(Two patients [a man and a woman, ages 66 and 70] with cirrhosis and hepatocellular carcinoma received zanamivir after exposure to influenza and developed rash and fever 1-2 days later, but without any changes in the already elevated serum enzymes and bilirubin).

Jefferson T, Demicheli V, Rivetti D, Jones M, Di Pietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. Lancet 2006; 367: 303-13. PubMed PMID: 16443037.

(Analysis of 51 reports of 52 controlled trials of antivirals for influenza; "Neuraminidase inhibitors are not associated with any adverse events when used as treatment as opposed to prophylaxis").

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, 8 were attributed to antiviral agents, but none to anti-influenza medications).

Antiviral drugs for influenza. Med Lett Drugs Ther 2009; 51: 89-92. PubMed PMID: 20220738.

(Review of status of antiviral agents for prevention and treatment of influenza A and B; no mention of hepatic toxicity of any of the anti-influenza agents).

Antiviral drugs. Treat Guidel Med Lett 2013; 11 (127): 19-30. PubMed PMID: 23459414.

(Review of status of non-antiretroviral antiviral agents; no mention of hepatotoxicity in discussion of side effects of zanamivir).

Heneghan CJ, Onakpoya I, Thompson M, Spencer EA, Jones M, Jefferson T. Zanamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. BMJ 2014 Apr 9; 348: g2547. PubMed PMID: 24811412.

(Systematic review of 26 clinical trials of zanamivir for treatment and prevention of influenza found no evidence for increased risk of harm or adverse events).

Marty FM, Man CY, van der Horst C, Francois B, Garot D, Mánez R, Thamlikitkul V, et al. Safety and pharmacokinetics of intravenous zanamivir treatment in hospitalized adults with influenza: an open-label, multicenter, single-arm, phase II study. J Infect Dis 2014; 209: 542-50. PubMed PMID: 23983212.

(Among 130 adults with influenza treated with intravenous zanamivir for a median of 5 days, acute, but self-limited liver injury was reported in 17 patients [13%] and was considered severe in 3 [2%] based upon ALT levels above 3 times ULN and jaundice).