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Oseltamivir

Updated: January 24, 2014.

OVERVIEW

Introduction

Oseltamivir is an inhibitor of the influenza neuramidase enzyme and is used as therapy and prophylaxis against influenza A and B. Oseltamivir has not been associated with clinically apparent liver injury.

Background

Oseltamivir (oh" sel tam' i vir) phosphate is an ester prodrug of an antiviral enzyme inhibitor which, after absorption, is converted in the liver to oseltamivir carboxylase, the active intermediate. Oseltamivir caryboxylase is a potent inhibitor of the enzyme neuramidase of the influenza virus particle. Inhibition of this enzyme causes a decrease in viral replication, probably as a result of interference with particle formation and release. Oseltamivir is active against both influenza A and B virus, but has no activity against other common upper respiratory tract viruses. In addition, resistance to oseltamivir can develop rapidly. Oseltamivir is indicated for therapy or post-exposure prevention of influenza A and B. Oseltamivir was approved for in the United States in 1999 and is commonly used during influenza outbreaks. Oseltamivir is available as capsules of 30, 45 and 75 mg and as an oral suspension (6 mg/mL) under the brand name of Tamiflu. The recommended oral dose for therapy in adults is 75 mg twice daily for 5 days; the usual prophylactic dose is 75 mg once daily for 10 days, starting within 2 days of close contact with an infected person. Side effects are uncommon and include mild nausea, gastrointestinal upset, dizziness and headache.

Hepatotoxicity

Despite widespread use, there is little evidence that oseltamivir when given orally causes liver injury, either in the form of serum enzyme elevations or clinically apparent liver disease. A proportion of patients with acute influenza A may have minor serum enzyme elevations during the acute illness, but these appear to be independent of therapy and are not exacerbated by osteltamivir.

Mechanism of Injury

Oseltamivir is metabolized by the liver to the active intermediate oseltamivir carboxylate, but has little further hepatic metabolism and is excreted largely in the urine. The typical course of oseltamivir is for 5 to 10 days only, and the brief exposure and minimal hepatic metabolism may account for the absence of hepatotoxicity.

Drug Class: Antiviral Agents

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

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Oseltamivir – Tamiflu®

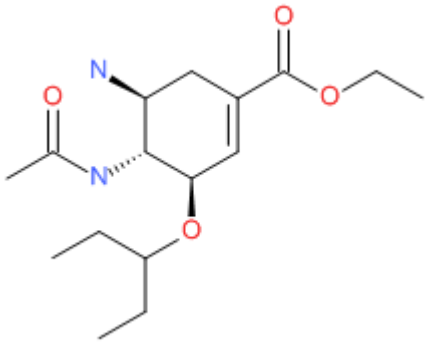
DRUG CLASS

Antiviral Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Oseltamivir	196618-13-0	C16-H28-N2-O4	

ANNOTATED BIBLIOGRAPHY

References updated: 24 January 2014

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"; oseltamivir is 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; oseltamivir 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).

Nicholson KG, Aoki FY, Osterhaus AD, Trottier S, Carewicz O, Mercier CH, Rode A, et al. Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. Neuraminidase Inhibitor Flu Treatment Investigator Group. Lancet 2000; 355: 1845-50. PubMed PMID: 10866439.

(Controlled trial in 726 adults given oseltamivir in two doses or placebo for 5 days; laboratory results "did not differ significantly from baseline" for any group; no serious adverse events, and no hepatitis or jaundice mentioned).

Treanor JJ, Hayden FG, Vrooman PS, Barbarash R, Bettis R, Riff D, Singh S, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. US Oral Neuraminidase Study Group. JAMA 2000; 283: 1016-24. PubMed PMID: 10697061.

(Controlled trial in 629 adults given oseltamivir in two doses or placebo for 5 days; no drug related serious adverse events, and standard laboratory tests did not change significantly in any group).

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).

Doucette KE, Aoki FY. Oseltamivir: a clinical and pharmacological perspective. Expert Opin Pharmacother 2001; 2: 1671-83. PubMed PMID: 11825310.

(Review of structure, pharmacology, antiviral activity, efficacy and safety of oseltamivir; no mention of ALT elevations or hepatotoxicity).

Dutkowski R, Thakrar B, Froehlich E, Suter P, Oo C, Ward P. Safety and pharmacology of oseltamivir in clinical use. Drug Saf 2003; 26: 787-801. PubMed PMID: 12908848.

(More than 11,000 subjects evaluated in premarketing studies and more than 4 million prescriptions worldwide, 2300 spontaneous reports of adverse events received, largely for gastrointestinal upset and rash; no hepatic adverse events reported).

Jones M, Del Mar C. Safety of neuraminidase inhibitors for influenza. Expert Opin Drug Saf 2006; 5: 603-8. PubMed PMID: 16907649.

(Neuraminidase inhibitors include oseltamivir and zanamivir [given by inhalation]; nausea is the only side effect found to be more common with receipt of oseltamivir vs placebo).

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").

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).

Dutkowski R, Smith JR, Davies BE. Safety and pharmacokinetics of oseltamivir at standard and high dosages. Int J Antimicrob Agents 2010; 35: 461-7. PubMed PMID: 20189775.

(Assessment of safety of higher doses [250-900 mg daily] of oseltamivir in 391 volunteers; headache, nausea and dizziness were common; laboratory data showed no significant changes from baseline or differences from placebo).

Yingying C. Abnormal liver chemistry in patients with influenza A H1N1. Liver Int 2011; 31: 902. PubMed PMID: 21645222.

(Among 131 patients admitted to a hospital for influenza A H1N1, 13% had abnormal ALT and 5% abnormal Alk P elevations, but the range of values was not provided).

Antiviral drugs for influenza 2013-2014. Med Lett Drugs Ther 2014; 55 (1429): 6-8. PubMed PMID: 24457560.

(Concise summary of safety and efficacy of medications for influenza appropriate for the 2013-14 season mentions that adverse effects of oseltamivir include nausea, vomiting and headache; no mention of liver injury).