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Fidaxomicin

Updated: August 8, 2017.

OVERVIEW

Introduction

Fidaxomicin is a semisynthetic macrolide antibiotic used to treat Clostridium difficile-associated diarrhea in adults. Fidaxomicin has minimal systemic absorption and has not been linked to serum enzyme elevations during therapy or to instances of clinically apparent, acute liver injury.

Background

Fidaxomicin (fye dax" oh mye' sin) is a semisynthetic macrolide antibiotic that is minimally absorbed and has potent bactericidal activity against Clostridia, but minimal or no antibacterial activity against normal gastrointestinal flora. Because of its lack of oral absorption and restricted antibacterial activity, fidaxomicin was developed as an oral therapy for Clostridium difficile and was approved for this use in the United States in 2011. Fidaxomicin is available in tablets of 200 mg under the brand name Dificid. The typical regimen is 200 mg twice daily for 10 days which is effective in eradicating C. difficile in 80% to 90% of patients. Fidaxomicin is generally well tolerated, but side effects can include nausea, vomiting, abdominal pain, diarrhea, dyspepsia, headache, gastrointestinal hemorrhage, anemia and neutropenia. Rare, but potentially severe adverse events include hypersensitivity reactions (rash, angioedema) and drug resistant bacterial infection.

Hepatotoxicity

In large clinical trials, therapy with fidaxomicin for ten days was associated with a low rate of serum aminotransferase elevations [1% to 3.2%], but rates with comparator agents such as vancomycin were similar [up to 2.7%]. There have been no reports of clinically apparent liver injury attributed to fidaxomicin. However, other oral macrolide antibiotics have been linked to many episodes of acute liver injury which can be severe and have resulted in fatalities. The onset of macrolide associated liver injury is typically 1 to 3 weeks after starting the drug and can arise after it is stopped. The injury is typically cholestatic, but can be mixed or hepatocellular. The hepatocellular cases are more likely to be severe and can result in acute liver failure. However, in most instances, recovery occurs within 4 to 8 weeks of withdrawal of the macrolide. No such cases, however, have been linked to use of fidaxomicin, which unlike the other macrolides is not absorbed orally.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

Fidaxomicin is minimally absorbed systematically and the cause of serum enzyme elevations or liver injury from its use is unknown.

Outcome and Management

The minor serum aminotransferase elevations that appear during therapy with fidaxomicin are usually benign, asymptomatic and resolve rapidly once fidaxomicin is stopped. It is unclear whether there is cross sensitivity to hepatic injury about the different macrolide antibiotics, but after severe injury from one macrolide, it is prudent to avoid use of the others.

Drug Class: Antiinfective Agents, Macrolide Antibiotics

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Fidaxomicin – Dificid®

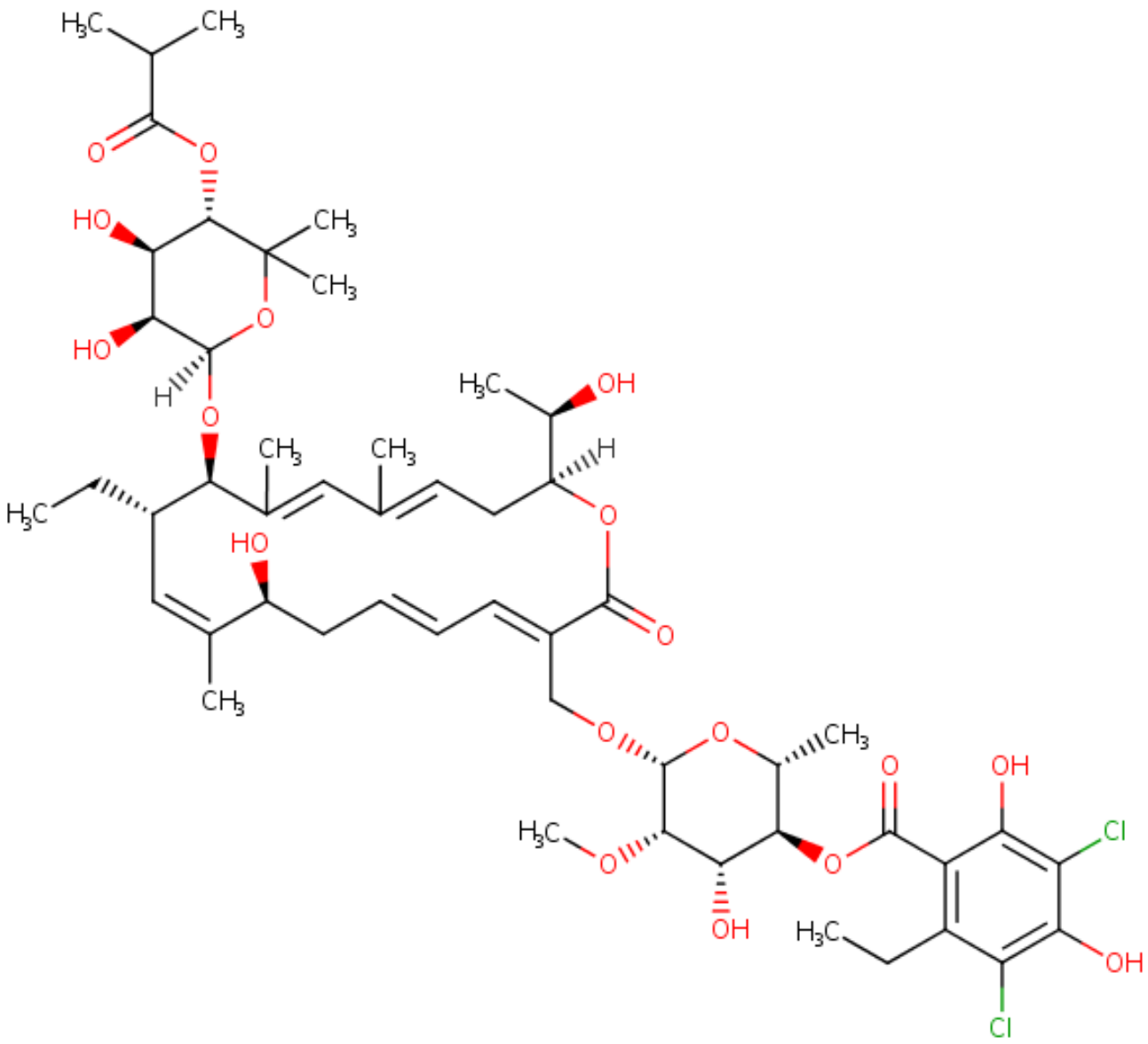
DRUG CLASS

Antiinfective Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Fidaxomicin	873857-62-6	C52-H74-Cl2-O18	

ANNOTATED BIBLIOGRAPHY

References updated: 08 August 2017

Moseley RH. Macrolide antibiotics. Hepatotoxicity of antimicrobials and antifungal agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced Liver Disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 466-7.

(Expert review of macrolide antibiotic induced liver injury does not discuss fidaxomicin).

MacDougall C, Chambers HF. Macrolides and ketolides. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1529-34.

(Textbook of pharmacology and therapeutics).

Leitner JM, Graninger W, Thalhammer F. Hepatotoxicity of antibacterials: pathomechanisms and clinical data. Infection 2010; 38: 3-11. PubMed PMID: 20107858.

(Review of antibiotic associated liver injury; the macrolide antibiotics may cause cholestatic hepatitis at an estimated rate of 3.6 per 100,000 prescriptions for erythromycin, 3.8 for clarithromycin, and 5.5 for telithromycin, compared to 10 for sulfonamides and 2000 per 100,000 for isoniazid; no mention of fidaxomicin).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, only one of which was due to a macrolide antibiotic [clarithromycin] and none were attributed to fidaxomicin).

Louie TJ, Miller MA, Mullane KM, Weiss K, Lentnek A, Golan Y, Gorbach S, et al.; OPT-80-003 Clinical Study Group. Fidaxomicin versus vancomycin for Clostridium difficile infection. N Engl J Med 2011; 364: 422-31. PubMed PMID: 21288078.

(Among 629 adults with acute, symptomatic C. difficile infection treated with oral vancomycin or fidaxomicin [200 mg twice daily] for 10 days, both response and adverse event rates were similar with both agents; 3 of 300 [1%] fidaxomicin- compared to none of 323 vancomycin-treated subjects had ALT or AST elevations that were considered "serious", but all resolved upon completing therapy).

Fidaxomicin (Dificid) for Clostridium Difficile Infection. Med Lett Ther 2011; 53: 23-4. PubMed PMID: 21921871.

(Concise review of the pharmacology, efficacy, safety and cost of fidaxomicin in comparison to vancomycin and metronidazole as therapy of C. difficile infection, mentions possible side effects of nausea, vomiting, abdominal pain, hemorrhage, anemia and neutropenia, but does not mention ALT elevations or hepatotoxicity).

Weiss K, Allgren RL, Sellers S. Safety analysis of fidaxomicin in comparison with oral vancomycin for Clostridium difficile infections. Clin Infect Dis 2012; 55 Suppl 2: S110-5. PubMed PMID: 22752858.

(Review of the safety of fidaxomicin from preclinical and clinical studies including results from 612 patients with C. difficile infection mentions that fidaxomicin was "well tolerated with a safety profile comparable to oral vancomycin", with liver test abnormalities arising in 3.2% fidaxomicin- vs 2.6% vancomycin-treated patients, and none in either group developing clinically apparent liver injury with jaundice).

Chen LF, Anderson DJ. Efficacy and safety of fidaxomicin compared with oral vancomycin for the treatment of adults with Clostridium difficile-associated diarrhea: data from the OPT-80-003 and OPT-80-004 studies. Future Microbiol 2012; 7: 677-83. PubMed PMID: 22702523.

(Summary of results from two phase 2 trials comparing fidaxomicin to vancomycin for symptomatic C. difficile associated diarrhea mentions that there were no significant drug-drug interactions and no "alterations of laboratory results attributable to fidaxomicin").

Cornely OA, Crook DW, Esposito R, Poirier A, Somero MS, Weiss K, Sears P, et al.; OPT-80-004 Clinical Study Group. Fidaxomicin versus vancomycin for infection with Clostridium difficile in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. Lancet Infect Dis 2012; 12: 281-9. PubMed PMID: 22321770.

(Among 535 patients with acute C. difficile infection treated orally with either fidaxomicin or vancomycin for 10 days, cure rates were similar between the two groups [92% vs 91%] and overall and serious adverse event rates were not different; no mention of ALT elevations or hepatotoxicity).

Fehér C, Múñez Rubio E, Merino Amador P, Delgado-Iribarren Garcia-Campero A, Salavert M, Merino E, Maseda Garrido E, et al. The efficacy of fidaxomicin in the treatment of Clostridium difficile infection in a real-world clinical setting: a Spanish multi-centre retrospective cohort. Eur J Clin Microbiol Infect Dis 2017; 36: 295-303. PubMed PMID: 27718071.

(Among 72 Spanish patients with C. difficile infection treated with fidaxomicin, the cure rate was 90% and adverse events were uncommon, although 2 patients had ALT elevations (mild-to-moderate), but neither was attributed to the drug treatment).