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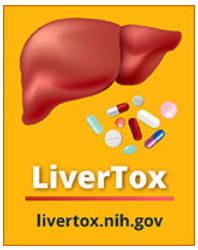

Antifungal Agents

Updated: May 18, 2017.

OVERVIEW

Antifungal drugs are a diverse group of medications used to treat fungal infections ranging from ringworm and athletes foot to esophageal candidiasis, coccidiomycosis, and cryptococcal meningitis. The antifungals are classified into several groups based on their structure and mechanisms of action. These classes include the polyenes, imidazoles, triazoles, allylamines, and echinocandins, as well as miscellaneous agents.

Polyene antifungals have an amphiphilic structure which binds to ergosterol, converting the fluid cell membrane of the fungal cell into a more crystalline state increasing permeability and precipitating cell lysis. Examples of polyenes (with date of approval and common brand names) include nystatin (1971: Mycostatin, Nystat) and amphotericin B (1971: Amphocin, Fungizone).

Imidazole and triazole antifungal drugs inhibit cytochrome P450 14α-demethylase which is responsible for converting lanosterol to ergosterol, which blocks cell membrane synthesis in fungi. Examples of imidazoles include ketoconazole (1981: Nizoral) and clotrimazole (1975: Mycelex). Examples of triazoles include fluconazole (1990: Diflucan), itraconazole (1992: Sporanox), posaconazole (2006: Noxafil) and voriconazole (2002: Vfend). Isavuconazonium (Cresemba: 2016) is a prodrug of isavuconazole and is available in both intravenous and oral forms, its indications restricted for serious, invasive fungal infections such as aspergilosis and mucormycosis. The triazoles are perhaps the most commonly used antifungal agents having excellent oral absorption, tolerance and tissue penetration.

The allylamines inhibit the enzyme squalene epoxidase, which is also required for ergosterol and thus fungal cytoplasmic membrane synthesis. An example of an allylamine is terbinafine (1998: Lamisil).

Echinocandins are the newest class of fungicidal agents. They inhibit the synthesis of β-D-glucan in fungal cell walls via inhibition of the enzyme 1,3-β glucan synthase. Examples of echinocandins include anidulafungin (2006: Eraxis), caspofungin (2001: Cancidas) and micafungin (2005: Mycamine). The echinocandins are administered intravenously and used largely for serious invasive fungal infections.

The miscellaneous fungicidal agents include the antimetabolite flucytosine (1971: Ancobon) and the microtubule inhibitor griseofulvin (2007: Grifulvin). Because pneumocystitis jiroveci (formerly carinii) is now considered a fungal agent, pentamine (1984: Pentam) may be considered a miscellaneous antifungal agent.

In general, the treatment of fungal infections is based upon inhibition of cell processes that are necessary in fungi, but do not harm critical cell pathways in human cells. Both fungi and humans are eukaryotic organisms and they share many cellular enzymes and pathways. These features account for the range of side effects seen with many antifungal agents. Most antifungal agents have been implicated in causing some degree of hepatotoxicity; clinically apparent liver injury with jaundice occurs most prominently with ketoconazole, fluconazole, voriconazole, and terbinafine.

The following drug records are discussed individually:

- Amphotericin B
- Anidulafungin
- Caspofungin
- Clotrimazole
- Echinocandins
- Fluconazole
- Flucytosine
- Griseofulvin
- Isavuconazonium
- Itraconazole
- Ketoconazole
- Micafungin
- Nystatin
- Pentamidine
- Posaconazole
- Terbinafine
- Voriconazole

ANNOTATED BIBLIOGRAPHY

References updated: 18 May 2017

Zimmerman HJ. Antifungal agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 609-11.

(Expert review of hepatotoxicity of antifungal agents published in 1999 discusses amphotericin, flucytosine, pentamidine, griseofulvin, ketoconazole, itraconazole, clotrimazole, and terbinafine).

Moseley RH. Antifungal agents. Antibacterial and antifungal agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 470-3. *(Review of hepatotoxicity of antifungal agents discusses amphotericin, caspofungin, ketoconazole, fluconazole, itraconazole, voriconazole, posaconazole, terbinafine, flucytosine and griseofulvin*

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Bennett JE. Antifungal agents. In, Brunton LL, Chabner B, Knollman K, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 157191.

(Textbook of pharmacology and therapeutics).

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 from 2004 to 2008, 8 cases [2.7%] were attributed to antifungal agents, including 4 due to terbinafine, 2 to fluconazole, 1 each to ketoconazole and itraconazole, none to voriconazole, amphotericin or the echinocandins).

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, of which 6 [4.5%] were caused by antifungal agents including 3 attributed to terbinafine, 2 ketoconazole, 1 itraconazole, but none to fluconazole, amphotericin B or the echinocardins).

Kao WY, Su CW, Huang YS, Chou YC, Chen YC, Chung WH, Hou MC, et al. Risk of oral anti-fungal agent-induced liver injury in Taiwanese. Br J Clin Pharmacol 2014; 77: 180-9. PubMed PMID: 23750489.

(Analysis of Taiwan National Health Insurance database from 2002-2008 identified 52 patients with drug induced liver injury among 90,847 users of oral antifungal agents; the incidence rates per 10,000 persons were 31.6 for fluconazole [12 cases, including the only 6 cases that were fatal], 4.9 for ketoconazole, 4.3 griseofulvin, 3.6 itraconazole and 1.6 terbinafine).

Antifungal drugs. Treat Guidel Med Lett 2012; 10 (120): 61-8. PubMed PMID: 22825657.

(Concise summary of recommendations and guidelines for use of antifungal drugs including the imidazoles and triazoles, echinocandins, terbinafine, flucytosine, and amphotericin; liver adverse events are mentioned for terbinafine, ketoconazole, fluconazole, itraconazole, posaconazole and voriconazole).

Raschi E, Poluzzi E, Koci A, Caraceni P, Ponti FD. Assessing liver injury associated with antimycotics: Concise literature review and clues from data mining of the FAERS database. World J Hepatol 2014; 6: 601-12. PubMed PMID: 25232453.

(Analysis of the FDA database on adverse reactions [2004 to 2011] identified 68,115 reports of liver injury including 1964 due to antifungal agents, the most common being terbinafine [422], fluconazole [412], voriconazole [361], amphotericin B [265], itraconazole [182], ketaconazole [94], and posaconazole [70]; among 112 cases with acute liver failure causes included fluconazole [31], terbinafine [27], voriconazole [19], amphotericin B [14], ketoconazole [6], posaconazole [5], and itraconazole [4]; liver injury from echinocandins was less frequent and cases attributed to nystatin, and nystatin even less).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 14 cases [1.6%] were attributed to antifungal agents including 7 due to terbinafine, 6 triazoles [4 fluconazole, 1 ketoconazole and 1 voriconazole], 1 micafungin and none amphotericin).

Lo Re V 3rd, Carbonari DM, Lewis JD, Forde KA, Goldberg DS, Reddy KR, Haynes K, et al. Oral azole antifungal medications and risk of acute liver injury, overall and by chronic liver disease status. Am J Med 2016; 129: 283-91. PubMed PMID: 26597673.

(Among 195,334 persons treated with oral azole antifungal agents analyzed from a Kaiser Permanente clinical database, the incidence of ALT or AST elevations above 200 U/L ranged from 1.3 to 19% and severe acute liver injury from none to 9.3%, highest rates associated with posaconazole and vorconazole; one death was reported which was attributed to ketoconazole).

Kyriakidis I, Tragiannidis A, Munchen S, Groll AH. Clinical hepatotoxicity associated with antifungal agents. Expert Opin Drug Saf 2017; 16: 149-165. PubMed PMID: 27927037.

(Review of the hepatotoxicity of antifungal agents states that all antifungal agents may cause hepatic toxicity).