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Clotrimazole

Updated: April 15, 2019.

OVERVIEW

Introduction

Clotrimazole is an imidazole antifungal agent used primarily in the treatment of skin, oral and vaginal candida infections. Clotrimazole is typically given topically or as oral or vaginal troches and has only modest systemic absorption. Nevertheless, clotrimazole given orally or as troches has been associated with transient and asymptomatic serum aminotransferase elevations during therapy, but it has not been linked to instances of clinically apparent acute liver injury.

Background

Clotrimazole (kloe trim' a zole) is a synthetic imidazole that has broad spectrum activity against Candida albicans and other yeast species. The azoles are believed to act by disruption of the fungal cell wall membrane. Clotrimazole is typically given topically or as oral or vaginal troches. When given as an oral troche, it should be allowed to dissolve in the mouth and not swallowed. Systemic absorption occurs even with the oral troche, but concentrations adequate as therapy of candida infections are found only in local oral tissue and saliva. Clotrimazole given orally (swallowed) was used in the past to treat various forms of candida infections, but it is not currently approved as tablets or capsules for gastrointestinal absorption. Clotrimazole was approved for use in the United States in 1975 and subsequently became available over-the-counter in topical creams (for superficial fungal infections) and vaginal formulations (for fungal vaginitis). The oral troche (lozenge) remains available only by prescription as large, slowly dissolving tablets (lozenges) containing 10 mg of clotrimazole generically and under commercial names such as Mycelex and Lotrimin. Current indications for the oral lozenges are as treatment or prevention of oropharyngeal candidiasis (oral thrush). The recommended regimen is one troche five times daily for 7 to 14 days. The vaginal troche is used once daily for 3 to 7 days. Side effects are not common but can include headache, nausea and itchiness. Side effects of topical administration include local rash, redness and burning. Serious adverse reactions are very rare.

Hepatotoxicity

Transient elevations in serum aminotransferase levels occur in up to 15% of patients treated with clotrimazole orally. The elevations are generally mild-to-moderate in degree and resolve spontaneously with or without discontinuation. Despite decades of widespread use, clotrimazole has not been linked to instances of clinically apparent hepatotoxicity.

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

Mechanism of Injury

The cause of the serum enzyme elevations during clotrimazole therapy is unknown, but many of the antifungal azoles have been implicated in causing liver injury. Because there is minimal systemic absorption, clotrimazole concentrations may not reach levels that could cause significant liver injury. Clotrimazole is metabolized in the liver via the cytochrome P450 system and can inhibit via CYP 3A4 activity and thus cause significant drug interactions with agents that are CYP 3A4 substrates. Because of its metabolism, the liver injury might be caused by a toxic or immunogenic intermediate.

Outcome and Management

The serum enzyme elevations attributed to clotrimazole therapy are usually mild and transient and rarely require dose adjustment or discontinuation. Nevertheless, the product labels for clotrimazole mention hepatotoxicity and recommend "periodic assessment of hepatic function", particularly in patients with preexisting liver disease. There is no information about cross sensitivity to hepatic injury between clotrimazole and other azole antifungal agents.

Drug Class: Antifungal Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Clotrimazole – Generic, Lotrimin®, Mycelex® (Troche)

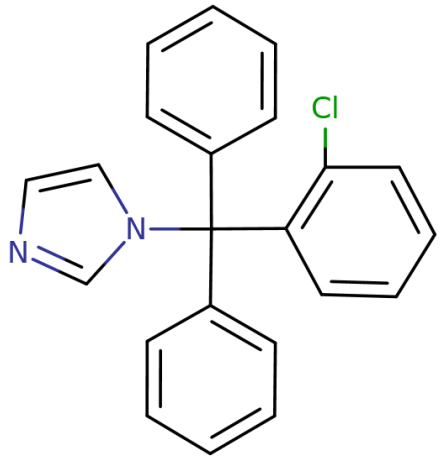
DRUG CLASS

Antifungal Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Clotrimazole	23593-75-1	C22-H17-Cl-N2	

ANNOTATED BIBLIOGRAPHY

References updated: 15 April 2019

1. 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; mentions that 5-15% of clotrimazole treated subjects have elevations of aminotransferase, alkaline phosphatase or bilirubin levels, but that there is inadequate information on its potential for hepatotoxicity).

Moseley RH. Antifungal agents. Antibacterial and antifungal agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 470-81.

(Review of hepatotoxicity of antifungal agents; clotrimazole is not discussed).

Rogers PD, Krysan DJ. Antifungal agents. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 1087-1104.

(Textbook of pharmacology and therapeutics).

Spiekermann PH, Young MD. Clinical evaluation of clotrimazole. A broad-spectrum antifungal agent. Arch Dermatol 1976; 112: 350-2. PubMed PMID: 769697.

(Among 1361 patients with various dermatomycoses treated with 1% clotrimazole solutions or creams vs matched placebos, clinical and mycological responses were higher with clotrimazole, and adverse events were rare [2.7%] and no more common than with placebo [3%]).

Rockoff AS. Chronic mucocutaneous candidiasis. Successful treatment with intermittent oral doses of clotrimazole. Arch Dermatol 1979; 115: 322-3. PubMed PMID: 434848.

(9 year old child with chronic mucocutaneous candidiasis was successfully managed with intermittent course of oral clotrimazole [500 mg 3 times daily for 2 weeks] and "the only toxicity was transient elevations of liver enzyme levels").

Yap BS, Bodey GP. Oropharyngeal candidiasis treated with a troche form of clotrimazole. Arch Intern Med 1979 139: 656-7. PubMed PMID: 375858.

(Among 56 cancer patients with 60 episodes of oropharyngeal candidiasis treated with clotrimazole [10 or 50 mg troches 5 times daily for an average of 14 days], 96% of both groups were cured and side effects "were minimal" and no abnormal biochemical finding "could be reasonably attributed to treatment").

Hughes D, Kriedman T. Treatment of vulvovaginal candidiasis with a 500-mg vaginal tablet of clotrimazole. Clin Ther 1984; 6: 662-8. PubMed PMID: 6383612.

(Among 26 women with vulvovaginal candidiasis enrolled in a randomized control trial, 9 of 10 treated with a single 500 mg tablet of clotrimazole but none of the placebo controls had a clinical and mycological response and no patients reported any adverse reactions).

Evans EG, Dodman B, Williamson DM, Brown GJ, Bowen RG. Comparison of terbinafine and clotrimazole in treating tinea pedis. BMJ 1993; 307 (6905): 645-7. PubMed PMID: 8401048.

(Among 211 patients with tinea pedis treated with terbinafine or clotrimazole cream for 4 weeks, clinical and mycological cure rates were higher with terbinafine and adverse events were minimal and limited to local side effects of burning, itching, redness and rash).

Stein GE, Mummaw N. Placebo-controlled trial of itraconazole for treatment of acute vaginal candidiasis. Antimicrob Agents Chemother 1993; 37: 89-92. PubMed PMID: 8381643.

(Among 95 women with vaginal candidiasis treated with itraconazole, clotrimazole or placebo, clinical and mycological responses were similar between the two drugs and greater than with placebo, while side effects arose in 17 [35%] on itraconazole, 1 [4%] on clotrimazole and 9 [41%] on placebo; one subject on itraconazole had transient [1 week] ALT elevations).

O-Prasertsawat P, Bourlert A. Comparative study of fluconazole and clotrimazole for the treatment of vulvovaginal candidiasis. Sex Transm Dis 1995; 22: 228-30. PubMed PMID: 7482105.

(Among 103 women with vulvovaginal candidiasis treated with a single oral dose of fluconazole or with 3 days of twice daily clotrimazole, clinical and mycological cure rates were similar and adverse event rates were uncommon, the vaginal clotrimazole troches associated with mild-to-moderate vaginal burning in 22% of subjects; no mention of hepatotoxicity).

Song J, Deresinski S. Hepatotoxicity of antifungal agents. Curr Opin Investig Drugs 2005; 6: 170-7. PubMed PMID: 15751740.

(Extensive review of hepatotoxicity from antifungals; clotrimazole is not discussed).

Vazquez JA, Patton LL, Epstein JB, Ramlachan P, Mitha I, Noveljic Z, Fourie J, et al.; SMiLES Study Group. Randomized, comparative, double-blind, double-dummy, multicenter trial of miconazole buccal tablet and clotrimazole troches for the treatment of oropharyngeal candidiasis: study of miconazole Lauriad® efficacy and safety (SMiLES). HIV Clin Trials 2010; 11: 186-96. PubMed PMID: 20974574.

(Among 577 patients with HIV infection and oropharyngeal candidiasis treated with miconazole [once daily] or clotrimazole [5 times daily] for 14 days, clinical cure rates were similar as were adverse event rates; GGT elevations occurring in 1% vs 3% and there were no hepatic serious adverse events or deaths).

Wang JL, Chang CH, Young-Xu Y, Chan KA. Systematic review and meta-analysis of the tolerability and hepatotoxicity of antifungals in empirical and definitive therapy for invasive fungal infection. Antimicrob Agents Chemother 2010; 54: 2409-19. PubMed PMID: 20308378.

(Systematic review of 39 controlled trials of antifungal agents in more than 8000 patients, but clotrimazole is not discussed).

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

(Concise summary of therapy of systemic fungal infections with recommendations on agents, dosage and duration of treatment and safety; no discussion of clotrimazole).

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, including 28 [54%] due to ketoconazole, 12 fluconazole, 8 griseofulvin, 3 itraconazole, 2 terbinafine, but clotrimazole was not included in the analysis).

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 were attributed to antifungal agents, including 6 to azoles but none to clotrimazole).