CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.2633205

Available online at: http://www.iajps.com ***Review Article***

GASTROINTESTINAL SIDE EFFECTS OF ANTIFUNGALS: A NARRATIVE REVIEW

Nehad J Ahmed[1*]

[1]Clinical Pharmacy department, College of Pharmacy, Prince Sattam Bin Abdulaziz University, ALkharj, Saudi Arabia.

Article Received: February 2019 **Accepted:** March 2019 **Published:** April 2019

Abstract:

Introduction*: Antifungals are used to treat different fungal infections which affect different body part. Systemic antifungals may result in many adverse effects especially gastrointestinal adverse effects. The Aim of these study is to illustrate the common and serious adverse effects of antifungals on gastrointestinal system.*

Methodology*: contains 3 parts, searching Micromedex, searching the Web of Science and searching Cochrane library for the adverse effects of antifungals.*

Results and Discussion*: The majority of the gastrointestinal adverse effects aren't serious such as nausea and vomiting, the only serious adverse effects results by systemic antifungals are gastrointestinal hemorrhage and pancreatitis.*

Conclusion

There are many common and serious adverse effects for antifungals. Clinicians should exclude the use of drugs associated with common or fatal adverse effects because numerous therapeutic alternatives exist for almost all potential infections.

Keywords : *Gastrointestinal , adverse Effects , Antifungals.*

Corresponding author:

Nehad J Ahmed,

Clinical Pharmacy department, College of Pharmacy,
Prince Sattam Bin Abdulaziz University, ALkharj, Saudi Arabia.
n.ahmed@psau.edu.sa, 00966543707806, tel:5886054.

QR code

Please cite this article in press Nehad J Ahmed., ***Gastrointestinal Side Effects Of Antifungals: A Narrative Review.,*** *Indo Am. J. P. Sci, 2019; 06(04).*

INTRODUCTION:

Fungal diseases are often caused by fungi that are common in the environment. These fungi sometimes live externally for example in soil and on plants and trees or internally for example in the inner surfaces or on human skin. Most of these fungi aren't dangerous, but some of fungi species can be harmful [1].

Antifungals are used to treat different fungal infections which affect different part especially skin, hair and nails. Antifungal agents may cause many adverse effects which are usually mild but occasionally can cause serious adverse effects [2].
The Aim of these study is to illustrate the common and serious adverse effects of antifungals on gastrointestinal system.

METHODOLOGY:

The methodology contains 3 parts, the first part includes searching Micromedex [3] for name of different antifungals and demonstrating the common or serious gastrointestinal adverse effects.

The second part includes searching the Web of Science [4] for articles related to the gastrointestinal adverse effects of antifungals.

The third part include searching Cochrane library [5] for the adverse effects of antifungals.

RESULTS AND DISCUSSION:

Do Antifungals cause common or serious adverse effects?

Many antifungal agents result in adverse effects on the gastrointestinal system. The majority of these adverse effects are common but not serious such as diarrhea, nausea, vomiting, indigestion, disorder of taste, abdominal pain, constipation, pancreatitis and loss of appetite. [3]. Table 1 shows the common and serious gastrointestinal adverse effects caused by antifungals.

Table 1. The common and serious gastrointestinal adverse effects on gastrointestinal system

Common	Serious
Diarrhea	Pancreatitis
Nausea	Gastrointestinal hemorrhage
Vomiting	
Disorder of taste	
Indigestion	
Abdominal pain	
Pancreatitis	
Constipation	
Loss of appetite	

Serious adverse effects include pancreatitis and gastrointestinal hemorrhage. Pancreatitis is caused by caspofungin Acetate and voriconazole , gastrointestinal hemorrhage is results from amphotericin B liposome and flucytosine[3]. Table 2 shows the antifungals that lead to serious gastrointestinal adverse effects.

Table 2. The antifungals that lead to serious gastrointestinal adverse effects

Antifungals that cause pancreatitis	Antifungals that cause gastrointestinal hemorrhage
Voriconazole	Flucytosine
Itraconazole	Amphotericin B Liposome

Out of these fourteen Antifungal medications, twelve medications cause nausea and vomiting, nine medications cause diarrhea, one causes indigestion, one causes disorder of taste, one causes abdominal pain, one causes constipation and one causes loss of appetite.

What are the Antifungals that result in common or serious gastrointestinal adverse effects?

The majority of systemic Antifungals cause adverse effects with the exception of nystatin that doesn't cause common or serious gastrointestinal adverse effects. A systematic review about the efficacy of nystatin in the treatment of oral candidiasis showed that the adverse effects for it are the poor taste and other gastrointestinal adverse effects such as nausea and vomiting but these adverse effects aren't common or serious [6].

Amphotericin B is available in more than one form. Amphotericin B is available as intravenous powder for solution and can cause renal impairment, infusion-related toxicity and gastrointestinal adverse effects [7]. Amphotericin B gastrointestinal adverse effects are caused commonly and include diarrhea, indigestion, loss of appetite, nausea and vomiting. Amphotericin B Lipid Complex is an intravenous suspension and doesn't cause common or serious adverse effects. Amphotericin B Liposome is an intravenous powder for solution and cause common adverse effects such as diarrhea, nausea and vomiting. In addition, Amphotericin B Liposome can cause a serious adverse effects which is gastrointestinal hemorrhage. Amphotericin B cholesteryl sulfate complex is available as intravenous powder for injection and causes nausea , vomiting commonly.

Liu M et al demonstrate that amphotericin B new formulations such as lipid formulations may have reduced adverse effects than the standard amphotericin and is suitable for the clinical practice [8]

Clotrimazole is available as topical cream and vaginal cream and may cause nausea and vomiting as a common adverse effects. Flucytosine is available as oral capsule and may cause abdominal pain, diarrhea, nausea and vomiting as a common adverse effects also can result in serious adverse effect which is gastrointestinal hemorrhage. Francis P et al demonstrated that there are many negative outcomes for the using of flucytosine in myelosuppressed patients such as the potentially dose-limiting, gastrointestinal, hepatic and hematologic toxicities of it. The major gastrointestinal adverse effects for it include reversible nausea and diarrhea [9].

Anidulafungin is available as intravenous powder for solution and can cause diarrhea as a common adverse effects. Caspofungin Acetate is available as intravenous powder for solution and can cause diarrhea as a common adverse effect and pancreatitis as a serious adverse effects.

Isavuconazonium Sulfate is available as intravenous powder for solution and oral capsule. Isacuconazole is generally well-tolerated, its adverse effects include elevated hepatic enzymes, headache, gastrointestinal effects and hypokalemia. Its gastrointestinal adverse effects include constipation, diarrhea, nausea and vomiting. [10,11,12]

Fluconazole is available as oral powder for suspension, oral tablet and intravenous solution and can cause gastrointestinal adverse effects and hepatic impairment. The gastrointestinal adverse effects of it include nausea and vomiting. Brown S reported that fluconazole commonly causes adverse effects such as headache, diarrhea and gastrointestinal pain [13]. Galgiani J reported that the adverse effects of fluconazole are primarily gastrointestinal [14]

Ketoconazole is used topically and systemically, and available as oral tablet and as topical (cream, foam, shampoo, gel) and causes nausea and vomiting commonly. Bok R et al reported that the most common adverse effects for ketoconazole is gastrointestinal intolerance, followed by fatigue, liver problems and changes in the skin [15].

Griseofulvin is available as oral suspension, oral tablet and causes common adverse effects such as diarrhea, nausea and vomiting. By comparison between the adverse effects between azole drugs and griseofulvin, the most common adverse effects for griseofulvin are allergic reactions and gastrointestinal disturbances and for azole medications nausea and vomiting [16].

Itraconazole is available as oral capsule, oral solution, oral tablet and causes abdominal pain, diarrhea, nausea and vomiting commonly also it causes serious adverse effects which is pancreatitis. Groll A et al demonstrated that only 11.5 % of the patient using cyclodextrin Itraconazole developed mild to moderate gastrointestinal disturbances [17]. Gupta A et al demonstrated that itraconazole is well tolerated and is effective, and the most common adverse effects are gastrointestinal upset, transient skin reaction and headache which are usually minor and reversible adverse effects [18]. Poirier M et al reported that itraconazole is generally well tolerated but can cause adverse effects, the most frequently reported adverse effects are dizziness and gastrointestinal disturbances [19]. Only 11.11 % of patients who used itraconazole

in another study developed minor gastrointestinal adverse effects [20]. Simon A et al demonstrated that itraconazole results in adverse effects such as gastrointestinal adverse effects in addition to other adverse effects that lead to the cessation of its using as a prophylaxis in about 11 % of all courses [21]

Terbinafine hydrochloride is used topically and systemically and is available as oral tablet, topical cream, topical spray and causes common adverse effects such as diarrhea, disorder of taste, indigestion, nausea and vomiting. Sacks PL et al comparing terbinafine tablets against placebo reported that systemic antifungals may lead to a fewer gastrointestinal disturbances compared to placebo [22]. Terbinafine can cause adverse effects such as gastrointestinal symptoms, headache and infections [16]. Ma Y et al reported that oral administration of terbinafine has been associated with many problems including gastrointestinal adverse effects [23].

Bell-Syer S et al showed that terbinafine, griseofulvin, itraconazole, fluconazole and ketoconazole caused adverse effects with gastrointestinal effects is the most commonly reported [24]. Darkes M.J.M et al demonstrated that the post marketing surveillance confirmed that the terbinafine is generally tolerable and only 10.5 % developed adverse events which are mainly gastrointestinal effects [25].

Effective treatment with griseofulvin, terbinafine, itraconazole and fluconazole in another study showed that adverse effects were reported only in griseofulvin group. [26]. Binder M et al showed that only 5.3 % of the patient receiving terbinafine developed adverse effects mainly gastrointestinal and skin rashes [27].

Goodfield M et al showed that only minor adverse-effects occurred in 33% of those taking terbinafine compared with 41% of the placebo-treated group, these adverse events were mainly affect the gastrointestinal system [28]. Oral treatment with terbinafine is effective and generally well tolerated in patients with onychomycosis, the adverse effects of terbinafine were mostly mild-to-moderate gastrointestinal symptoms [29]

Micafungin is another antifungal agent that causes common adverse effects such as diarrhea, nausea, vomiting and is available as intravenous powder for solution. Posaconazole is available as intravenous solution, oral suspension, oral tablet and causes diarrhea, nausea, vomiting commonly. Epstein D et al showed that Micafungin should be used as antifungal prophylaxis in myelodysplastic syndrome and in acute leukemia instead of posaconazole due to gastrointestinal intolerance or adverse effects of it [30]. Posaconazole is well tolerated, the most common complaint of it is gastrointestinal adverse effect mainly diarrhea and nausea [31].

Voriconazole is available as intravenous powder for injection, oral powder for suspension, oral tablet and causes common adverse effects such as diarrhea, nausea and vomiting and serious adverse effects such as pancreatitis. Voriconazole use results in gastrointestinal, neurological, dermatological, renal and hepatobiliary adverse drug reactions [32].

The main toxicities for the using of high dose of voriconazole are gastrointestinal and neuropsychiatric toxicities [33]. Xu SX et al reported that voriconazole results in lower gastrointestinal adverse effects over fluconazole [34]. Xu S et al study about the pharmacokinetics of voriconazole demonstrated that voriconazole results in mild to moderate gastrointestinal adverse effects [35]. Lemetayer J et al stated that both posaconazole and voriconazole cause lower gastrointestinal adverse effects but greater hepatic adverse effects than fluconazole [36]

CONCLUSION:

There are many common adverse effects for antifungals such as diarrhea, nausea, vomiting, abdominal pain, loss of appetite, constipation and other adverse effects that occur commonly with systemic antifungals. Serious adverse effects include pancreatitis that is caused mainly by caspofungin acetate and voriconazole , and gastrointestinal hemorrhage that is caused mainly from amphotericin B liposome and flucytosine. Clinicians should eliminate the use of drugs associated with common or fatal adverse effects because numerous therapeutic alternatives exist for almost every potential infection.

REFERENCES:

1. CDC [Internet]. Centers for Disease Control and Prevention. 2018 [cited 18 December 2018]. Available from: https://www.cdc.gov/Antifungal medicines [Internet]. nhs.uk. 2018 [cited 18 December 2018]. Available from: https://www.nhs.uk/conditions/antifungal-medicines/
2. Antifungals: Adverse effects. (November 27, 2018). IBM Micromedex® Drug Ref. [Mobile application software] Retrieved from https://play.google.com
3. Web of Science - Clarivate [Internet]. Clarivate. 2018 [cited 18 December 2018]. Available from: https://clarivate.com/products/web-of-science/
4. Cochranelibrary.com. (2019). *Cochrane Library*. [online] Available at:

https://www.cochranelibrary.com/cdsr/reviews/topics [Accessed 4 Mar. 2019].
5. Lyu X, Zhao C, Hua H, Yan Z. Efficacy of nystatin for the treatment of oral candidiasis: a systematic review and meta-analysis. Drug Design, Development and Therapy. 2016;:1161.
6. Johansen H, Gøtzsche P. Amphotericin B versus fluconazole for controlling fungal infections in neutropenic cancer patients. Cochrane Database of Systematic Reviews. 2014;.
7. Liu M, Chen M, Yang Z. Design of amphotericin B oral formulation for antifungal therapy. Drug Delivery. 2017;24(1):1-9.
8. Francis P, Walsh T. Evolving Role of Flucytosine in Immunocompromised Patients: New Insights into Safety, Pharmacokinetics, and Antifungal Therapy. Clinical Infectious Diseases. 1992;15(6):1003-1018.
9. Slain D, Cleary J. Isavuconazonium Sulfate: a Novel Antifungal Agent. Current Fungal Infection Reports. 2015;9(4):302-313.
10. Yamazaki T, Desai A, Han D, Kato K, Kowalski D, Akhtar S et al. Pharmacokinetic Interaction Between Isavuconazole and a Fixed-Dose Combination of Lopinavir 400 mg/Ritonavir 100 mg in Healthy Subjects. Clinical Pharmacology in Drug Development. 2016;6(1):93-101.
11. Shirley M, Scott L. Isavuconazole: A Review in Invasive Aspergillosis and Mucormycosis. Drugs. 2016;76(17):1647-1657.
12. Brown S. Efficacy of Fluconazole for the Treatment of Onychomycosis. Annals of Pharmacotherapy. 2009;43(10):1684-1691.
13. Galgiani J. Fluconazole, a New Antifungal Agent. Annals of Internal Medicine. 1990;113(3):177.
14. Bok R, Small E. The Treatment of Advanced Prostate Cancer with Ketoconazole. Drug Safety. 1999;20(5):451-458.
15. Kreijkamp-Kaspers S, Hawke K, Guo L, Kerin G, Bell-Syer S, Magin P et al. Oral antifungal medication for toenail onychomycosis. Cochrane Database of Systematic Reviews. 2017;.
16. Groll A, Wood L, Roden M, Mickiene D, Chiou C, Townley E et al. Safety, Pharmacokinetics, and Pharmacodynamics of Cyclodextrin Itraconazole in Pediatric Patients with Oropharyngeal Candidiasis. Antimicrobial Agents and Chemotherapy. 2002;46(8):2554-2563.
17. Gupta A, Chwetzoff E, Del Rosso J, Baran R. Hepatic Safety of Itraconazole. Journal of Cutaneous Medicine and Surgery. 2002;6(3):210-213.
18. Poirier M, Cheymol G. Optimisation of Itraconazole Therapy Using Target Drug Concentrations. Clinical Pharmacokinetics. 1998;35(6):461-473.
19. Gupta, Solomon, Adam. Itraconazole oral solution for the treatment of tinea capitis. British Journal of Dermatology. 1998;139(1):104-106.
20. Simon A, Besuden M, Vezmar S, Hasan C, Lampe D, Kreutzberg S et al. Itraconazole prophylaxis in pediatric cancer patients receiving conventional chemotherapy or autologous stem cell transplants. Supportive Care in Cancer. 2006;15(2):213-220.
21. Sacks PL, Harvey RJ, Rimmer J, Gallagher RM, Sacks R.Topical and systemic antifungal therapy for the symptomatic treatment of chronic rhinosinusitis. Clinical Otolaryngology. 2011;36(5):489-490.
22. Ma Y, Chen X, Guan S. Terbinafine: Novel formulations that potentiate antifungal activities. Drugs of Today. 2015;51(3):197.
23. Bell-Syer S, Khan S, Torgerson D. Oral treatments for fungal infections of the skin of the foot. Cochrane Database of Systematic Reviews. 2012;.
24. Darkes M.J.M., Scott L.J., Goa K.L. Terbinafine: A review of its use in onychomycosis in adults. American Journal of Clinical Dermatology. 2003;4:39–65.
25. Gupta A, Adam P, Dlova N, Lynde C, Hofstader S, Morar N et al. Therapeutic Options for the Treatment of Tinea Capitis Caused by Trichophyton Species: Griseofulvin Versus the New Oral Antifungal Agents, Terbinafine, Itraconazole, and Fluconazole. Pediatric Dermatology. 2001;18(5):433-438.
26. Binder M, Nell G. Oral terbinafine (LamisilR) in the short-term treatment of fungal infections of the skin: results of a post-marketing surveillance study. Mycoses. 1999;42(9-10):555-558.
27. GOODFIELD M. Short-duration therapy with terbinafine for dermatophyteonychomycosis: A multicentre trial. British Journal of Dermatology. 1992;126(s39):33-35.
28. SCHROEFF J, CIRKEL P, CRIJNS M, DIJK T, GOVAERT F, GROENEWEG D et al. A randomized treatment duration-finding study of terbinafine in onychomycosis. British Journal of Dermatology. 1992;126(s39):36-39.
29. Epstein D, Seo S, Huang Y, Park J, Kimek V, Tallman M et al. Micafungin vs. Posaconazole Prophylaxis in Patients with Acute Leukemia or Myelodysplastic Syndrome: A Randomized, Open-label Study. Open Forum Infectious Diseases. 2017;4(suppl_1):S538-S538.

30. SCHILLER D, FUNG H. Posaconazole: An extended-spectrum triazole antifungal agent. Clinical Therapeutics. 2007;29(9):1862-1886.
31. Beata S, Donata U, Jarosław D, Tomasz W, Anna W. Influence of CYP2C19*2/*17 genotype on adverse drug reactions of voriconazole in patients after allo-HSCT: a four-case report. Journal of Cancer Research and Clinical Oncology. 2017;143(6):1103-1106.
32. Levine M, Chandrasekar P. Adverse effects of voriconazole: Over a decade of use. Clinical Transplantation. 2016;30(11):1377-1386.
33. Xu SX, Shen JL, Tang XF, Feng B, Xu HQ. Newer antifungal agents micafungin and voriconazole for fungal infection prevention during hematopoietic cell transplantation: a meta-analysis. European Review for Medical and Pharmacological Sciences. 2016;20(2):381-90.
34. Xu S, Shen J, Tang X, Feng B. Newer Antifungal Agents for Fungal Infection Prevention During Hematopoietic Cell Transplantation: A Meta-Analysis. Transplantation Proceedings. 2013;45(1):407-414.
35. Lemetayer J, Dowling P, Taylor S, Papich M. Pharmacokinetics and distribution of voriconazole in body fluids of dogs after repeated oral dosing. Journal of Veterinary Pharmacology and Therapeutics. 2015;38(5):451-456.