International Journal of Scientific and Innovative Research 2017; 5(1) : 55-58
P-ISSN 2347-2189, E- ISSN 2347-4971

ANTIFUNGAL DRUGS- ITRACONAZOLE AND FLUCONAZOLE INDUCED HEPATOTOXICITY AND IT'S AMELIORATION BY HERBAL PLANT EXTRACTS

Shivam Tiwari [2], Anil K. Meena [1], Pallavi Singh[3], Rishi Saxena [2] and *R.K. Singh[1]

[1]Division of Toxicology, CSIR-Central Drug Research Institute, Lucknow, Uttar Pradesh, India, [2] Department of Microbiology, Bundelkhand University, Jhansi, Uttar Pradesh, India, [3]Department of Biotechnology, IILM Academy, Greater Noida, Uttar Pradesh, India

*Address for Correspondence : Dr. R. K. Singh, Professor & Chief Scientist, Division of Toxicology , CSIR- Central Drug Research Institute, Lucknow , Uttar Pradesh, India,
Email : rktox@yahoo.com, rk_singh@cdri.res.in

ABSTRACT

Itraconazole and fluconazole are oral antifungal drugs, which have a wide spectrum antifungal activity and better efficacy than the older drugs. However, both drugs have been associated with hepatotoxicity in susceptible patients. The mechanism of antifungal drug-induced hepatotoxicity is largely known. Therefore, the aim of this present study was to investigate and compare the hepatotoxicity induced by these drugs in vivo. Rats were treated intraperitoneally with itraconazole or fluconazole at dose of 100 and 200 mg/kg body weight of the period of 14 days doses. Plasma and liver samples were taken at the end of the study. A statistically significant and dose dependent increase of plasma alanine aminotransferase (ALT) and alkaline phosphatase (ALP) activities were detected in itraconazole-treated group. In addition, dose-dependent hepato cellular necrosis, degeneration of periacinar and mizonal hepatocytes, bile duct hyperplasia and biliary cirrhosis and giant cell granuloma were observed histologically in the same group.
***Keywords**:* Itraconazole; Fluconazole; Hepatotoxicity.

INTRODUCTION

Itracona zole and fluconazole are triazole antifungal drugs, which are multi-ringed synthetic compounds containing three nitrogen atoms in the azole ring; the imidazoles (ketoconazole and miconazole) contain only two nitrogen atoms in the azole ring Both of the triazole drugs are broad spectrum antifungal agents and exhibit many similarities in their pharmacological attributes. These drugs are currently used to treat infections caused by *Candida albicans*, *As per gillus-paracoccidioidesbrasiliensis*, *Sprothrixschenckii*, *Histoplasmacapsulaturm*, *Cryptococcus neoformans* and many others The drugs are shown to be active both using animal models or clinically. As other azole antifungal drugs, the triazole antifungals are primarily fungi-static at clinically achieved plasma levels. Mechanistically, these inhibit the synthesis of ergosterol which is an essential component of fungal cell membrane causing abnormalities in the membrane permeability, membrane-bound enzyme activity and increased saturation of fatty acids in the lipid bi-layer. The triazoles are thought to have greater anti-fungal potency, lower toxicity and a wider antifungal spectrum than the imidazoles . However, it has been reported that itraconazole and fluconazole induce adverse drug reactions (ADRs). These include mild reversible ADRs such as gastrointestinal disturbances (dyspepsia, nausea, abdominal pain and constipation),dizziness and pruritis. However, rare but severe hepatotoxicity has been reported in patients undergoing itraconazoleor fluconazole therapy and this is important clinically due to the fatalities. The mechanism of triazole-induced liver damage is unknown. Previous studies had suggested that the hepatotoxicity could be due to metabolic idiosyncrasy.

Mechanism of Fluconazole Induced hepatotoxicity

Fluconazole has excellent *in-vitro* activity against *C. Albicans*[1] . Fluconazole also effective against some non-*albicans Candida*species, including *Candida parapsilosis*, *Candida tropicalis* and *Candida glabrata*, although higher doses may be required[2,3]. Fluconazole is effective against *C. albicans* infections at a wide range of body sites and tissues, irrespective of the patient's immune status[4,5]. Indications in adults include vaginal, mucosal, dermal and systemic candidosis. Prophylactic administration of fluconazole can be useful in patients considered at risk of fungal infections as a consequence of neutropenia following chemotherapy or radiotherapy. Experimental evidence and clinical case reports suggest that prophylaxis with fluconazole may be useful in preventing *C. albicans*-associated endocarditis. Fluconazole is suitable and effective for use in children, but appropriate dosage adjustments should be made. In the elderly, normal adult dose regimens should be used if there is no evidence of renal impairment. In those with renal impairment, no adjustments in single-dose therapy are required; for multiple-dose therapy, either the dosage interval should be increased or the daily dosage should be reduced. Itraconazole has *in-vitro* activity against a greater range of *Candida*species than fluconazole

Itraconazole was enhanced by a cytochrome P450 inhibitor SKF 525A as judged by assessing LDH, AST, and ALT activities. This inhibitor had no effect on the cytotoxicity of fluconazole. From a mechanistic perspective, cytochrome P450 plays a key role in the deactivation/detoxification of itraconazole or its metabolite/s. In addition, the hepatotoxicity of itraconazole also reduced hepatocytes ATP levels. *In vitro* techniques are useful tools for investigating toxicity of drugs and their metabolites. The function of cytochrome P450 in toxicity process was tested with P450 inhibitors (SKF 525A and curcumin). SKF 525A was slightly toxic to hepatocytes at 25 mg/kg pre-treatment. Based from our previous and current findings, we can strongly conclude that cytochrome P450 is involved in the detoxification of itraconazole or its reactive metabolites. Indeed, cytochrome P450 is responsible for the metabolism of itraconazole and many other azole in the liver. However, we are still unsure of which metabolites or the parent drug itself is responsible for the hepatotoxicity observed clinically

Itraconazole and Fluconazole as anti HIV Therapy

Itraconazole capsules are effective and indicated for the treatment of a number of localized and systemic fungal infections in adults, irrespective of their immune status These include vulvovaginal and oropharyngeal candidasis. Because of its lipophilicity, itraconazole distributes to the nails and the capsule formulation is effective in the treatment of onychomycosis. Itraconazole capsules can be used as maintenance therapy in patients with AIDS and as prophylaxis before expected neutropenia, but as absorption is often impaired, blood monitoring should be performed and, if necessary, the dose should be increased. There are inadequate data on itraconazole capsules in children (<12 years) and the elderly for their use to be recommended in these special patient populations (unless the potential benefits outweigh the risks).

Most studies examining the effcacy of itraconazole solution have been in patients with impaired immunity. Two large comparative studies with fluconazole were in HIV-positive patients with oral(n = 244), or oropharyngeal (n = 190) candidiasis: 14 days of itraconazole solution was at least as effective as fluconazole in effecting a clinical response (≥87%). In a further study of 126 immunocompromised patients with oesophageal candidiasis, itraconazole solution and fluconazole led to a clinical response in 94% and 91% of cases, respectively.A comparative study examining the prophylactic use of itraconazole solution and fluconazole in 445 patients who were expected to be neutropenic following chemotherapy demonstrated that both agents prevent fungal infections in most cases (>97%) [6,7]. At present, itraconazole solution, in a dosage of 200 mg od or 100 mg bd for 1 week, repeated as necessary, is indicated solely for the treatment of oral and oesophageal candidiasis in HIV-positive or immune compromised adults. No data are available on the suitability of itraconazole solution for use in children and the elderly and, as with the capsule formulation, itraconazole solution should not be

used routinely in these patients.

Hepatoprotective medicinal plants

Plants and polyherbal formulations are used for the treatment of liver diseases. However, in most of the severe cases, the treatments are not satisfactory. Although experimental evaluations were carried out on a good number of these plants and formulations, the studies were mostly incomplete and insufficient. The therapeutic values were tested against a few chemicals-induced subclinical levels of liver damages in rodents. Even common dietary antioxidants can provide such protection from liver damage caused by oxidative mechanisms of toxic chemicals. However, experiments have clearly shown that plants such as *Hibiscus rosa sinensis, Saraca indica, Plumbago zylenica, Eclipta alba, Silibum marianum,* and *Trichopus zeylanicus* are sufficiently active against, at least, certain hepatotoxins. Screening plants for antihepatitis activities remains in its infancy. *E. alba, Glycyrrhiza glabra, A. paniculata* and *P. amarus* are likely to be active against Hepatitis B virus. In the case of severe liver damage, most of the liver cells die or turn into fibrotic state. In this case, the treatment should include in addition to the therapeutic agents, agents which can stimulate liver cell proliferation. For developing satisfactory herbal combinations to treat severe liver diseases, plants have to be evaluated systematically for properties such as antiviral activity (Hepatitis B, Hepatitis C, etc), antihepatotoxicity (antioxidants and others), stimulation of liver regeneration and choleretic activity. The plants with remarkable activities for each of the above properties have to be identified. Single plant may not have all the desired activities. A combination of different herbal extracts/'fractions is likely to provide desired activities to cure severe liver diseases. Development of such medicines with standards of safety and efficacy can revitalise treatment of liver disorders and hepatoprotective activity.

DISCUSSION

The purpose of the present study is to compare the hepatotoxicity of clinically used doses of fluconazole and itraconazole. The pattern of liver enzyme levels indicated that ketoconazole, fluconazole and itraconazole caused mixed hepatic injury (i.e., cholestatic-hepatocellular injury). Azole antifungal agents have been reported to cause both hepatocellular and cholestatic injury . [8] The increase in liver enzymes with longer treatment duration was noted with the antifungal agents, with itraconazole and fluconazole recording the highest changes in liver enzymes. In contrast, significant histological changes were observed with itraconazole. An in vitro study using rat hepatocyte cultures also reported similar findings regarding the relative hepatotoxicity itraconazole and fluconazole. [9]

CONCLUSION

Liver enzyme levels suggested that fluconazole is likely to cause liver injury than itraconazole while histopathological examinations revealed that fluconazole is more hepatotoxic than itraconazole. The diagnostic criteria used in the evaluation of hepatotoxicity of antifungal agents should be taken into consideration when reviewing the evidence on their relative hepatotoxicity. Given the poor correlation between liver enzymes and the extent of liver injury ,it is important to confirm liver injury through histological examination before diagnosis of hepatotoxicity can be made in clinical settings.

Medicnal plants are good sourec of antioxidents due to the presence of secondary metabolites of flvonoids, terpenoids, and essential oils. These are good source of hepatoprotcetive agents. Present review revels the hepatotpro tective activity of medicinal plants.

REFERENCES

1. Arévalo, M. P., Arias, A., Andreu, A., Rodríguez, C. & Sierra, A. (1994 Fluconazole, itraconazole and ketoconazole in vitro activity against Candida sp. Journal of Chemotherapy
2. Van'tWout, J. W. 1996 Fluconazole treatment of Candidal infections caused by non-albicans Candida species. European Journal of Clinical Microbiology and Infectious Diseases15238–42.
3. Anaissie, E., Bodey, G. P., Kantarjian, H., David, C., Barnett, K. & Bow, E. et al. (1991 Fluconazole therapy for chronic disseminated candidiasis in patients with leukemia and prior amphotericin B therapy. American Journal of Medicine 9114250.
4. Finlay, P. M., Richardson, M. D. & Robertson,

patients undergoing radiotherapy for head and A. G. (1996). A comparative study of the effcacy of fluconazole and amphotericin B in the treatment of oropharyngeal candidosis in neck tumours. British Journal of Oral and Maxillofacial Surgery 34, 23–5.

5. Kaplan, B., Rabinerson, D. & Gibor, Y. (1997). Single-dose systemic oral fluconazole for the treatment of vaginal candidiasis.International Journal of Gynaecology and Obstetrics 57, 281–6.
6. Ikemoto, H. (1989). A clinical study of fluconazole for the treatment of deep mycoses. Diagnostic Microbiology and Infectious Disease 12, 239S–47S.
6. Rex, J. H., Bennett, J. E., Sugar, A. M., Pappas, P. G., van der Horst, C. M., Edwards, J. E. et al. (1994). A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia. New England Journal of Medicine 331, 1325– 30.
7. M.Thiim and L.S . Friedman,"Hepatotoxicity of antibiotics and antifungals," Clinics in Liver Disease, vol. 7, no. 2, pp. 381–399, 2003.
8. N. Somchit, S. M. Hassim, and S. H. Samsudin, "Itraconazole and fluconazole-induced toxicity in rat hepatocytes: a comparative *in vitro* study," Human and Experimental Toxicology, vol. 21,no.1,pp.43–48,2002