Journal of Biomedical and Pharmaceutical Research
Available Online at www.jbpr.in
CODEN: - JBPRAU (Source: - American Chemical Society)
NLM (National Library of Medicine): ID: (101671502)
Index Copernicus Value 2018: 88.52
Original Research Article
Volume 9, Issue 5: September-October: 2020, 16-21
ISSN (Online): 2279-0594
ISSN (Print): 2589-8752

ADVERSE DRUG REACTION MONITORING OF FLUCONAZOLE IN A TERTIARY CARE HOSPITAL

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Article Info: Received 16 September 2020; Accepted 08 October. 2020
DOI: https://doi.org/10.32553/jbpr.v9i5.807
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Conflict of interest statement: No conflict of interest

Abstract:
Objective: To study the incidence and pattern of adverse effects of Antifungal drug Fluconazole and to assess the severity of its adverse effects.
Methodology: The study was approved by Institutional ethics committee and informed consent was obtained from all willing participants. Patients fulfilling inclusion and exclusion criteria were enrolled. Age sex, diagnosis, dose and duration of treatment were recorded. 2ml of blood was collected for liver function test. The adverse drug reaction (ADR) was documented. The causality assessment was done by WHO assessment scale and severity assessment by using modified Hartwig severity assessment scale.
Results: In this study, most of the patients were in 31-40 years age group. Among the 100 patients who were on Fluconazole 58 developed adverse drug reactions. 64 percentage of ADRs were reported in patients with treatment duration of more than 12 weeks. The most common adverse drug effect documented was abdominal pain followed by headache. Increase in serum transaminases was noted in 7 percentage of patients who were taking Fluconazole for more than 12 weeks, which did not require treatment termination or dosage alteration. Most of the ADRs were in possible category of causality assessment scale. In severity assessment most of the ADRs were in mild category.
Conclusion: Adverse drug reaction to Fluconazole was mostly noted in patients who were on treatment for more than12 weeks of which elevated serum transaminases were observed in 8 patients. Hence regular liver function monitoring is advised in all patients receiving Fluconazole for more than 12 weeks to prevent further liver damage.
Keywords: Adverse drug reaction, Fluconazole

Introduction

An adverse drug reaction is defined by WHO as "a response to a drug that is noxious and unintended and occurs at doses normally used in humans for the prophylaxis, diagnosis and treatment of disease, or for modification of physiological function[1]

Generally the drugs acts by interfering with one or more aspects of molecular and cellular function, all of them have the risk of producing some reaction which may not be desirable all the times.[2]

About 10-15% of all patients receiving medications are affected by ADR. The incidence of serious ADR is 6.7 %. ADR accounts for 5 to 9 % of hospital expenditure and almost 1 lakh death globally per year. ADRs has been recognised as a major public health issue since they contribute to a sizeable percentage of hospital admissions and also an economic burden to the society.[3]

Fluconazole is a bis-triazole broad spectrum antifungal agent discovered by Richardson et al. during a programme initiated by Pfizer Central Research in 1978[4] Its antifungal activity is achieved by preventing fungal membrane sterol synthesis through the inhibition of cytochrome P450 (CYP)-dependent lanosterol C14α-demethylase which is involved in the conversion of lanosterol to ergosterol, resulting in inhibition of fungal cell replication.[5,6]

It is used to treat Candidiasis, Cryptococcosis, Meningeal coccidioidomycosis, and Tinea infection. Its major advantages are the availability of both oral and IV formulations, a long half-life, satisfactory penetration of most body fluids (including ocular fluid and CSF).Its disadvantages include side effects like GI disturbances, dry mouth with a metallic taste, headache, alopecia, increased serum transaminases, rash, dizziness and dyspepsia.[7]Liver damage is common and serious in the immunocompromised person.[8-11]

The long term use of fluconazole for the treatment of fungal infections like Onychomycosis is increasing nowadays. The purpose of this study is to identify the nature, incidence and severity of adverse reactions associated with use of Fluconazole in Dermatophytosis.

Creating awareness about the adverse effects and their preventability helps in safe use of the medicine.

Monitoring adverse drug reaction will play a vital role in alerting physicians about the possibility and circumstances of such events and thereby protecting the user population from avoidable harm.

In India, pharmacovigilance activities are in developing stage and there are few reports available on the profile of medicines in general. This prompted us to evaluate the adverse drug profile of fluconazole in a tertiary care hospital

Study objective:

- To study the incidence and pattern of adverse effects of Fluconazole
- To assess the severity of adverse effects of Fluconazole

Methodology:

STUDY DESIGN: Prospective, Cross sectional study
STUDY POPULATION: Patients diagnosed with Dermatophytosis and receiving Fluconazole therapy.
STUDY CENTRE: Outpatient Department of Dermatology, Rajiv Gandhi Government General Hospital, Chennai
SAMPLE SIZE: 100
STUDY DURATION: 6 months
STUDY PERIOD: July –December 2019

Inclusion criteria

- Age : above 18 years
- Gender: both male and female
- Patients diagnosed with Dermatophytosis on T.Fluconazole
- Patients willing to give informed consent

Exclusion criteria

- Patients not willing to give informed consent.
- Patient with pre-existing liver disease
- Patients with any other chronic systemic illness
- Patients taking any other chronic medications
- Pregnant and lactating mothers.
- Patients diagnosed with HIV, Malignancy
- Patients with H/O Organ transplantation

Study procedure:

After obtaining approval from the Institutional Ethics committee, patients diagnosed with Dermatophytosis infections (Ring worm) receiving only Tablet Fluconazole 150mg bi-weekly at Dermatology outpatient clinic were explained about the study purpose and procedure in their local language. Informed consent was obtained from those who were willing to participate in the study.

The following parameters were recorded in WHO ADR reporting form

- Age
- Gender
- Past medical history.
- Diagnosis
- Dose and duration of Tab.Fluconazole prescribed
- Adverse drug reaction incidence and pattern
- Severity of adverse drug reactions and outcome

2ml of blood was collected from the patient to assess the liver functions. The following adverse effects were noted

ADVERSE EFFECTS	YES	NO	DON'T KNOW
NAUSEA			
VOMITING			
ABDOMINAL PAIN			
DIARRHOEA			
HEADACHE			
DYSGEUSIA			
DIZZINESS			
DYSPEPSIA			
ALOPECIA			
OTHERS			

Assessment:

Causality assessment of the adverse drug reaction was done by establishing the temporal association of drug with adverse drug reaction using WHO causality assessment scale and Severity of adverse drug reaction was assessed with modified Hartwig and Siegel scale

Results:

226 patients were screened and 100 patients who fulfilled the inclusion criteria were analysed. Data were entered in excel spread sheet and descriptive statistics was used to analyse the data. The results of the study were as follows:

Table 1: Age distribution

Age in years	Number	Percentage (%)
18-20	**5**	**5%**
21-30	**12**	**12%**
31-40	**36**	**36%**
41-50	**23**	**23%**
51-60	**18**	**18%**
>60	**6**	**6%**
TOTAL	**100**	

Table-1 shows the age distribution
Age group 31-40 years had the maximum number of patients followed by age group 41-50years.

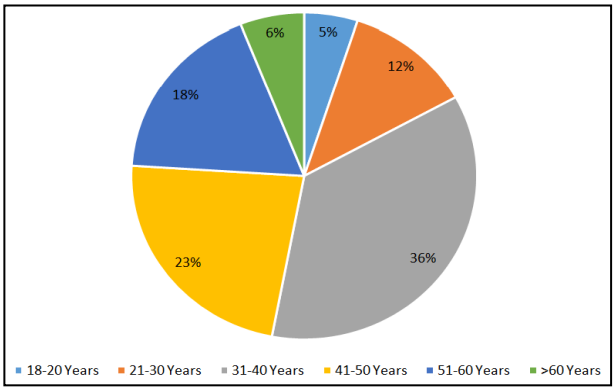

Figure 1: Age distribution

Figure1 is the diagrammatic representation of age distribution

TABLE 2: SEX DISTRIBUTION

SEX	NUMBER OF PATIENTS	PERCENTAGE (%)
MALE	38	38%
FEMALE	62	62%
TOTAL	100	100%

Table 2: shows sex distribution of patients. Females were maximum in numbers than males

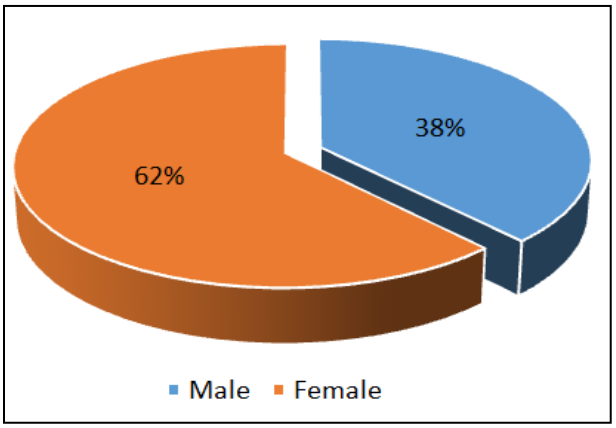

FIGURE 2: SEX DISTRIBUTION

Figure-2 is the diagrammatic representation of Table-2

TABLE 3: OCCURRENCE OF ADVERSE DRUG REACTIONS (ADRS)

	NUMBER OF PATIENTS	PERCENTAGE (%)
PATIENTS WITH ADR	58	58%
PATIENTS WITHOUT ADR	42	42%
TOTAL	100	100%

Table-3 Shows the occurence of Adverse Drug Reaction

Adverse reaction were observed in 58% of patients

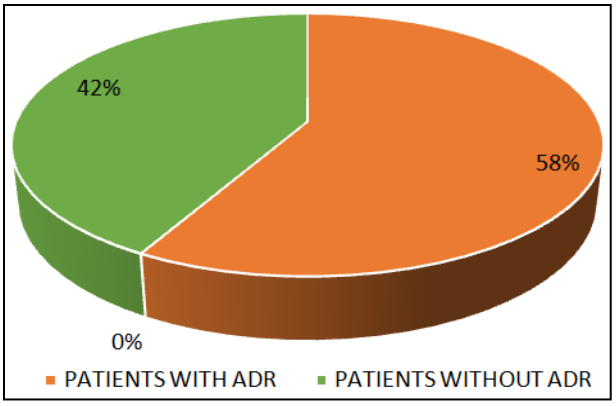

FIGURE 3: OCCURRENCE OF ADR

Figure-3 is the diagrammatic representation of occurrence of ADR.

TABLE 4: PATTERN OF ADVERSE DRUG REACTIONS

ADVERSE DRUG REACTION	NUMBER	PERCENTAGE (%)
Nausea	11	10%
Vomiting	8	7%
Abdominal Pain	19	17%
Diarrhoea	6	5%
Headache	18	16%
Dysgeusia	12	11%
Dizziness	7	6%
Dyspepsia	8	7%
Alopecia	14	12%
Rash	2	2%
Increased Serum transaminases	8	7%
	113	100%

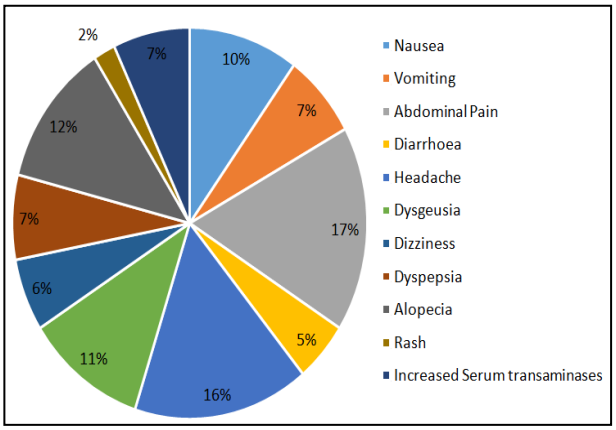

FIGURE 4: PATTERN OF ADR

Table-4 and Fig-4 shows the adverse drug reaction pattern of fluconazole recorded

In this study abdominal pain was the common adverse reaction followed by headache, alopecia. The serum transaminases were elevated in 8 patients.

TABLE 5: DISTRIBUTION OF NUMBER OF ADRs

NUMBER OF ADRs NOTED	TOTAL NUMBER OF PATIENTS	TOTAL NUMBER OF ADRs	PERCENTAGE (%)
1 ADR	18	18	31%
2 ADRs	28	56	48%
3ADRs	9	27	16%
4ADRs	3	12	5%
TOTAL	58	113	

Table 5 shows the Distribution of ADRs among the patient.

Patients with 2ADRs were maximum in number compared to other groups. The maximum ADRs recorded in a patient was 4.

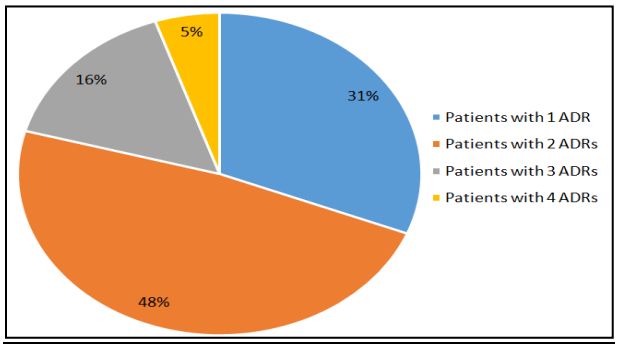

FIGURE 5: DISTRIBUTION OF NUMBER ofadrs

Figure-5 is the diagrammatic representation of Table-5

TABLE 6: DURATION OF TREATMENT & OCCURRENCE OF ADR

DURATION OF TREATMENT (weeks)	NUMBER OF PATIENTS ON TREATMENT	No. OF PATIENTS DEVELOPED ADR	PERCENTAGE (%)
<4	11	6	55%
5-8	17	8	47%
9- 12	16	7	43%
13-16	24	15	63%
17-20	20	14	70%
>20	12	8	67%
TOTAL	100	58	

Table-6 shows the percentage of ADR developed in relation to the duration of treatment

About 70% of patients developed adverse reaction in between 17-20weeks, 67% of patients developed ADR with Fluconazole therapy of >20 weeks.

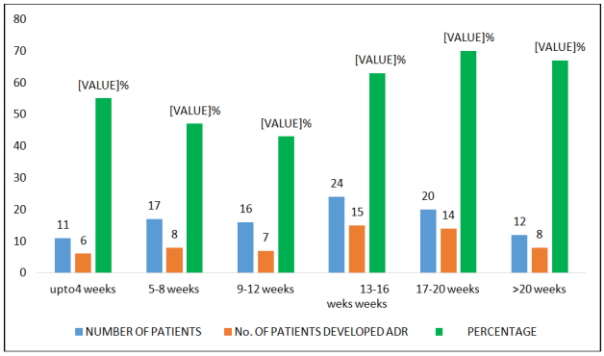

FIGURE 6: DURATION OF TREATMENT AND OCCURENCE OF ADRs

Figure-6 is the diagrammatic representation of table-6.

TABLE 7: LIVER FUNCTION TEST RESULTS

LIVER FUNCTION TEST	NUMBER OF PATIENT WITH ABNORMALITIES	PERCENTAGE (%)
TOTAL BILIRUBIN(>1mg/dl)	0	0%
SGOT(>40IU/L)	8	8%
SGPT(>40IU/L)	8	8%
ALKALINE PHOSPATASE (>145IU/L)	0	0%

Table-7 shows the Liver function test pattern
Among 100 patients only 8 patients had elevated levels of both SGOT and SGPT

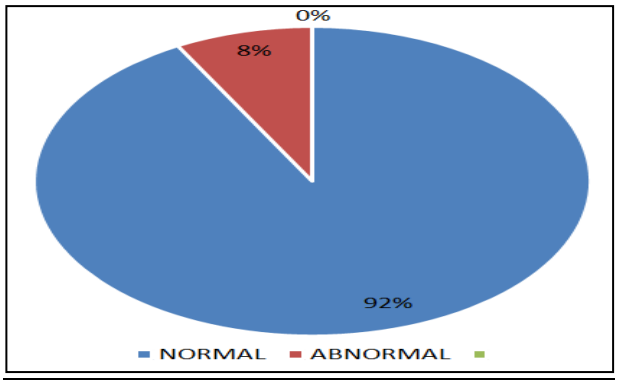

FIGURE 7: SERUM TRANSAMINASES VALUES

Figure-7 shows the serum transaminases values

TABLE 8: SERUM TRANSAMINASES AND DURATION OF TREATMENT

DURATION OF TREATMENT (WEEKS)	TOTAL NUMBER OF PATIENTS ON TREATMENT	PATIENTS WITH ELEVATED LIVER ENZYMES	PERCENTAGE (%)
<4	**11**	**0**	**0%**
5-8	**17**	**0**	**0%**
9-12	**16**	**0**	**0%**
13-16	**24**	**2**	**8%**
17-20	**20**	**3**	**15%**
>20	**12**	**3**	**25%**

Table-8 shows the serum transaminases level in relation to the duration of treatment with fluconazole

Patients with more than 12 weeks of therapy had elevation of serum transaminases

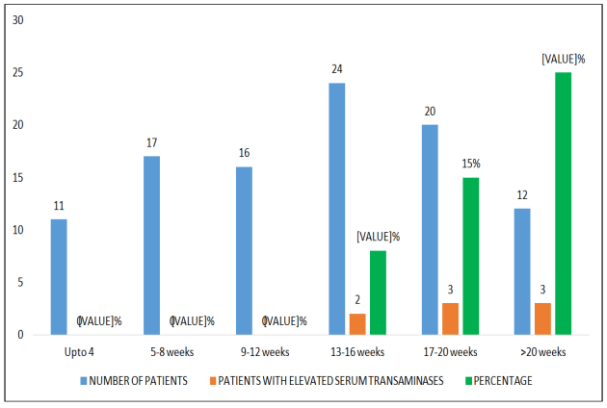

FIGURE 8: SERUM TRANSAMINASES AND DURATION OF TREATMEN

Figure-8 shows Diagrammatic representation of Table 8

TABLE 9: SEVERITY ASSESSMENT

ASSESSMENT CATEGORY	NUMBER OF ADRs	PERCENTAGE %
MILD	97	86%
MODERATE	16	14%
SEVERE	0	0%
TOTAL	113	100%

Table -9 shows the severity assessment of Adverse Drug Reaction.
86%% were categorised as mild,
14% as moderate and
No severe adverse drug reaction were reported

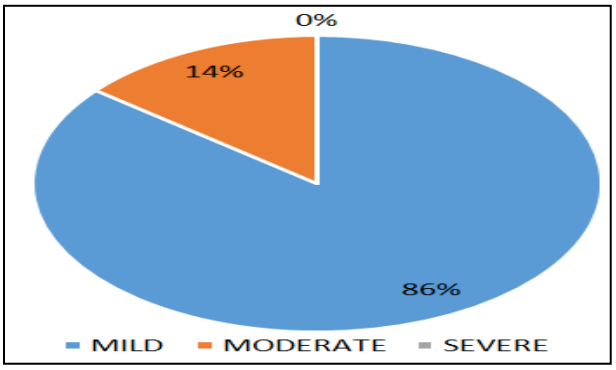

FIGURE 9: SEVERITY ASSESSMENT

Figure-9 shows the diagrammatic representation of severity assessment of ADR.

TABLE 10: CAUSALITY ASSESSMENT

ASSESSMENT CATEGORY	NUMBER OF ADRs	PERCENTAGE
CERTAIN	0	0%
PROBABLE	19	17%
POSSIBLE	94	83%
TOTAL	113	100%

Table -10 shows the Causality Assessment of Adverse Drug Reaction.
83% of adverse drug reaction belongs to possible category,
17% of adverse drug reaction belongs to probable category.

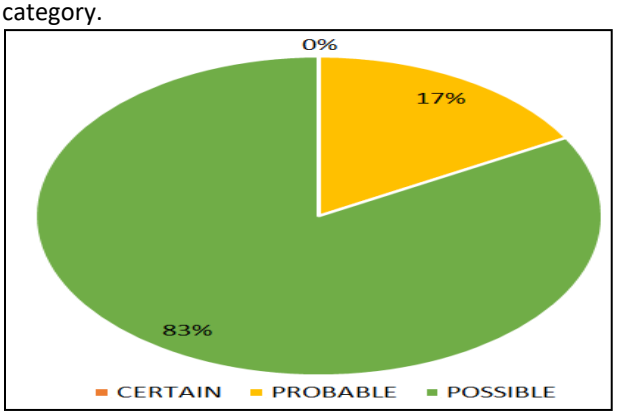

FIGURE 10: CAUSALITY ASSESSMENT

Figure-10 shows the diagrammatic representation of Causality Assessment of ADRs.

DISCUSSION

Dermatophytosis is a common superficial fungal infection affecting skin, hair and nail. Fluconazole is the commonly used oral systemic antifungal drug for this infection.[12]In our Institution fluconazole is widely used to treat Dermatophytosis. So this study was undertaken to assess the ADR pattern of Fluconazole.

In our study, 100 patients were evaluated for adverse drug reactions to Fluconazole. Majority of the patients were in the age group of 31-50 years with females being more in number than males.

Among 100 patients evaluated, ADRs were noted in 58 patients of which 40 patients had more than one ADR. The maximum ADRs reported in a patient was 4 and this was observed in 3 patients.

The usual common adverse reactions to Fluconazole like nausea, vomiting, diarrhoea and abdominalpain[13] were observed in this study also.

Usually the incidence and severity of side effects increase with duration of treatment.[14] In our study also more number of adverse effects were noted in patients who received >12 weeks of treatment.

Fluconazole has been reported to cause hepatic or cholestatic liver injury but the exact mechanism involved remains unknown.[15]This may probably be due to inhibition of cytochromeP450 enzyme. [15]

Prolonged duration of treatment increases the serum transaminase level.[16] In this study, similar findings of elevated serum transaminases of more than 2 times the upper limit of normal were noted in 8 patients who had completed >12 weeks of treatment. This however did not require treatment termination or dosage alteration in the patient. After completion of treatment liver enzymes returned to normal within 8 weeks.

Our study showed a higher incidence of elevated liver enzymes at 7% compared to the study done by Chia-Hsuin Chang et al [17] and Jiun-Ling Wang et al[18] where the incidence was 2%.

Causality assessment by WHO scale showed that most of the ADRs (83%) were in possible category and 17% were in probable category.

According to Modified Hartwig scale, most of the ADRs (86%) came under mild category and 14% in the moderate category.

Our study offers a representative idea of ADR profile of fluconazole. The limitations of this study were a small sample size without baseline liver function data.

CONCLUSION:

From this study we conclude that most of the ADRs to antifungal drug fluconazole occured in patients who were on treatment for more than 12 weeks.

Most common adverse drug reaction noted was abdominal pain. Majority of the ADRs belonged to possible category and were mild in severity.

Asymptomatic elevations of liver enzymes were observed in patients on Fluconazole therapy for more than 12 weeks duration.

RECOMMENDATION:

Regular monitoring of liver function should be done in all patients who are on treatment with Fluconazole for more than 12 weeks duration so as to prevent further liver damage.

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