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The effects of terbinafine on the lipid profile in humans and rabbits

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ABSTRACT

Objectives: To investigate the effects of the azole antifungal agent, allylamine terbinafine, on the lipid profile of patients attending the dermatology clinics and any changes in serum creatinine associated. In order to compare the results between people and rabbits, we also want to investigate the lipid profile of normolipidemic rabbits and any changes in serum creatinine related to the use of these antifungal drugs in the experimental animals. *Methods:* In this study the effects of the antifungal drugs, terbinafine on the levels of serum lipids (triglycerides, cholesterol, high density lipoproteins and low-density lipoproteins) and serum creatinine were investigated in humans and rabbits. Blood samples were taken before and 1 week following drug treatment. Blood samples were analyzed using commercially available kits. Treatment of humans with terbinafine (250 mg/day) for one week had no significant effects on serum triglycerides, total cholesterol HDL-cholesterol or LDL-cholesterol levels. *Results:* Treatment with terbinafine for 1 week to humans produced no significant changes in serum creatinine. Treatment of rabbits with terbinafine (10 and 20 mg/kg/day) for six weeks produced significant reductions in serum triglycerides, total cholesterol and LDL-cholesterol levels. HDL-cholesterol levels, however, were not significantly changed. *Conclusion:* The present results demonstrate that terbinafine, an allylamine antifungal drug, has no significant effects on the serum lipids of humans. The results demonstrate that terbinafine has produced significant reductions in serum lipids (except HDL-cholesterol) in rabbits. This discrepancy in the results between rabbits and humans may be explained by differences in the enzyme squalene epoxidase (SE).

Keywords: Terbinafine, Lipid profile, Humans, Rabbits

1. INTRODUCTION

In humans, increase of systemic mycoses is due in part to improved recognition and diagnosis of fungal infestations, but also due to the prolonged survival of patients with global defects in their host defence mechanisms, including patients with neoplastic diseases, organ transplant recipients, diabetics and patients with AIDS. These patient populations are

susceptible to an ever-growing list of opportunistic fungi (Pfaller and Diekema, 2004).

Terbinafine has been proven to be highly efficient in treating dermatophyte infestations of the skin in clinical studies when used either orally (250 or 500mg/day) or topically (1% cream, twice daily) (Newland and Abdel-Rahman, 2009). Over 90% of patients with tinea corporis/cruris and tinea pedis (including those with chronic and/or recurring infections) experience a mycological cure as a result and in about 80% of instances, there is also an accompanying clinical cure (Sahoo and Mahajan, 2016).

Terbinafine acts by inhibiting squalene epoxidase that is an essential enzyme in sterol biosynthesis in fungi (Sahoo and Mahajan, 2016). Inhibition of squalene epoxidation by terbinafine predictably results in decreased ergosterol and increased squalene content in fungal cells (Sagatova, 2021). Both of these effects appear to contribute to the antifungal action of terbinafine. Ergosterol is an essential constituent of fungal cell membranes, as is cholesterol in mammalian cell membranes (Alajlan et al., 2020).

So far, there are not many published studies reporting the effects of terbinafine on the concentrations of serum lipids in human or animals (Hammoudi-Halat et al., 2022). Many studies have been carried out to assess the effect of ketoconazole, an imidazole antifungal drug, on serum cholesterol, triglycerides and lipoproteins (Rodrigues, 2018).

From the present review it appears that ketoconazole has a hypocholesterolemic potential (Stalenhoef et al., 1997). Terbinafine caused hypertriglyceridemia but there is a lack of information regarding the effect of this drug on other lipid parameters (Katsikis et al., 2017). Because of that it was felt necessary to investigate in detail the effect of this antifungal drug namely the allylamine terbinafine on the lipid profile in patients attending KKUH dermatology clinics as well as in normolipidemic rabbits.

2. MATERIAL AND METHODS

Ethical Approval

Informed consent was attained from all participants who involved in the study voluntarily according to the ethical approval number# 387621. Study period between 22nd of April 2022 to 29th of December 2022. Clinical trial number was obtained from KSUMC #08972098NA.

Patients

From the dermatology clinic, 15 patients with fungal infestation which required the use of terbinafine were chosen. Terbinafine tablets were prescribed to these patients to be taken orally. The indication to use this drug, dose and duration of the antifungal treatment were determined by the treating physician.

Patients on drugs that may increase or decrease serum lipids were excluded from the study. A fasting blood sample was obtained from the 15 patients before drug administration and at one- or two-weeks post-treatment. The blood samples were analysed for triglycerides, total cholesterol, HDL-C, LDL-C. So, analysis of Biochemical Parameters was as follows:

LDL-cholesterol determination

The low-density lipoprotein-cholesterol was quantitated by using the following formula:

$$\text{LDL cholesterol} = \text{total cholesterol} - (\text{HDL cholesterol} + \text{triglyceride})/2.2$$

This is a simple and reliable method for estimating LDL-cholesterol and involves only the estimation of triglyceride, HDL-cholesterol and total cholesterol. It is widely used in clinical chemistry for LDL-cholesterol estimation.

Triglyceride determination

Lipids have presented an analytical problem in the past as they are insoluble and have large masses. The old methods for determining triglycerides involved extraction with organic solvents and tedious methodologies. However, with the advent of enzymatic methods direct estimation of serum or plasma lipids is carried out accurately. Triglycerides were determined in serum.

Total cholesterol determination

The plasma level of cholesterol was measured by using Bio Merieux enzymatic kits. This method estimates cholesterol as free cholesterol in the plasma. Since in plasma almost 70% of the cholesterol is present in the form of esterified cholesterol, cholesterol esters were first converted to free cholesterol by cholesterol esterase.

HDL-cholesterol determination

HDL cholesterol was determined. The high-density lipoproteins were separated and cholesterol bound to to these fractions was estimated using Bio Merieux HDL-cholesterol kit.

Serum Creatinine Determination

The Bio Merieux enzymatic kit was used to test the plasma level of creatinine. Briefly, picrate and creatinine react to generate a red chromophore in the presence of strong bases like NaOH. At 492 nm, the rate of rising absorbance brought on by the creation of this chromophore is directly proportional to the level of creatinine present in the sample.

Experimental animals

Animals

Sixty male, white rabbits of New Zealand strain, weighing 2.5–3 kg was obtained from the Animal Care Center of the College of Medicine, King Saud University, Riyadh.

Drugs

Terbinafine (Lamisil) were purchased as commercially available tablets from the market. Starch, lactose and carboxymethyl cellulose were obtained from Sigma Chemical Company, St. Louis, M, USA.

Administration of Drugs

Terbinafine tablets were triturated to 8 mg/ml and 4 mg/ml in 90 ml normal saline (0.9% NaCl) with the aid of 10 ml of CMC 1%. Vehicle (starch 25 mg, lactose 115 mg, and magnesium hydrogen orthophosphate 5 mg suspended in 90 ml normal saline (0.9% NaCl) with 10 ml of CMC 1%.

Experimental Procedures

The rabbits were kept in air-conditioned rooms in separate cages with full access to food and water (20oC). The rabbits were placed into five groups of (10-13) animals each. Itraconazole was given to Group I at a dose of 40 mg/Kg/day, Terbinafine to Group II at a dose of 20 mg/Kg/day, Terbinafine to Group III at a dose of 10 mg/Kg/day, Itraconazole to Group IV at a dose of 80 mg/Kg/day and Vehicle to Group V (lactose and starch suspended in carboxymethyl cellulose and normal saline). Each drug was given to the corresponding group once daily via the oral route for six weeks (5 days/week). A fasting blood sample was obtained before drug administration and at the end of the first, fourth and sixth week. The central ear artery was cannulated with a polyethylene cannula 22 gauge for blood sampling. Blood was collected in venoject tubes. Serum samples were taken after centrifugation at 3500 rpm for 20 min for evaluating triglycerides, total cholesterol, high density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C). Analysis of Biochemical Parameters was done as follows:

LDL-cholesterol determination

The low-density lipoproteins were separated and cholesterol bound to these fractions was estimated using the Bio Merieux LDL-cholesterol kit. The various classes of lipoproteins are differentiated according to their density, electrical behaviour and reactivity with specific antibodies. The addition of certain amphipathic polymers precipitated certain lipoprotein fractions specifically. There is a good correlation between the levels of cholesterol and phospholipids measured in the precipitated fractions and in the LDL isolated by ultracentrifugation.

Triglyceride determination

Lipids have presented an analytical problem in the past as they are insoluble and have large masses. The old methods for determining triglycerides involved extraction with organic solvents and tedious methodologies. However, with the advent of enzymatic methods direct estimation of serum or plasma lipids is carried out accurately. Triglycerides were determined in serum according to the method previously described by Cox.

Total cholesterol determination

The plasma level of cholesterol was measured by using Bio Merieux enzymatic kits. This method estimates cholesterol as free cholesterol in the plasma according to the method previously described by Richmond. Since in plasma almost 70% of the cholesterol is present in the form of esterified cholesterol, cholesterol esters were first converted to free cholesterol by cholesterol esterase.

HDL-cholesterol determination

HDL cholesterol was determined. The high-density lipoproteins were separated and cholesterol bound to to these fractions was estimated using Bio Merieux HDL-cholesterol kit.

Serum Creatinine Determination

The techniques outlined by Larsen and Knapp will be used to determine creatinine levels. The Bio Merieux enzymatic kit was used to test the plasma level of creatinine. Briefly, picrate and creatinine react to generate a red chromophore in the presence of strong bases like NaOH. At 492 nm, the rate of rising absorbance brought on by the creation of this chromophore is directly proportional to the level of creatinine present in the sample.

Statistical analysis

The results of patient study are expressed as the mean+SEM and are presented in the form of tables. Statistical analysis of patient data was performed using the student two-tailed t-test for matched pairs. P values < 0.05 were considered significant. The results of animal study are expressed as the mean+SEM and are presented in the form of bar chart and also tables. Statistical analysis of animal data was performed using the repeated measure ANOVA for comparison within the group; ordinary ANOVA for comparison between groups at the same duration of treatment. P values<0.05 were taken as significant. Post ANOVA Tukey-Kraemer test was used them in assessment of significance between and within groups.

3. RESULTS

Patients

A total of 15 patients were enrolled for the study, 6 patients did not turn up after the first visit. Nine patients completed the study. There were 7 males and 2 females. Their age ranges were 19-44 years with an average of 30 years.

Effect of terbinafine on the concentrations of serum triglycerides, total cholesterol, HDL-cholesterol and LDL- cholesterol

The administration of terbinafine (250 mg/day) for 1 week produced no significant effects on the concentrations of serum triglycerides, total cholesterol, HDL-cholesterol and LDL-cholesterol (Table 1, 2, 3, 4).

Table 1 Effect of terbinafine on the concentrations of serum triglycerides (mmol/l)

Variables	n	TG Pre-treatment (mmol/l)	TG Post-treatment (mmol/l)	P-value	(%) Change
TG	9	1.36±0.29	1.11±0.26	0.12	-12.14±11.58

Results represent the mean±SEM of 9 samples.
TG: Triglycerides.
n: Number of patients.

Table 2 Effect of terbinafine on the concentrations of total serum cholesterol (mmol/l)

Variables	n	TG Pre-treatment (mmol/l)	TG Post-treatment (mmol/l)	P-value	(%) Change
TG	9	5.38±0.27	5.08±0.28	0.25	-3.25±2.79

Results represent the mean±SEM of 9 samples.
TC: Total cholesterol.
n: Number of patients.

Table 3 Effect of terbinafine on the concentrations of serum HDL-cholesterol (mmol/l)

Variables	n	HDL Pre-treatment (mmol/l)	HDL Post-treatment (mmol/l)	P-value	(%) Change
HDL	6	1.15+0.04	1.11+0.03	0.48	-2.61+4.21

Results represent the mean±SEM of 6 samples.
HDL: High density lipoproteins.
n: Number of patients.

Table 4 Effect of terbinafine on the concentrations of serum LDL-cholesterol (mmol/l)

Variables	n	LDL Pre-treatment (mmol/l)	LDL Post-treatment (mmol/l)	P-value	(%) Change
LDL	6	3.82±0.26	3.88±0.32	0.84	1.79±6.73

Results represent the mean±SEM of 6 samples.
LDL: Low density lipoproteins.
n: Number of patients.

Effect of terbinafine on the concentrations of serum creatinine

The administration of terbinafine (250 mg/day) for 1 week produced no significant effects on the concentrations of serum creatinine in humans (Table 5).

Table 5 Effect of terbinafine on the concentrations of serum creatinine (μmol/l)

Variables	N	Creatinine Pre-treatment (mmol/l)	Creatinine Post-treatment (mmol/l)	P-value	(%) Change
Creatinine	9	82.44+8.02	83+6.73	0.86	2.97+3.77

Results represent the mean±SEM of 9 samples.
N: The number of patients.

Animals

Effect of terbinafine on the concentrations of serum triglycerides

Terbinafine (10 mg/kg/day) when it was given orally for six weeks, it produced an initial increase in serum triglycerides concentrations in the first week. This increase was statistically significant ($p<0.01$) when it was compared with the vehicle but not significant as compared to pretreatment levels. This rise was followed by a reduction in serum triglycerides levels when values obtained were compared to pretreatment level following the fourth and sixth weeks of treatment. Terbinafine (10mg/kg/day) produced statistically significant reduction in serum triglycerides concentrations following six weeks of treatment. The level of significance, when values obtained were compared to pretreatment levels of same animals, was $p<0.05$ but it was not statistically significant as compared to the values obtained in the vehicle treated group (Figure 1).

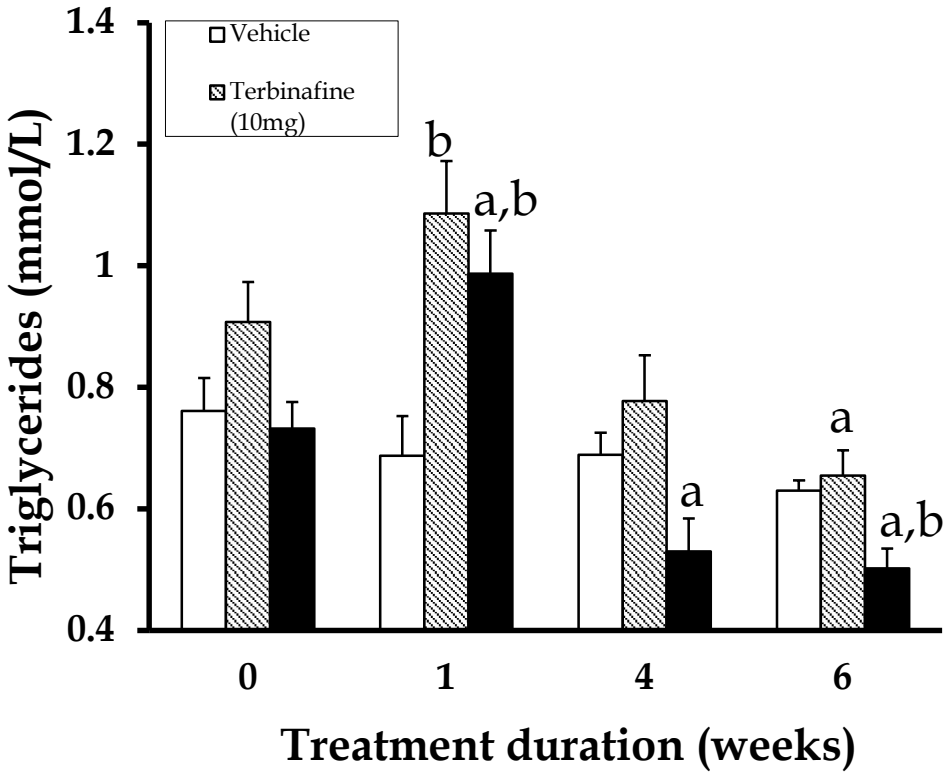

Figure 1 The effect of terbinafine on the concentrations of serum triglycerides in rabbits

Data represent the mean±SEM. Vehicle (starch+lactose+magnesium sulphate) and terbinafine were administered daily by the oral route for six weeks. [a]$p<0.05$ as compared to pretreatment levels (comparison within same group by using repeated measure ANOVA). [b]$p<0.05$ as compared to vehicle (comparison between groups at the same duration of treatment by using ordinary ANOVA).

Terbinafine (20 mg/kg/day) when it was administered orally for six weeks produced the same effects as was seen with low dose but the effect was more pronounced ($p<0.01$) in the first week of treatment as compared to pretreatment level or the values in

animals which had received the vehicle. Significant reductions in serum triglycerides concentration were observed after the fourth week as compared to pretreatment levels ($p<0.05$) but not significant as compared to vehicle). A significant decrease in triglycerides concentrations was observed following the sixth week of treatment when these values were compared with vehicle or pretreatment levels ($p<0.01$, Figure 1).

Effect of terbinafine on the concentrations of total serum cholesterol

Following the first week of treatment with terbinafine (10 and 20 mg/kg/day) there was a transient increase in serum cholesterol levels ($p<0.001$) as compared to vehicle and pretreatment levels. This increase was followed, on continuation of treatment, by return to almost the pretreatment levels following the fourth week of treatment. Terbinafine (20 mg/k/day), however produced a statistically significant increase in the total cholesterol levels as compared to vehicle ($p<0.05$) but not to pretreatment levels following the fourth week of treatment. There was a significant reduction of total serum cholesterol level by both doses of terbinafine following the sixth week of treatment as compared to pretreatment levels ($p<0.05$) but no such change was observed with it as compared to vehicle (Figure 2).

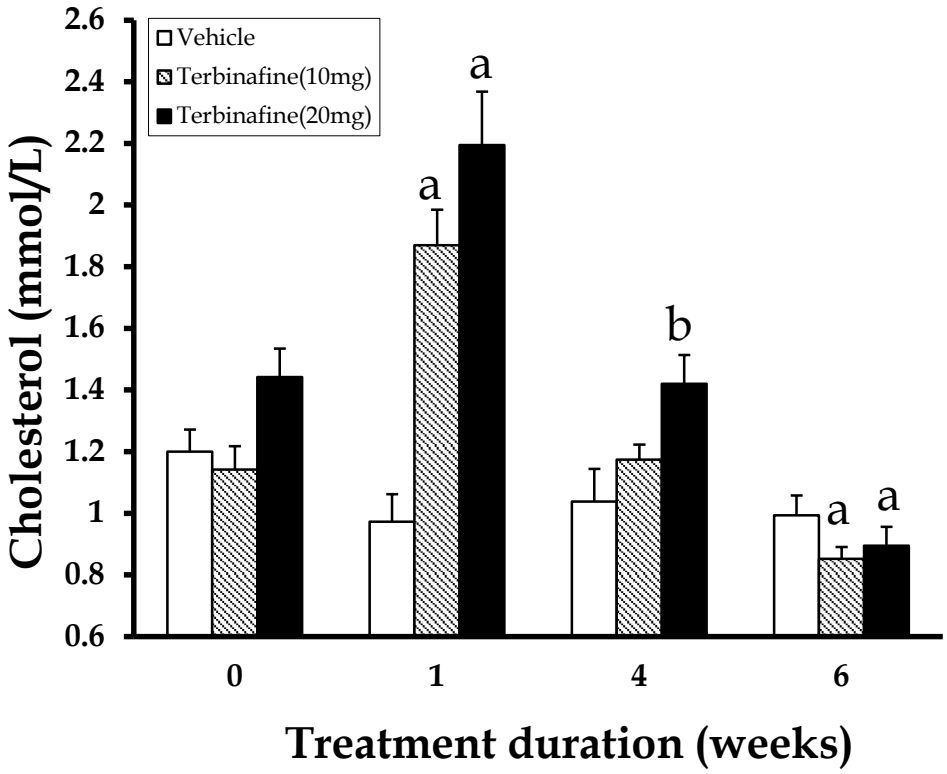

Figure 2 The effect of terbinafine on the concentrations of total serum cholesterol in rabbits

Data represent the mean ± SEM. Vehicle (starch+lactose+magnesium sulphate) and terbinafine were administered daily by the oral route for six weeks. [a]$p<0.05$, as compared to pretreatment levels (comparison within same group by using repeated measure ANOVA). [b]$p<0.05$, as compared to vehicle (comparison between groups at the same duration of treatment by using ordinary ANOVA).

Effect of terbinafine on the concentrations of serum HDL-cholesterol

Treatment with either dose of terbinafine orally for six weeks did not result in significantly different changes in HDL-cholesterol levels. At both dose levels, there were declines in HDL-cholesterol but it was only significant with terbinafine (20 mg/kg/day) following one week of treatment ($p<0.05$) as compared to pretreatment levels but not to vehicle (Figure 3).

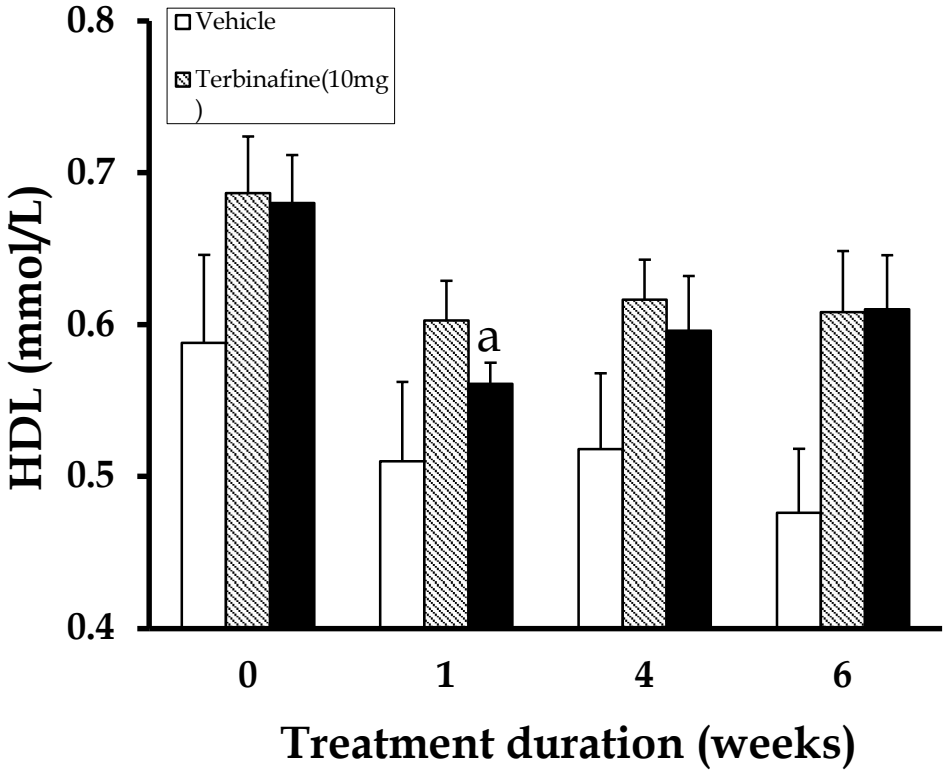

Figure 3 The effect of terbinafine on the concentrations of serum HDL-cholesterol in rabbits

Data represent the mean ± SEM. Vehicle (starch+lactose+magnesium sulphate) and terbinafine were administered daily by the oral route for six weeks. [a]p<0.05, as compared to pretreatment levels (comparison within the same group by using repeated measure ANOVA).

Effect of terbinafine on the concentrations of serum LDL-cholesterol

Terbinafine (10 or 20 mg/kg/day) when it was given orally for six weeks, it produced an initial increase in the concentrations of serum LDL following one week of treatment. The level of significance for terbinafine (10 mg/kg/day) was (p<0.001) as compared to pretreatment levels and to the values obtained in animals which had received the vehicle. The level of significance for terbinafine (20 mg/kg/day) was (p<0.01) as compared to pretreatment levels and to the vehicle treated group.

Following four weeks of treatment, mean serum LDL level decreased by both doses of terbinafine as compared to vehicle. It was only statistically significant with terbinafine (10 mg/kg/day), (p<0.01) as compared to vehicle and not significant as compared to pretreatment levels). Both doses of terbinafine caused significant decrease in serum LDL level following six weeks of treatment. The level of significance was (p<0.001) for both dose levels as compared to vehicle but not significant as compared to pretreatment levels (Figure 4).

Data represent the mean ± SEM. Vehicle (starch+lactose+magnesium sulphate) and terbinafine were administered daily by the oral route for six weeks. [a]p<0.05, as compared to pretreatment levels (comparison within the same group by using repeated measure ANOVA). [b]p<0.05, as compared to vehicle (comparison between groups at the same duration of treatment by using ordinary ANOVA).

Effects of terbinafine on serum lipids are summarized (Table 1). Both dose levels of terbinafine produced an initial increase in triglycerides level in the first week of treatment. The increase produced by terbinafine (10 mg/kg/day) were 21.68%, but not statistically significant as compared to values obtained in animals which had received the vehicle. Terbinafine (20 mg/kg/day) produced an increase in triglycerides level of 39.54%, (p<0.01) as compared to vehicle. Then triglycerides level decreased for both dose levels of terbinafine. Group of rabbits treated with terbinafine (10 mg/kg/day) for six weeks showed a statistically significant decrease, 9.59% (p<0.05) and 24.4% (p<0.001) in the fourth and sixth week of treatment respectively. These significant changes were in comparison with mean percent change in the first week. Group of rabbits treated with terbinafine 20 mg/kg/day for six weeks

showed a statistically significant decrease of serum triglycerides level, 24.93 ($p<0.001$) and 27.14 ($p<0.001$) in the fourth and sixth week of treatment respectively.

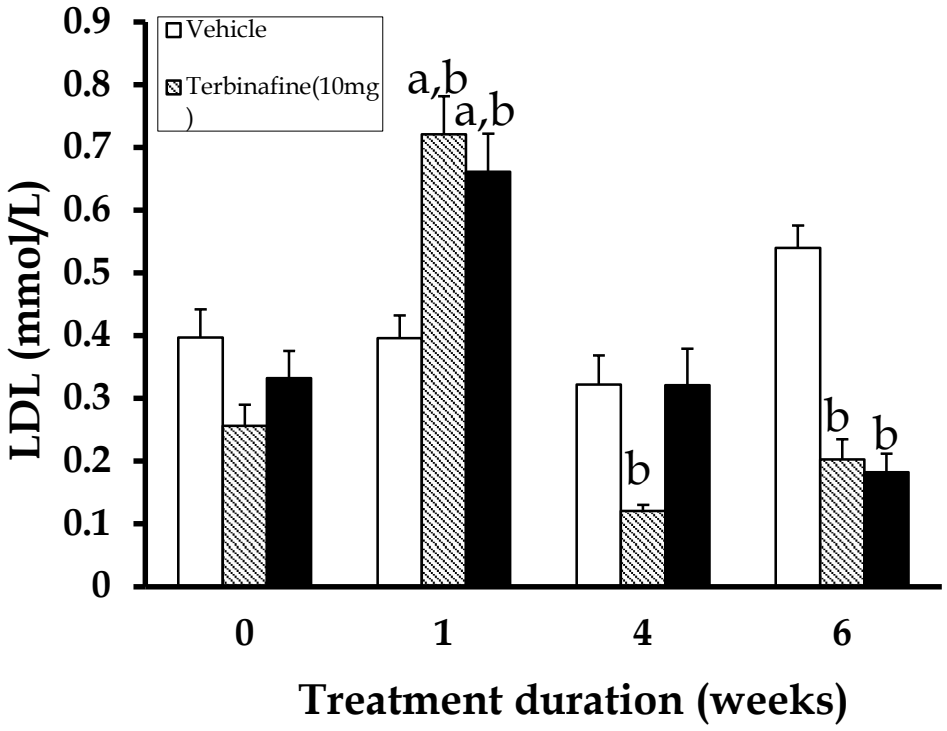

Figure 4 The effect of terbinafine on the concentrations of serum LDL-cholesterol in rabbits

Table 6 The effect of terbinafine on the concentrations of serum lipid (mmol/l) in rabbits

Parameter	Duration of treatment (weeks)								
	1			4			6		
	Terbinafine (mg/kg/day, p.o.)								
	Veh	10	20	Veh	10	20	Veh	10	20
TG	-9.92 ±8.28	21.68 ±9.21	39.54 ±12.6[b]	-8.93 ±5.38	-9.59 ±12.2[a]	-24.93 ±8.39[a]	-17.10 ±1.67	-24.4 ±6.29[a]	-27.14 ±7.66[a]
TC	-19.01 ±5.68	67.29 ±10.6[b]	55.55 ±12.6[b]	-13.70 ±7.19	6.26 ±6.66[a]	4.51 ±12.4[a]	-13.10 ±7.31	-22.8 ±5.31[a]	-36.09 ±4.86[a,b]
HDL	-9.35 ±10.9	-11.10 ±3.42	-15.3 ±5.49	-9.14 ±8.45	-7.80 ±5.73	-12.33 ±3.42	-16.30 ±6.76	-7.82 ±9.04	-9.36 ±5.12
LDL	5.53 ±8.25	291.1 ±105[b]	123.9 ±28.2	-9.03 ±15.9	-33.9 ±16.7[a]	7.96 ±22.6[a]	58.61 ±25.9	-14.6 ±12.3[a,b]	-37.73 ±14.2[a,b]

Data represent the mean percent change ± SEM of 9-12 rabbits. Terbinatine (10 or 20 mg/kg orally) and vehicle (starch+lactose+magnesium sulphate) were administered once daily for 6 weeks. [a]$p<0.05$, as compared to one week of treatment (comparison within the same group by using repeated measure ANOVA). [b]$p<0.05$, as compared to vehicle (comparison between groups at the same duration of treatment by using ordinary ANOVA). Legend: TG = triglycerides; TC = total cholesterol; HDL = high density lipoprotein; LDL = low density lipoprotein; Veh = vehicle. These changes in serum triglycerides level were within group. There were no statistically significant differences between vehicle and any terbinafine group in triglycerides level in the fourth or sixth week of treatment.

Both dose levels of terbinafine produced an initial increase in total serum cholesterol level in the first week of treatment. The increase in total cholesterol caused by terbinafine (10 and 20 mg/kg/day) in the first week of treatment were 67.29% ($p<0.001$) as compared to vehicle and 55.55% ($p<0.001$) as compared to vehicle respectively.

Following four weeks of treatment, total serum cholesterol level decreased in comparison to mean percent change in the first week. Terbinafine (10 mg/kg/day) caused significant reduction in the concentrations of serum total cholesterol from 67.29% to 6.26%, within group ($p<0.001$), but not significant as compared to vehicle. Terbinafine (20 mg/kg/day) caused significant reduction in the concentrations of serum total cholesterol from 55.55% to 4.5%, within group ($p<0.01$), but not significant as compared to vehicle. Terbinafine (10 mg/kg/day) caused decrease in total cholesterol serum levels in the sixth week of treatment 22.8%, within group ($p<0.001$), but it was not significant as compared to vehicle. Terbinafine (20 mg/kg/day) caused decrease in total cholesterol serum levels in the sixth week of treatment 36.09%, within group ($p<0.001$); compared to vehicle, $p<0.05$ (Table 6).

There were no significant changes produced by terbinafine treatment on HDL-levels. There were significant changes in LDL levels caused by terbinafine treatment. These changes were comparable, similar to those exerted on serum total cholesterol level. Both dose levels of terbinafine produced an initial increase in LDL-cholesterol levels in the first week of treatment, with the (10 mg/kg/day) terbinafine treated group showing a statistically significant increase, compared with vehicle, $p<0.05$, but not significant within the group (Table 6). Following four weeks of treatment, mean serum LDL-cholesterol levels decreased significantly by both dose level of terbinafine in comparison to the mean percent change in the first week of treatment i.e., within group ($p<0.01$, $p<0.001$) due to terbinafine (10 and 20 mg/kg/day) treatment respectively, but not significant as compared to vehicle.

Mean serum LDL level further decreased significantly following six weeks of treatment with terbinafine (10 and 20 mg/kg/day). This reduction in LDL was significantly different from mean percent change in the first week of treatment and at the same time from vehicle treated group, within group ($p<0.01$); compared to vehicle ($p<0.05$) for terbinafine (10 mg/kg/day) treated group, within group ($p<0.001$); compared to vehicle ($p<0.01$) for terbinafine (20 mg/kg/day) treated group (Table 6).

Effect of terbinafine on the concentrations of serum creatinine

Terbinafine (10 and 20 mg/kg/d) produced no significant effects on the concentrations of serum creatinine in rabbits (Table 7).

Table 7 The effect of terbinafine on the concentration of serum creatinine (μmol/l) in rabbits

Treatment	Dose (mg/kg/day p.o.)	N	Duration of treatment			
			0	1 wk	4 wks	6 wks
Vehicle		11	128.64 ±10.15	112.09 ±11.09	129.45 ±5.24	131.36 ±2.65
Terbinafine	10	11	117.09 ±8.13	113.75 ±5.63	130.09 ±4.93	134 ±5.58
Terbinafine	20	10	117.35 ±7.89	117.71 ±7.74	133.45 ±9.33	130.20 ±6.82

Data represent the mean±SEM. Vehicle (starch+lactose+$MgHPO_4$) and terbinafine were administered daily via the oral route for six weeks.
N: Number of animals used.
wks: Weeks

4. DISCUSSION

Researchers and clinicians have recognized hypertriglyceridemia as a possible risk factor for development of IHD for over 30 years. Studies demonstrated that triglyceride levels are a predictor of CHD, even after adjusting for low HDL and other risk factors. In a recent study, there was a gradient increase in rates of CHD as triglyceride levels increased, even after adjustment for major CHD risk factors, including high LDL cholesterol levels. Recent data from studies controlling for HDL have tended to support a clinically relevant interaction between cholesterol and triglycerides in assessing the risk of coronary heart disease. In a carefully performed study, serum triglyceride concentrations were a strong and independent predictor of outcome (myocardial infarction) over seven years of follow up, independently of HDL. Therefore, hypertriglyceridemia has a deleterious effect on the body.

In humans, terbinafine produced no significant reductions in serum triglycerides concentrations. In a preliminary report it has been shown that treatment with terbinafine at a dose of 250 mg/day for a period of 1 week in humans with tinea pedis or tinea manus produced hypertriglyceridemia as a side effect of the medication. This communication is at variance with our present findings. The difference between our study and this report is that the latter is not a properly-controlled clinical study. This transient increase in serum triglycerides concentrations may have disappeared if drug administration was continued for a longer period of time. Other investigators have reported no significant changes in serum triglycerides concentrations in patients who had been

treated with terbinafine at a dose of 250 mg/day for a period of 1-12 weeks. The results reported by these investigators in humans are in agreement with our present findings.

In the present study terbinafine was not able to produce any significant reductions in human serum total cholesterol concentrations. Similar to our results it has been reported that terbinafine did not produce any significant changes in serum total cholesterol concentrations in patients who had been treated with the drug at a dose of 250 mg/day for a period of 1-12 weeks. The results reported by these investigators in humans are in total agreement with our present finding. In the present study terbinafine did not produce a significant effect in HDL-cholesterol concentrations in humans. It has been reported by that terbinafine produced no significant changes in lipid profile in patients who were receiving terbinafine for the treatment of tinea capitis. This result is in agreement with our present finding.

Terbinafine had no significant effects on serum triglycerides, total cholesterol, HDL and LDL-cholesterol in humans and this was expected since terbinafine is selective for fungal SEs and it also does not interfere with cytochrome P450. Terbinafine lowering effect on serum triglycerides, total cholesterol and LDL-cholesterol in rabbits can be explained by its inhibitory effects on SEs, thus interfering with cholesterol synthesis. In the present study terbinafine produces a significant reduction in serum triglyceride concentrations in rabbits. As far as I am aware there are no published reports to date relating to the effects of terbinafine on serum triglycerides concentrations in animals.

In the present study terbinafine produces a significant reduction in total cholesterol concentrations in rabbits. The effect of other allylamine derived drugs such as NB-598 on serum total cholesterol concentrations had been reported. The allylamine, NB-598 have been shown to lower cholesterol levels. The authors explained the cholesterol lowering effct of NB-598 by being a highly potent, competitive and specific inhibitor of vertebrate squalene epoxidase (SE) enzyme. Surprisingly, this compound although active as an inhibitor of SE, has no antifungal activity. 18 Chronic administrations of oral doses of NB-598 decreased serum total cholesterol levels in dogs with a similar potency to simvastatin. The result of this study is in agreement with our present finding although; there are differences in the chemical structure of drugs tested and animal species.

In the present study terbinafine was not able to produce any significant effect on HDL-cholesterol concentrations in rabbits. By surveying the literature there are no published studies regarding the effects of terbinafine or other allylamine-derived compounds on HDL-cholesterol concentrations in animals.

In the present study terbinafine produced a significant reduction in LDL-cholesterol concentrations in rabbits. In the scientific literature to date there are no published reports regarding the effects of terbinafine or other allylamine-derived compounds on LDL-cholesterol concentrations in animals. Terbinafine did not produce any significant changes in human serum LDL-cholesterol concentrations. It has been reported that terbinafine produced no significant changes in lipid profile in patients who were receiving terbinafine for the treatment of tinea capitis. The results of these authors are in total agreement with our present findings.

Treatment of humans or animals with terbinafine did not cause any significant changes in serum creatinine concentrations. This is in agreement with the results of a study who had reported that terbinafine produced no significant effects on serum creatinine concentrations in patients. Furthermore, it had been shown that treatment with terbinafine did not produce any clinically significant changes in the tests of liver and kidney function. This was a comparative study to evaluate the efficacy of these two drugs when they were given for the treatment of tinea pedis for a period of 2 weeks. Our study was further supported by other authors who compared the effects of terbinafine and itraconazole on routine laboratory tests. They found that both drugs had no significant effects on the routine laboratory tests including serum creatinine. It had also been demonstrated that treatment of humans with terbinafine had no significant effects on serum creatinine concentrations. The results of the latter authors are consistent with the findings of present study. However, it must be stated there was only one report that treatment with terbinafine may lead to increase in serum creatinine concentrations as a result of renal impairment (Stalenhoef et al., 1997).

5. CONCLUSION

In humans, it has no effect on serum lipid concentration following 1 week of treatment. In animals terbinafine caused significant reduction in serum triglycerides, total cholesterol and LDL-cholesterol following 6 weeks of treatment. Terbinafine was safe in animals and humans and there were no significant changes in serum creatinine.

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Author Contributions

Sami Alsuwaidan: Data analysis; Abdulmajeed Alajlan: Writing; Huda Alkrea: Supervisor and principal investigator.

Ethical approval

The study was approved by the Medical Ethics Committee of KSUMC (Ethical approval code: KSUMC #08972098NA).

Informed consent

Written & Oral informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

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Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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