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Antimalarial evaluation of tamoxifen: A study in parasitized mice

Abstract

Malaria parasites resistance to currently used antimalarial drugs is a clinical challenge, which adds to socio-economic burden. A quick and cost-effective solution is to discover new treatment alternatives through drug repurposing. Tamoxifen (TMX) is an anticancer drug with some discrepancies in documented antimalarial activity. The current study assessed the *in-vivo* antiplasmodial activity of TMX on *Plasmodium berghei*-infected mice. Adult Swiss albino mice (both sexes) inoculated with *Plasmodium berghei* ($1x10^7$) intraperitoneally were used for curative and suppressive antiplasmodial studies. The inoculated mice were treated orally with TMX (1, 2 and 4 mg/kg/day) while the parasitized and standard controls were treated with normal saline (0.2mL/day) and chloroquine (CQ) (10mg/kg/day) for 4 days, respectively. Blood samples were collected and evaluated for parasitamia and haematological indices. The effects of TMX on body weight and rectal temperature were not significantly ($p>0.05$) different from the parasitized control. TMX did not produce significant ($p>0.05$) curative and suppressive antiplasmodial effects when compared to the parasitized control. Curatively, TMX at 1, 2 and 4 mg/kg produced 8.00 %, 14.39 % and 20.16 % parasitamia inhibitions, respectively compared to 79.21% parasitamia inhibition produced by CQ. In the suppressive study, 10.06 %, 17.44 % and 21.02 % parasitamia inhibitions were produced by TMX; 1, 2 and 4 mg/kg, respectively while CQ produced 82.10 % parasitamia inhibition. TMX had no significant ($p>0.05$) effects on red blood cells, white blood cells, packed cell volume and haemoglobin levels when compared to the parasitized control. This study showed that TMX lacks suppressive and curative antiplasmodial activities on *Plasmodium berghei*-infected mice.

Keywords: tamoxifen, repurpose, antimalaria, hematology, mice

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Introduction

Malaria is a major public health threat in tropical and subtropical regions of the world. Despite the fact that less than 1% of malaria infections are fatal, it causes about 430,000 deaths per year, especially among young children in sub-Saharan Africa.[1] Globally, 229 million cases of malaria and 409,000 deaths were reported in 2019.[2] African countries account for about 94% cases of malaria and deaths globally while South-East Asia regions account for 3% cases of malaria infection.[2] One of the primary strategies for malaria management is early diagnosis and treatment. However, this strategy was progressively impaired by the emergence of resistance malaria parasites to antimalarial drugs including artemisinin based combination therapies (ACTs) the main stay for malaria therapy.[3] Hence there is an urgent need for new and innovative treatments with novel targets to overcome the occurrence of resistance malaria parasites. One of the strategies to quickly and cost-effectively discover new treatment alternatives is to repurpose drugs approved for the treatment of other diseases.[4] This approach has a very low risk of failure, because most clinically used drugs have been shown to be safe in humans. It is also less time consuming, therefore less investment is needed.[4] Reliance on the traditional drug development pathways for new drugs has enormous implications on both cost and time.[5]

Tamoxifen (TMX) is a selective oestrogen-receptor modulator used for the treatment of oestrogen receptor positive breast cancer.[6] Due to its low cost and safety profile, it is used worldwide.[7] TMX has shown additional activities other than anticancer such as antibacterial and antiviral.[6] It has also shown possible therapeutic benefits in parasitic infections, which include the inhibition of *Taenia crassiceps* activity in infected mice,[8] *Taenia solium* cisticerci in hamsters[9] and reduced *Echinococcus granulosus* survival.[10] However, the effects of TMX on *Plasmodium* parasites remain conflicting. Studies showed it had no antiplasmodial effects on *P. falciparum* growth,[11] *Plasmodium yoelii nigeriensis*-infected mice[12] and chloroquine (CQ) resistant *Plasmodium berghei*-infected mice.[13] But some studies documented *in-vitro* and *in-vivo* antiplaspmodial activities of TMX on *Plasmodium falciparum* and *Plasmodium berghei (ANKA),* respectively.[14] Thus it is imperative that further studies are performed to ascertain the antiplasmodial activity of TMX. The current study assessed the *in-vivo* antiplasmodial activity of TMX on *Plasmodium berghei* (NK65) - infected mice, which has no available literature.

Materials and methods

Animals and drugs

TMX (Sigma Aldrich, St Louis, MO, USA) and CQ (Evans Pharm Nigeria Ltd) were used. The mice were purchased from the animal house of the Department of Pharmacology, Faculty of Basic Clinical Sciences, University of Port Harcourt, Rivers State, Nigeria. The mice were housed in plastic cages under natural laboratory conditions. They were fed with food pellets and given water *ad libitum*. CQ sensitive *Plasmodium berghei* (*P. berghei*) (NK65) was sourced from Nigerian Institute of Medical Research, Yaba, Lagos. The mice were infected by intraperitoneal (i.p) inoculation of red blood cells containing *P. berghei* ($1x10^7$). Parasitamia was determined in Giemsa-stained thin blood smears by microscopy. TMX (1, 2 and 4 mg/kg).[15] and CQ (10 mg/kg)[16] were used. National Institute of Health Guidelines for the Care and Use of Laboratory Animals were followed.[17]

Curative antiplasmodial assessment of tamoxifen

The protocol on established malaria infection (4-day curative Test) was used.[18] Thirty adult Swiss albino mice (both sexes) were inoculated as described above. The mice were grouped randomly into 6 of n=5/group and allowed for 3 days. On day 4, the mice were orally

treated with TMX (1, 2 and 4 mg/kg/day) for 4 days, respectively. The normal and parasitized controls were treated orally with normal saline (0.2mL/day) while the standard control was treated with CQ (10mg/kg/day) for 4 days, respectively. Drops of tail blood were collected on slides daily and thin blood smears prepared. The blood smears were fixed with absolute methanol and stained with Giemsa stain (Sigma Aldrich, St Louis, MO, USA). Parasitamia levels were assessed using a light microscope. Percentage parasitamia and inhibitions were calculated as shown below.

Suppressive antiplasmodial assessment of tamoxifen

The protocol for early infection used was described by Peters.[19] Thirty Swiss albino mice (both sexes) were inoculated as described above and randomly divided into 6 groups of 5 mice per group and allowed for 2hrs. Thereafter, the mice were orally treated with TMX (1, 2 and 4 mg/kg/day) for 4 days, respectively. The normal and negative controls were treated orally with normal saline (0.2mL/day) while the standard control was treated with CQ (10mg/kg/day) for 4 days. Tail blood samples were collected after treatment and thin blood smears were produced and processed as stated above. Percentage parasitamia and inhibitions were calculated as shown below.

$$\%\,Parasitamia = \frac{Number\ of\ parasitized\ red\ blood\ cells\ (RBCs)}{Total\ number\ of\ RBCs\ count} \times 100\%$$

$$\%\ Inhibition = \frac{(\%Parasitamia\ of\ negative\ control - \%Parasitamia\ of\ treated\ group)}{\%Parasitamia\ of\ negative\ control} \times 100\%$$

Determination of body weight and rectal temperature

The mice in the curative study were weighed using a digital weighing balance. The pre- and post-treatment rectal temperature of the mice were measured using a digital rectal thermometer.

Evaluation of haematological parameters

Blood samples were collected from the mice used for the curative study and assessed for red blood cells (RBCs), white blood cells, (WBCs), packed cell volume (PCV) and hemoglobin (HB) concentrations using an auto analyser.

Determination of mean survival time

Mortality was monitored daily for each mouse in the control and experimental groups from the time of parasite inoculation up to death and was recorded in days. The mean survival time (MST) was calculated as expressed below.

$$\mathrm{MST} = \frac{Sum\ of\ survival\ time\ of\ all\ mice\ in\ group\ (days)}{Total\ number\ of\ mice\ in\ that\ group}$$

Statistical analysis

Graph pad prism version 5.02 was used to analyse data and expressed as mean ± standard error of mean. The differences between means were compared using one way analysis of variance (ANOVA) and Dunnet's test. $p<0.05$ was considered significant.

Results

Effects of tamoxifen on body weight and rectal temperature of parasitized mice

In the curative study, treatment with TMX (1, 2 and 4 mg/kg) had no significant ($p>0.05$) effect on the body weight of parasitized mice when compared to the parasitized control. However, CQ significantly ($p<0.05$) restored the body weight of the parasitized mice when compared to the parasitized control (Table 1). TMX (1, 2 and 4 mg/kg) did not produce significant ($p>0.05$) effect on the rectal temperature of the parasitized mice when compared to the parasitized control. On the other, CQ significantly ($p<0.05$) increased rectal temperature of the parasitized mice when compared to the parasitized control (Table 2).

Table 1 Effect of tamoxifen on body weight of parasitized mice

Treatment	BW (g) Day 1	BW (g) Day 4	BW Change
P C	25.01±4.21	22.77±3.44	-2.24[a]
CQ	24.33±3.60	25.34±2.32	+1.01[b]
TMX 1mg/kg	25.21±3.45	23.03±3.23	-2.18[a]
TMX 2 mg/kg	24.22±2.33	22.56±3.11	-2.16[a]
TMX 4 mg/kg	25.18±3.41	23.02±2.61	-2.10[a]

Data as mean ± standard error of mean, n=5, BW, body weight; PC, parasitized control; CQ, chloroquine (Standard), TMX, tamoxifen. Values with difference superscripts down the column differ significantly at $p<0.05$ (ANOVA).

Table 2 Effect of tamoxifen on temperature of parasitized mice

Treatment	Temp°C Day 1	Temp°C Day 4	Temp°C Difference
P C	35.18±2.09	32.81±0.91	-2.62[a]
CQ	35.01±3.06	37.10±0.44	+2.09[b]
TMX 1 mg/kg	35.17±2.02	32.67±0.67	-2.50[c]
TMX 2 mg/kg	35.19±3.04	32.87±0.19	-2.32[c]
TMX 4mg/kg	35.04±2.08	32.90±0.55	-2.14[c]

Data as mean ± standard error of mean, n=5, Temp, temperature; PC, parasitized control; CQ, chloroquine (Standard), TMX, tamoxifen. Values with difference superscripts down the column differ significantly at $p<0.05$ (ANOVA).

Curative antiplasmodial effect of tamoxifen on parasitized mice

TMX did not produce significant ($p>0.05$) curative antiplasmodial effect on day 1, 2, 3 and 4 of treatments when compared to the parasitized control (Tables 3 and 4). On the other hand, CQ showed significant ($p<0.05$) curative antiplasmodial activity on day 1, 2, 3 and 4 of treatments when compared to the parasitized control (Tables 3 and 4). On day 4 of treatment, TMX at 1, 2 and 4 mg/kg produced 8.00 %, 14.39 % and 20.16 % parasitamia inhibitions, respectively when compared to 79.21% parasitamia inhibition produced by CQ (Table 4). Treatment with TMX had no significant ($p>0.05$) effect on MST when compared to the parasitized control. On the other hand, CQ significantly ($p<0.05$) prolonged MST when compared to the parasitized control (Table 4).

Table 3 Curative antiplasmodial effect of tamoxifen on daily parasitamia of parasitized mice

Treatment	% Parasitamia Day 1	% Parasitamia Day 2	% Parasitamia Day 3
PC	25.74±2.23[a]	32.44±3.00[b]	42.75±2.62[c]
CQ	19.43±2.00[d]	10.53±1.71[e]	5.12±0.56[e]
TMX 1mg/kg	22.24±2.47[f]	30.60±3.65[g]	39.61±3.42[h]
TMX 2mg/kg	22.64±2.73[f]	28.82±2.54[g]	37.65±3.00[h]
TMX 4mg/kg	21.39±2.54[f]	27.67±2.63[g]	35.33±2.81[h]

Data as mean ± standard error of mean, n=5, PC, parasitized control; CQ, chloroquine (Standard); TMX, tamoxifen. Values with difference superscripts differ significantly at $p<0.05$ (ANOVA: Analysis of variance).

Suppressive antiplasmodial effect of tamoxifen on parasitized mice

TMX (1, 2 and 4 mg/kg) had no significant ($p>0.05$) suppressive antiplasmodial effect when compared to the parasitized control (Table 5). However, CQ produced significant ($p<0.05$) suppressive antiplasmodial effect when compared to the parasitized control (Table

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5). TMX at 1, 2 and 4 mg/kg produced 10.06 %, 17.44 % and 21.02 % parasitamia inhibitions, respectively while CQ produced 82.10 % parasitamia inhibition (Table 5). The effect of TMX on MST was not significantly ($p>0.05$) different from the parasitized control. However, MST was significantly ($p<0.05$) prolonged by CQ when compared to the parasitized control (Table 5).

Table 4 Curative antiplasmodial effect tamoxifen on parasitized mice

Treatment	% Parasitamia	% Inhibition	MST
PC	54.80±2.00[a]	0	9.30±0.46[a]
CQ	1.53±0.33[b]	79.21	30.56±2.33[b]
TMX 1mg/kg	50.42±3.52[c]	8.00	9.50±0.71[c]
TMX 2mg/kg	46.91±3.00[c]	14.39	9.63±0.23[c]
TMX 4 mg/kg	43.75±3.81[c]	20.16	9.80±0.34[c]

Data as mean ± standard error of mean, n=5, PC, parasitized control; CQ, chloroquine (Standard); TMX, tamoxifen. Values with difference superscripts down the column differ significantly at $p<0.05$ (ANOVA: Analysis of variance).

Table 5 Suppressive antiplasmodial effect of tamoxifen on parasitized mice

Treatment	% Parasitamia	% Inhibition	MST
PC	15.22±1.33[a]	0	9.60±0.66[a]
CQ	2.73±0.55[b]	82.10	35.56±2.11[b]
TMX 1mg/kg	13.60±1.33[c]	10.06	9.70±0.25[c]
TMX 2mg/kg	12.57±1.64[c]	17.44	10.00±0.54[c]
TMX 4 mg/kg	12.02±1.45[c]	21.02	10.63±0.11[c]

Data as mean ± standard error of mean, n=5, PC, parasitized control; CQ, chloroquine (Standard); TMX, tamoxifen. Values with difference superscripts down the column differ significantly at $p<0.05$ (ANOVA: Analysis of variance).

Effect of tamoxifen on haematological parameters of parasitized mice

P. berghei-infected mice showed ($p<0.05$) low levels of RBCs, Hb, PCV and high ($p<0.05$) levels of WBCs when compared to the normal control (Table 6). Treatment with TMX (1, 2 and 4 mg/kg) had no significant ($p>0.05$) effect on RBCs, Hb PCV and WBCs of parasitized mice when compared to the parasitized control (Table 6). On the other hand, CQ significantly ($p<0.05$) increased RBCs, Hb, PCV and significantly ($p<0.05$) decreased WBCs when compared to the parasitized control (Table 6).

Table 6 Effect of tamoxifen on haematological parameters of parasitized mice

Treatment	RBC (x106)	WBC (cells/L)	PCV (%)	HB (g/dL)
N C	6.07±0.54	3.86±0.63	59.34±4.45[a]	17.46±1.32[a]
P C	3.21±1.32[a]	9.36±0.67[a]	31.33±3.00[b]	10.24±0.14[b]
CQ	5.21±0.72[b]	4.83±0.32[b]	54.33±5.42[c]	16.25±0.42[c]
TMX 1mg/kg	3.33±0.33[c]	8.45±0.45[c]	32.37±3.56[c]	10.33±0.71[c]
TMX 2mg/kg	3.46±0.25[c]	8.36±0.63[c]	33.47±3.43[c]	10.63±1.32[c]
TMX 4mg/kg	3.55±0.17[c]	8.24±0.22[c]	35.21±2.54[c]	11.00±0.52[c]

Data as mean ± standard error of mean, n=5, NC, normal control; PC, parasitized control; CQ, chloroquine (Standard); TMX, tamoxifen; RBCs, red blood cells; WBCs, white blood cells; PCV, packed cell volume; Hb, hemoglobin; Values with difference superscripts down the column differ significantly at $p<0.05$ (ANOVA).

Discussion

Regardless of the constant effort to reduce the burden of malaria infection, it was responsible for more than 260,000 deaths in children under 5 years in 2017.[20] The emergence of new resistant strains of *Plasmodium* parasites to available antimalarial drugs[21] is jeopardizing the international effort to combat malaria, which creates the need for the development of new therapies through drug repurposing. Drug repurposing is a very successful strategy, which accounts for around 25% of the annual income of the pharmaceutical industry.[22] The selection of drugs for repurposing mostly considers clinically used drugs as well as drugs removed from the markets due to unprofitability or other strategic reasons.[23] This study assessed the antimalarial activity of TMX on mice infected with CQ sensitive strain of *P. berghei*. A rodent model was used, because it produces disease features similar to those of human plasmodial infection when infected with *P. berghei*.[24] CQ, which has been used in most antiplasmodial studies as a reference standard was used.[25] *P. berghei* a rodent malaria parasite though, not able to infect man and other primates has been frequently used for the assessments of antimalarial drug candidates.[25] *In-vivo* model was used in this study to allow for the possible prodrug effect and the eradication of infections by the immune system.[26] Body weight loss and reduction in body temperature are symptoms of malaria-infected mice.[27] In infected mice, decreased metabolic rate occurs before death and is accompanied by decreased internal body temperature.[28, 29] In this study, TMX did not produce notable effects on the body weight and rectal temperature of the parasitized mice. A 4-day curative study, which allows for established infection and a 4-day suppressive study, which allows for early infections were used.[30] TMX exhibited no curative and suppressive antiplasmodial activities in this study. Similarly, Cervantes-Candelas et al.,[13] reported that TMX had no antiplasmodial effect on CQ resistant *P. berghei*-infected mice. Staines et al.,[11] also showed that TMX had no antiplasmodial effect on *P. falciparum* while Sing et al.,[12] reported no antiplasmodial effect on *P. yoelii nigeriensis*-infected mice. In contrast to findings in the current study, Weinstock et al.,[14] showed that TMX and its primary metabolite 4-HO-tamoxifen produced *in-vitro and in- vivo* antiplaspmodial activities on *P. falciparum* and *P. berghei* (ANKA) respectively. The observations in this study differ from findings by Weinstock et al.,[14] probably due to differences in the dose of TMX, species of *P. berghei* and mice used. MST experimentally measures the ability of a potential antimalarial drug to prevent or reduced malaria associated death.[30] Treatment with TMX did not prolong MST of *P. berghei*-infected mice. *Plasmodium* parasites are common cause of anaemia especially in children leading to decreased RBCs, Hb and PCV. Malaria parasites use host Hb as an essential nutrient for multiplication and growth. Malaria parasites ingest more than 75% of Hb during their intra-erythrocytic phase and metabolize heme into hemozoin.[31] One of the characteristic of an antimalarial drug candidate is to surmount anaemic condition caused by *Plasmodium* parasites. This study observed the inability of TMX to prevent *P. berghei*-induced anemia. In contrast, Cervantes-Candelas et al.,[13] reported deceased anemia in *P. berghei ANKA*-infected mice treated with TMX.

Conclusion

Tamoxifen did not produce antiplasmodial activity on *P. berghei*-infected mice.

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None.

Conflicts of interest

Authors declare that there is no conflict of interest.

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