Effects of artemether on parasite burden and liver pathology in mice infected with Ibadan isolate of *Schistosoma mansoni*

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Abstract

This study aimed at evaluating the pathological features associated with *Schistosoma mansoni* infection and assessment of the efficacy of artemether in the treatment of intestinal schistosomiasis in laboratory mice. Cercariae harvested from naturally infected *Biomphalaria pfeifferi* obtained from Odo Ona River in Ibadan, Oyo State, Nigeria, were used to infect Swiss albino mice in the laboratory. A total of 50 mice were divided into 5 groups and artemether (300mg/kg) was administered to two of the groups at 15th and 42nd day post-infection respectively, Praziquantel (600mg/kg) was administered to a group as the control drug and another group was used as the infected control group while the last group was uninfected. Mice were sacrificed and perfused at 8th week post-infection for worm recovery, examination of the visceral organs and histopathology were conducted on liver and spleen of infected and uninfected groups. *Schistosoma mansoni* isolate from Ibadan, caused severe liver pathology in mice, and thus presents features indicative of epidemiological importance in human schistosomiasis. Worm burden reduction (98%) was observed in mice treated at day 15 post-infection with artemether (300 mg/kg) while 77% worm reduction was observed in the group of mice treated at day 42 post infection with artemether (300 mg/kg). Granulomas were not observed in the liver of mice treated at day 15 post-infection while those of untreated group, which had multiple granulomas. Inflammatory cellular infiltrations were observed in liver of infected mice however, the mice treated at day 15 post-infection had mild infiltration likely due to fewer eggs present in the liver. Praziquantel used as the routine control drug was less effective compared to artemether. Worm reduction (53%) was recorded for mice treated with praziquantel, gross and histopathology also revealed eggs diffusely deposited in the liver of the mice. Artemether, a derivative of artemisinin, showed a good antischistosomal effect that could be an alternative and/or complement praziquantel in the control of schistosomiasis in endemic areas.

Keywords: Artemether; *Schistosoma mansoni*; Ibadan isolate; Swiss albino mice; gross pathology; histopathology.
Accepted: 19 September, 2018.

Introduction

Schistosomiasis is one of the neglected tropical diseases that are widespread in areas where the snail intermediate hosts are present. It is caused mainly by five *Schistosoma* species which are *Schistosoma haematobium* (the cause of urinary schistosomiasis), *S. mansoni*, *S. japonicum*, (both causing intestinal schistosomiasis), *S. intercalatum*, and *S. mekongi*. The disease caused by *S. mansoni* and *S. haematobium* is wide spread in Nigeria. Schistosomiasis affects the intestine or the urinary tract of infected people and it may lead to abdominal pain, enlarged spleen and liver, diarrhea, bloody stool or hematuria respectively. It may sometimes predispose to cancer and lead to death (Rambau *et al* 2013). In children, schistosomiasis is a cause of poor growth and learning difficulty, (WHO, 2014). About 85% of world cases are present in Africa and the prevalence rate can exceed 50% in some local communities (WHO, 2002; Steinmann, *et al* 2006; Montgomery, 2015).

The control of schistosomiasis is focused on reduction of morbidity and mortality to levels below public health significance (Useh, 2013). Strategies put in place to achieve this revolve around implementation of preventive chemotherapy in conjunction with health education, access to clean water, improved sanitation and ecological control of snail intermediate host, including the use of molluscicides (WHO, 2013). Drugs presently used for treatment of schistosomiasis are oxamniquine, metrifonate, and praziquantel (PZQ). Artemisinins earlier synthesized for the treatment of malaria is being used in some endemic communities to treat schistosomiasis (Utzinger *et al* 2001; Lescano *et al* 2004; Liu *et al* 2011). Schitozim, a herbal drug has been reported to be locally used in Kenya for treatment of schistosomiasis and it is said to be as effective as praziquantel (Allan, 2014).

The cost of praziquantel is high and not readily affordable by the people who are mostly affected and this is one of the greatest impediments in the control of the disease (Useh, 2013). Also, no vaccine has yet been developed for the effective control of schistosomiasis and there are increasing concerns about the emergence of resistance by some *Schistosoma* isolates (Stelma,

http://dx.doi.org/10.4314/tzool.v16i1.8

et al 1995; Mountford, 2005; WHO, 2014) to praziquantel. Countries such as Cameroon (Tchuenté *et al* 2004), Zimbabwe (Midzi, 2008) and Egypt (Barakat and El morshedy, 2011), and have reported low cure rates of PZQ. Therefore, there is the need for establishment of alternative, better and highly effective products for the cure of schistosomiasis caused by the local isolate.

Chinese scientists discovered that artemether was not only effective against malarial but also effective against the blood flukes (Xiao, 2005). Artemether (ART) is a methyl ether derivative of artemisinin, which is a peroxide lactone, isolated from the antimalarial plant *Artemisia annua*. It is also known as dihydroartemisinin methyl ether. It is an antimalarial used for the treatment of multiple drug-resistant strains of *Plasmodium falciparum* malaria. Since artemether is used in Nigeria for treatment of malaria, it is used as a compound drug against schistosomiasis along with malaria may be of great advantage. This study was therefore designed to evaluate the efficacy of artemether in the treatment of intestinal schistosomiasis caused by an Ibadan isolates of *S. mansoni*.

Materials and methods

Intermediate host and parasites

Naturally infected snails, *Biomphalaria pfeifferi* were collected from Odo Ona River in Ibadan, Nigeria. The snails were placed in glass beakers containing dechlorinated tap water and then exposed to direct sunlight for about one hour to initiate shedding of *S. mansoni* cercariae into water. Snails were removed from the water and the water was examined under dissecting microscope after which 60±10 cercariae were counted and used for experimental infection of mice.

Experimental animals

Fifty laboratory-bred female Swiss albino mice, 8 weeks old, with average weight of 27.5 g obtained from the Animal House of the Zoology Department, University of Ibadan, Ibadan, were used for the experiment. The mice housed in plastic cages with wire-net tops and fed on dry pellet feed and water *ad libitum*, were acclimatized for two weeks prior to induction of experimental infection.

Experimental design

Mice were randomly distributed into 5 groups as follows: Group 1: Infected and treated with ART day 15 PI (Post-infection) (10 mice); Group 2: Infected and treated with ART day 42 PI (10 mice); Group 3: Infected and treated with PZQ day 42 PI (5 mice); Group 4: Infected untreated control (10 mice); Group 5: Uninfected control (10 mice).

Experimental infection of mice

Mice were percutaneously infected with 60±10 *S. mansoni* cercariae using a modified tail immersion method (Christensen *et al* 1984). Water containing 60±10 cercariae were transferred into test tubes and a funnel was placed on it and each anaesthetized (ketamine and xylazine) mouse was respectively placed in the funnel with the tail extended into the water in the test tube. Each mouse tail was immersed for thirty minutes in the water before being transferred to their respective cages.

Drugs and doses

An injectable Artemether (Philomether®) produced in China purchased from a pharmaceutical store in Nigeria was used for the treatment. A 0.1mg/g dose was given to each treated mouse for three consecutive days (300mg/kg) intramuscularly using tuberculin syringe and needle. Praziquantel 600 mg (prizilcide® tablets) Yanzhou Xier Kangtai Pharmaceutical Co., Ltd in China was dissolved in water and administered per os to control mice at a dose of 0.6mg/g body weight.

Post-infection worm recovery

Mice were euthanized at 8th week post-infection (PI) after which they were perfused as described by Christensen *et al* (1984), for the recovery of adult worms post infection.

Liver egg burden

The liver of each mouse was weighed and digested with 5% KOH in the ratio of 1:10 w/v in an incubator at 70^{o}C for 40 minutes (Christensen *et al* 1984). After digestion of the liver tissue, the mixture was double diluted with fresh water to inhibit further digestion of parasite eggs. The average egg count per ml was determined and the number of ova/liver tissue was estimated. Counts were expressed as number of eggs per gram of liver.

Pathological evaluation of livers

The livers were on served for gross morphological changes including colour, texture and presence of granulomas prior to organ perfusion. Representative tissue section of liver of mice from each group were obtained and fixed in 10% buffered formalin, and processed routinely for histopathology. Tissue sections were stained with haematoxylin and eosin (H and E) stain (Junqueira and Caneira, 2005).

Statistical analysis

The results were presented as mean ± standard deviation (S.D). Microsoft Excel Software Package (2016) was used for result analysis. *t*-test was used to test differences between variables of each group. Values of $p< 0.05$ were considered statistically significant.

Results

Effect of artemether (ART) and praziquantel (PZQ) on parasitological parameters

The percentage schistosome worm burden reduction in mice treated with ART (300mg/kg) at day 15 PI

(Group 1), ART (300mg/kg) at day 42 PI (Group 2) and PZQ (600 mg/kg) at day 42 PI are shown in Table 1. Treatment with artemether at day 15 induced highest worm reduction (98%) followed by ART at day 42 (77%) while PZQ at day 42 (53 %) produced the lowest worm burden reduction. The total worms recovered from *S. mansoni*-infected mice 8 weeks PI was significantly ($p<0.05$) reduced in ART-treated group. There was also a significant worm reduction between mice treated with ART day 15 PI (Group 1) and infected untreated mice (group 4) ($p<0.05$) and between mice treated with ART day 42 post-infection (Group 2) and infected untreated mice (Group 4) ($p<0.05$). There was however, no significant difference ($p>0.05$) between mice treated with PZQ at day 42 post-infection and infected untreated mice, indicating poor *Schistosoma* cure rate with PZQ.

Table 1. Percentage worm recovery and worm burden reduction in experimental groups.

Mice group*	% worm recovery	% worm reduction	*p*–value
Group 1	1.83	98	0.007
Group 2	23.08	77	0.024
Group 3	46.89	53	0.101
Group 4	100	0	

*Group 1(treated with ART day 15 post-infection), Group 2 (treated day with ART day 42 post-infection) and Group 3 (treated with PZQ day 42 PI).

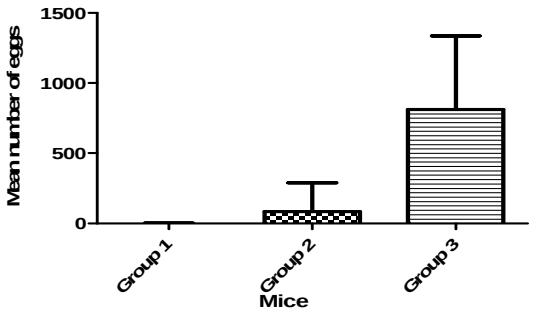


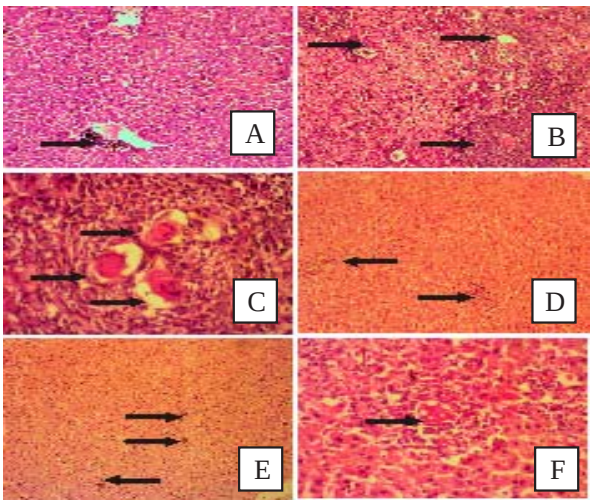
Figure 1. Mean number of eggs recovered from liver of mice in Group 1 (treated with ART day 15 post-infection), Group 2 (treated day with ART day 42 post-infection) and Group 3 (treated with PZQ day 42 PI).

The mean egg counts recovered from the liver of mice treated with ART day 15 PI (Group 1), ART day 42 PI or PZQ day 42 PI were 0.9 (± 0.9), 84.1 (± 65.4028), and 812 (±261.6286) respectively (Figure 1). Total number of eggs recovered from the liver of mice treated at day 15 PI was less than that recovered from mice treated day 42 PI.

Effects of artemether on liver pathology of Schistosoma-infected mice

At 8 weeks PI, multiple grayish *foci* (granuloma) were observed widely distributed in the liver of mice treated with PZQ at day 42 PI, similar to these observed in the untreated control mice. Fewer granulomas were observed in mice treated with ART at day 42 PI at each necropsy while no grossly visible granuloma was found in liver of mice treated with ART day 15 PI. Liver of mice in the Control Group (uninfected and untreated – Group 5) reveals few f*oci* of mild perivascular mononuclear (lymphocytic) cellular infiltration (Figure 2A) in the hepatic periportal region. *S. mansoni*-infected and untreated mice (Group 4) liver showed multiple *foci* of granulomas consisting of severe lymphocytic and few eosinophilic cellular infiltrations throughout the liver parenchyma (Figure 2B). Many of the granulomas have intra-lesional parasite eggs (Figure 2C) as well as severe distortion of hepatocellular cords and moderate hepatocytic vacuolation.

Hepatic granulomas of varying severity were encountered in all the treated-groups while mice treated with PZQ day at 42 PI also showed intralesional has *S. mansoni* eggs. Liver sections of mice treated with ART at day 15 PI (Group 1) showed moderate diffuse vacuolar degeneration of hepatocytes, multiple foci of mild parenchyma lymphocytic infiltration and few perivascular lymphocytic infiltrates (Figure 2D). Mice treated with ART at day 42 PI (Group 2) however showed few parasitic granulomas and multiple foci of moderate lymphocytic infiltrates (Figure 2E) as well as foci of haemosiderosis and parenchyma haemorrhage. The mice treated with PZQ day at 42 PI (Group 3), showed multiple discrete hepatic *foci* of very severe lymphocytic and eosinophilic infiltrates and parasitic nodules (degenerating *S. mansoni* eggs) (Figure 2F). Moderate diffuse vacuolation of hepatocytes were also observed.



Figures 2. Photomicrograph of mice liver. (H and E stain). **A**: Uninfected liver showing mild perivascular lymphocytic cellular infiltration (x100). **B**: Infected-untreated liver (x100) showing granuloma consisting of lymphocytic and eosinophilic cellular infiltration. **C**: Infected-untreated showing intra-lesional *S. mansoni* eggs(x400). **D**: Infected-ART-treated at day 15 PI showing few perivascular lymphocytic infiltrates. (x 100). **E**: Liver of mice treated with ART day 42 PI showing few parasitic granulomas with multiple foci of few lymphocytic infiltrates. (x100). **F**: Liver section of mice infected and treated with PZQ day 42 PI. (x400) showing degenerating *S. mansoni* egg.

Discussion

Schistosomiasis is the disease resulting from infection with parasitic trematode worms of the genus *Schistosoma* (WHO, 2013). Although the standard treatment for the disease has been dependent on the use of the three drugs – metrifonate (for *S. haematobium*), oxamniquine (*S. mansoni*) and praziquantel (all human species). Increasing prevalence of drug resistance of schistosomes to these drugs especially PZQ has necessitated the search for alternatives (Botros *et al* 2005; Doenhoff *et al* 2008). ARTs with anti-schistosomal potential were described in China in the 1980s and later approved as schistosomiasis preventing drugs in China (Wang, 2000). In Nigeria, PZQ remain the anti-schistosomal drug of choice as there is paucity of research studies on the effects of ART on the local isolates of *Schistosoma* species. This study investigated the effect of artemether as alternative anti-schistosomal drug on both juvenile and adult stages of an Ibadan isolate of *S. mansoni* infection in mice.

Mice treatment at day 15 post-infection with artemether (100 mg/kg mice body weight) for three consecutive days resulted in 98% worm burden reduction compared to other treated groups. This is similar to but higher than what was recorded by Xiao *et al* (2004) when ART (200 mg/kg) was used against juvenile *S. mansoni*, and resulted in a 81% worm burden reduction.

Keiser *et al* (2010) also reported a range of 75.6-85.3% female worm burden reduction in mice challenged ~80 *S. mansoni* cercariae and treated with 400 mg/kg ART. The similar but relatively higher cure rate observed with ART given at a lower dose rate of 100 mg/kg in the present study may be attributed to higher sensitivity of the local isolate to ART. In Nigeria, PZQ is the drug of choice for the treatment of human schistosomiasis, thus with minimal exposure of the prevalent isolate to ART, there would be less drug resistant property compared to PZQ.

Treatment with 100 mg/kg ART at day 42 PI produced a lower (77%) worm burden reduction compared to treatment at day 15 PI. This observation supports the report of Utzinger, 2002 and El-Ahl *et al* 2013, who observed that ART and its derivatives are mainly effective against juvenile stages of *Schistosoma* species. It is noteworthy that treatment with the standard drug, 600 mg/kg PZQ at day 42 PI induced only a 53% worm burden reduction compared to the ART treated-groups, indicating a remarkable lower cure rate of PZQ with the local isolate. This lower cure rate may partly be due to the single dose treatment used in this study or increased resistance of the Ibadan isolate to PZQ which is the major drug for schistosomiasis treatment in Africa (Ferrari *et al* 2003) more so, the previous study on the use of 500 mg/kg PZQ indicated an 87% worm burden reduction (Jatsa *et al* 2015).

Similar resistance to praziquantel has been reported by workers in some countries such as Egypt (Ismail *et al* 1996); Brazil/Africa (Silva *et al* 2005); Kenya (Melman *et al* 2009). As the use of PZQ, the selection for worms with diminished susceptibility become possible and the probability of emergence of resistance will increase as large reservoirs of unexposed worms diminish (Melman *et al* 2009). The *S. mansoni* worm used by Melman was isolated from a patient who had never been fully cured despite multiple treatments with PZQ. This might also be the case with the isolate used in this study which was obtained from snails collected Odo Ona River in a highly populated urban city of Ibadan where people living around the river might have been treated with praziquantel at one time or the other. Previous study by Muchirah *et al* (2012) showed a dose dependent cure rate and host protection with PZQ with a 1,350 mg/kg dose being more effective in cure rate than lower dosages.

Treatment with ART at day 15 PI also produced significantly lower egg burden in the liver of infected mice compared to ART treatment at day 42 PI. The lower egg burden with early ART treatment also correlates positively with adult worm burden reduction in mice treated at day 15 PI. It is expected that as juvenile worm burden is reduced with early treatment fewer adults that produce eggs emerge resulting in the lower egg burden in the liver (Xiao *et al* 2002), as observed in this study.

A comparative evaluation of treatments at day 42 PI with ART and PZQ respectively showed a significantly higher liver egg burden in PZQ compared to ART with the Ibadan isolate. This observation highlights the epidemiological importance of periodic studies/ assessment of the efficacy of drugs on the target pathogens.

Widespread multiple greyish *foci* (granulomas) in the liver of infected mice treated with PZQ at day 42 PI, and similar to those of infected control mice represent hepatic typical lesions of schistosomiasis as reported by previous workers (Fallon and Dune, 1999; Muchirah *et al* 2012). The relative similarity in the gross hepatic lesions in the infected control and PZQ treated groups at day 42 PI indicate the poor cure rate of PZQ at 600 mg/kg which was also supported by the high liver egg burden observed in this group compared to ART treated group. However, PZQ doses of 1,350 mg/kg and 900 mg/kg have been observed to induce less schistosomal lesions in the liver (Muchirah *et a*l 2012), but the possible toxicity of such higher doses remain undetermined. Interestingly, ART administered at day 15 resulted in absence of visible gross hepatic lesions of schistosomiasis while only few hepatic granulomas were observed in mice treated at day 42 PI. This observation highlights the curative potentials of ART which is a commonly available drug in Nigeria as a better alternative drug against local *Schistosoma* isolates.

Histopathology of infected untreated mice liver tissue is characterized by the presence of multiple granulomas with parasitic eggs as the tissue reaction to the infection.

Silva-Souza and Vasconcelos (2005) described similar lesions in *S. mansoni* infected liver. Other hepatocytic vacuolation observed in infected mice could be as a result of tissue anoxia sequel to high intra-hepatic blood pressure are factors in the formation of hepatocytic vacuolation formed by intracytoplasmic influx of fluid secondary to sinusoidal congestion (Sykes *et al* 1976; Li *et al* 2003). Severe diffuse distortion of hepatocellular cords observed was due to the presence of multiple granulomas, which resulted in disorganization of the hepatic cords and lobular structure.

Conclusion

Schistosoma mansoni Ibadan isolates, produced severe pathology in mice comparable to other isolates worldwide, and thus presents epidemiological importance in human schistosomiasis especially as there is high infection rate in the snail intermediate host in the water body associated with high human activities. Artemether which is an antimalarial drug had curative effects on both the juvenile and adult stages of *S. mansoni* in infected mice compared to the standard drug PZQ. ART however, is more effective against the juvenile stages than the adult stages of the parasitic worm. Artemether was observed to have therapeutic effects on the worm burden, liver egg count and reduced pathology on the liver of infected mice.

Acknowledgements

The authors wish to thank the Departments of Zoology and Veterinary Pathology, University of Ibadan for providing the equipment used for carrying out the experiment.

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Citation: Adejoro, F. T., Ilo, E., Ohore, O. G. and Odaibo, A. B.
Effects of artemether on parasite burden and liver pathology in mice infected with Ibadan isolate of *Schistosoma mansoni*
http://dx.doi.org/10.4314/tzool.v16i1.8

The Zoologist, 16: 43-48 December 2018, ISSN 1596 972X.
Zoological Society of Nigeria.