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Full Length Research Paper

Efficacy of artesunate in the treatment of urinary schistosomiasis in an endemic area in Anambra state, Nigeria

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The efficacy of artesunate in the treatment of urinary schistosomiasis was assessed among school children aged 5-16 years. Urine samples from 367 primary school children were examined for ova of *Schistosoma haematobium*. Using standard parasitological procedures (filtration method), *S. haematobium* ova was found in the urine samples of 29(7.9%) pupils. High infection rates of 16.0% and 13.2% were recorded in two primary schools with an overall egg output of 10.55 eggs/10mls urine (geometric mean). The prevalence was higher in the males (10.10%) than in the females (5.0%) and among the 12-16 years age group (15.1; $p \leq 0.05$). Infected pupils who reported for treatment were given oral dose of artesunate (4mg/kg/day) for 3 days. When the treated children were examined 2 weeks post treatment, the intensity reduced to 1.59eggs/10ml urine and the drug had an 85.12% egg reduction and efficacy rates. The treatment regimens were well tolerated. This study confirmed that the treatment of urinary schistosomiasis with artesunate is safe and effective but its widespread use for the treatment of schistosomiasis has to be considered carefully so that it does not compromise the efficacy of the drug as an anti-malaria and thereby increasing the risk of resistance developing in local *Plasmodium.*

Keywords: Urinary schistosomiasis, school children, artesunate

INTRODUCTION

Schistosomiasis is a serious debilitating, sometimes fatal parasitic disease. It is the second most prevalent tropical disease in Africa after malaria and of great public health and socio- economic importance in the developing world (WHO, 2002). The first obvious symptom of the infection is blood in the urine. Early signs of morbidity common to the infection and which manifest in school age children are anaemia, impaired growth, and development, poor cognition and substandard school performance (Cetron *et al.*, 1996). The late and life threatening consequences of schistosomiasis include bladder cancer or serious kidney malfunction caused by *S. haematobium*, and severe complications of the liver and spleen in the case of intestinal schistosomiasis (Cheesbrough, 2002).

Globally up to 120 million of the estimated 200 million infected people are believed to be symptomatic and as many as 20 million may well be suffering severe consequences of this infection. The annual deaths associated with schistosomiasis are estimated at 20,000 while about 500-600 million people worldwide are at risk

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(WHO, 2001). Nigeria is one of the countries known to be highly endemic where it is reported to affect all the 36 states of the country including Abuja.

There is yet no vaccine available for the prevention of schistosomiasis. The current mainstay of control is chemotherapy with praziquantel which is given as a single oral dose against all human schistosome parasite (WHO, 2002). Recently, Borrman *et al* (2001), Inyang-Etoh *et al* (2004) and Inyang- Etoh *et al* (2005) have variously studied the efficacy of the artemisinin derivatives (well known for its anti-malarial properties) for the treatment of all human schistosomiasis. Some compounds exhibiting activities against the young developmental stages of the parasites are relevant as praziquantel is ineffective in this area (Cioli, 2000).

Artesunate has also been used in human to obtain cure and egg count reduction against *Schistosoma* species infection. Report on the efficacy of artesunate in the treatment of urinary schistosomiasis is scarce especially in Nigeria and Anambra state in particular.

MATERIALS AND METHODS

Area and population

The work was carried out in Umuikwu-Anam, one of the schistosomiasis endemic areas of Anambra State, Nigeria. Umuikwu-Anam lies on longitude 6^0 45`E and latitude $6^0$ 18`N, with the area experiencing annual flooding during the peak of the rainy season (Ekejindu *et al*., 2002). The area is surrounded by several rivers/streams including the popular River Niger and manmade ponds for agricultural use particularly fishing. The main occupation of the inhabitants is farming as well as fishing. Majority of the people spend much of their lives in farm settlements where they carry most of their farming activities. Their children attend nearby primary and secondary schools in the farm settlements. They rely on streams, rivers and ponds for their domestic needs and livelihood. Latrines are not commonly found in the area and so the bushes behind houses, schools and those near ponds and streams are commonly polluted with human wastes.

The study population consisted of school children aged 5-16 years attending the primary schools in the area.

Ethical consideration

Ethical approval was obtained from the Nnamdi Azikiwe University Teaching Hospital Ethical Committee (NAUTHEC). Informed consent was obtained from the parents and pupils for the study.

Sample collection and examination

A total of 367 urine samples were collected from the pupils between 11:00 hours and 14:00 hours. Wide mouthed transparent containers with covers were given out to the pupils to collect their urine up to 15mls mark.

The urine samples were examined in the laboratory using the standard filtration technique (WHO, 1991) and the number of eggs/10mls of urine was counted.

Drug adminstration

Infected pupils were administered with artesunate (oral dose- 4mg/kg/day) for 3days (Borrman *et al*., 2001) and were examined for drug tolerance by the community physician.

Post treatment examination

Samples of the previously treated individuals were recollected and re-examined for egg of *S. haematobium* in order to evaluate the effect of the drugs on the parasite after 2weeks of drug administration.

RESULTS

Prevalence of *S. Haematobium* among the primary schools examined

Table 1 shows the prevalence of *S. haematobium* among the primary schools. Out of the 367 pupils examined from the 9 schools in the area, 29 pupils (7.90%) tested positive with an overall mean egg output of 10.55 eggs/10ml urine (Geometric mean intensity). Among the 9 schools used for the study, Oraka Community Primary School had the highest prevalence rate of 16.0% and egg output of 15.67eggs/10ml urine. Ukwubili Migrant Fishermen's School had the least with the prevalence rate of 6.10% and egg output of 2.33 eggs/10ml urine while no parasite was seen in Okpiijoku and Aribor Migrant Fishermen's School. Onono had the highest egg output of 31.0eggs/10mls urine but a prevalence rate of 6.8%. The proportion of the infected pupils is not statistically significant in all the schools ($P \leq 0.05$).

Prevalence of *S. Haematobium* by sex among the schools

Tables 2 below shows the prevalence of *S. haematobium* by sex among the schools examined. Of

Table 1. Prevalence of *S. haematobium* among the primary schools examined.

Names of Schools	No. Examined	No. Infected	Mean egg Output	Percentage Prevalence
Onono Community School	59	4	31.00	6.80
Ukwubili Migrant Fishermen School	49	3	2.33	6.10
Okpiijoku Migrant Fishermen School	21	0	0.00	0.00
Aniachlla Central School	32	3	4.67	9.40
Mbato Central School	42	4	6.75	9.50
Aniero Community School	46	4	18.00	8.70
Aribor Migrant Fishermen School	40	0	0.00	0.00
Abitor Central School	53	7	4.14	13.20
Oraka Community School	25	4	15.67	16.00
Total	**367**	**29**	**10.55**	**7.90**

Table 2. Prevalence of *S. haematobium* by sex among the schools

SCHOOL	MALES				FEMALES			
	No examined	No infected	Egg output	% prevalence	No examined	No infected	Egg output	% prevalence
Onono	36	8	4.70	22.22	27	1	5.00	3.7
Ukwubili	24	1	2.00	4.17	25	2	2.45	8.0
Okpiijoku	12	-	-	-	9	-	-	-
Aniachalla	31	5	4.79	16.13	18	1	1.00	5.56
Mbato	40	5	3.73	12.50	44	3	3.92	6.82
Aribor	21	-	-	-	19	-	-	-
Aniero	32	9	10.74	28.13	23	4	7.76	17.39
Abitor	42	11	8.60	26.19	36	11	2.57	30.56
Oraka	20	8	9.77	40.00	12	3	19.50	25.0
Total	258	47	4.93	18.22	213	25	4.69	11.74

Table 3. Prevalence of *S. haematobium* by age group

Age Interval (years)	No examined	No infected	Egg output	% Prevalence
5-7	126	1	1.00	0.8
8-11	168	17	12.19	10.1
12-16	73	11	9.30	15.1
Total	**367**	**29**	10.55	7.9

the 207 males and 160 females examined, more males 21(10.10%) than the females 8 (5.0%) were infected with an overall egg output of 13.19eggs/10ml urine in males and 3.63eggs/10ml urine egg output in females. The males in Oraka School had the highest number of infection (25%) with an egg output of 12.25eggs/10ml urine while the males in Ukwubili had the least prevalence of 4.2% with egg output of 2 eggs/10ml urine. The females in Abitor had the highest infection (13.0%) with egg output of 2eggs/10mls urine while the females in Mbato Community School had the highest egg output of 8.5eggs/10ml urine. The females in Ukwubili had a least prevalence rate of 8.0% with egg output of 2.5eggs/10ml urine. There is no significant relationship between sex and infection ($P \geq 0.05$). More males than females were infected.

Prevalence of *S. Haematobium* by age group

Tables 3 above shows the prevalence of *S. haematobium* by age group. Among the age groups examined, 12-16 years age group had the highest prevalence rate of 15.10% and egg output of 9.3eggs/10ml urine (GMI). Age group 8-11 years had the highest egg output of 12.19eggs/10ml urine while

Table 4 Intensity of *S. haematobium* infection before and after treatment with the drugs in the schools studied.

Schools	Pre-treatment intensity	Post treatment intensity	Mean number of eggs lost	Egg reduction rate (%)
Onono	31.00	10.67	20.33	65.59
Ukwubili	2.33	0.00	2.33	100.00
Anichalla	4.67	0.00	4.67	100.00
Mbato	6.75	0.25	6.50	96.30
Aniero	18.00	0.50	17.5	97.22
Abitor	4.14	0.14	4.00	96.55
Oraka	15.67	2.33	13.33	85.11
Total	10.70	1.59	9.11	85.12

the age group 5-7 years had the least rate of infection (0.8%) with mean egg output of 1.0eggs/10ml urine. Infection of the pupils is significantly related to the age of the pupils ($P \leq 0.05$). Prevalence of infection increases with increase in age of pupils.

Intensity of *S. Haematobium* infection before and after treatment with the drugs in the schools studied

Table 4 shows the intensity of *S. haematobium* infection before and after treatment with the drugs in the schools studied. There was a marked drop in the mean egg counts between the pre and post treatment counts. The overall intensity before treatment was 10.70eggs/10ml urine and after treatment, it was 1.59eggs/10ml. The mean number of eggs lost was 9.11eggs/10ml of urine. Egg reduction rate of 85.12% was obtained.

DISCUSSION

Among the 367 primary school children from Umuikwu-Anam farm settlement examined for urinary schistosomiasis, there was an overall prevalence of 7.90%. This is similar to the observation of Chidozie and Danijan, (2008) in Minna, where a prevalence rate of 12.9% was recorded. Ekejindu *et al* (2002) also recorded a higher prevalence rate of 25.5% in the farm settlements of Ezi-Anam while Inyang-Etoh *et al*, (2009) recorded a very high prevalence rate of 38.5% in their study in Adim community, all in Nigeria. These high prevalence were attributed to the human- water contact patterns which play a decisive role in the distribution of urinary schistosomiasis in the localities. The study recorded a prevalence rate of 16.0% in Oraka which still follows the trend of high rates as recorded by Ekejindu *et al* (2002) due to the fact that the children depend largely on the streams and ponds for their domestic activities especially during the dry season. There is no improved health facilities, people still depended on the patent medicine dealers for their health care needs. Few water bore holes provided are only utilized by the elderly while the school children go to the streams to swim and do other chores. The least prevalence rate was recorded in Ukwubili (6.10%) while no *S. haematobium* infection was recorded in Okpiijoku and Aribor Migrant Fishermen's schools. This could be attributed to the fact that the children are not Umuikwu indigenes but migrants from other towns around the area for fishing and other agricultural activities. Meanwhile, they do not make use of the streams and ponds but rather depend on River Niger and Omambara river that are around their settlements. Oraka and Abitor depend on Nwaowali and Otu Ogenemgboo streams for their water needs at different but very close water points. Studies have also shown that distance from home to a contaminated water source plays an important role in the risk of infection (Clennon *et al* (2004).

Males were found to be more infected than the females (though not statistically significant) with a prevalence rate of 10.1%. This is similar to the work of Ekejindu *et al* (2002) where the males had a significantly higher rate of 29.3% than the females. Mbah and Useh (2008) also recorded a significant higher rate in males (23.5%) than in the females (15.7%) in a rural community in Cameroun ($P \leq 0.05$). This could be attributed to the observation made that although both sexes were exposed to the same water bodies which were close to their dwellings, females generally stayed out of the water while processing their foods (e.g. cassava) or washing of plates and clothes while males stayed longer in water while swimming or fishing. In the African settings, girls are more associated with indoor activities. Among the Muslims, the females are restricted from swimming and bathing in water bodies due to religious and socio-cultural practices and therefore reduce their chances of being highly infected as their male counterparts.

Highest prevalence was recorded among school children aged 12-16 years ($p \leq 0.05$). Ekejindu *et al* (2002) recorded a high prevalence rate among the age group 10-14 years; Okon *et al* (2007) recorded highest prevalence rate among 12-13 years. Children are more

engaged in unrestrained water contact activities such as bathing and swimming therefore they are more likely to contact cercariae and acquire infection.

The study showed that age group 5-7 years had the least infection rate because they rarely go to the stream for any domestic chores as also collaborated by Nale *et al* (2003).

An egg reduction rate of 85.12% was observed in the treatment of infected pupils with artesunate. Inyang-Etoh *et al* (2004) observed a cure rate of 70.1% in Adim community, Nigeria; Okon *et al* (2010) also recorded a cure rate of 64% in Ogoja, Cross river State. A lower cure rate of 27% was recorded by Borrman *et al* (2001) while Ayoub *et al* (2009) also recorded a cure rate of 58.6%. Although artesunate had a 100% cure rate in 1995, recent clinical trials and animal experiment found out that the sensitivity of many schistosomes to artesunate including *S.mekongi* and *S. mansoni* decreased in China. A double-blind trial found out that the cure rate decreased to 13.5% after 10 years of 100% cure rate but an increase in concentration of artesunate during the first and third weeks yielded a cure rate of 74.8% (Hua *et al.,* 2010). The low cure rate may be attributed to the time lapse between administration of drug and end point. Artesunate orally administered at a dose of 4mg/kg once daily for three days result in no drug related adverse effect and significantly reduces the intensity and incidence of the infection. The significant reduction in the number of eggs produced by surviving worms and the status of egg maturation suggested that artesunate inhibits sexual maturation (Utzinger *et al*., 2003). Electron microscopy revealed that artesunate caused morphological damage especially on the worm tegument (Lu *et al*., 2005).

Urinary schistosomiasis is still on a high trend in Umuikwu-Anam and there are more foci of endemic urinary schistosomiasis in the South Eastern Nigeria than previously reported. Urinary schistosomiasis contributes to malnutrition among residents of rural agricultural community in developing countries where poverty, ignorance, ecological conditions and lack of government commitment among other factors constitute serious threat to public health. This disease is thus highly prevalent in most settlements in Nigeria and would be a threat to important socio-economic development in all the infected areas. Notwithstanding the efforts made to control schistosomiasis in endemic areas, global incidence of the disease is still increasing. To disrupt transmission more effectively and achieve prolonged disease control, there is need for health education, supply of good drinking water, diagnosis, treatment, management of the environment and control of the intermediate host. The government has provided just one bore hole in the community which is not used by the children. There are no latrines for the inhabitants. This should be provided so that the children will have little or no reason to visit the streams until the vector and intermediate host are eliminated.

Efficacy of artesunate is hoped to increase in dosage. Research is still necessary in order to ascertain the proper dosages, mechanism of action and interval of time within which treatment should be given so as to obtain a 100% cure rate. Artesunate is primarily used for the treatment of malaria; its widespread use for the treatment of schistosomiasis has to be considered carefully so that it does not compromise the efficacy of the drug as an anti-malaria and thereby increasing the risk of resistance developing in local *Plasmodium.*

Federal government agencies should also intervene by adopting the integrated control measures in the total eradication of this scourge in all the rural settlements in Nigeria in general and in Umuikwu-Anam, Anambra State in particular so as to attain the 2015 millenium development goal.

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