Educational Forum
Toxicology International, *May-Aug 2016 / Vol-23 / Issue-2, 107-111*
ISSN (Print) : 0971-6580
ISSN (Online) : 0976-5131
DOI: 10.22506/ti/2016/v23/i2/146684

Antimalarial Therapies and Infertility: A Comprehensive Review

Earnest Oghenesuvwe Erhirhie[1,2*]

[1]Department of Pharmacology and Toxicology, Nnamdi Azikiwe University, Awka, Anambra
[2]Department of Pharmacology and Therapeutics, Delta State University, Abraka, Nigeria.
*erhirhieochuko@yahoo.com

Abstract

Apart from other factors associated with infertility, scientific literatures had shown that synthetic and herbal antimalarial agents are also associated with reproductive disorders. However, there is paucity of review update on the reproductive toxicity posed by these antimalarial agents. With the aid of the internet data base, relevant literatures on this subjects matter were reviewed in this evaluation. Among the synthetic and herbal antimalarials investigated, Quinine, Piperaquine phosphate, Chloroquine, Proguanil, halofantrine hydrochloride, Pyrimethamine, Arthemeter- Lumefantrine, ACTs (artesunate), Artemether, *Azadirachta indica* (Neem), *Phyllanthus amarus, Alstonia boonei*, except (sulfadoxine/pyrimethamine), were associated with diverse reproductive toxicities. Proposed mechanisms of such toxicities include; reduction in follicle stimulating hormone, leuteinizing hormone and testosterone levels, impairments in sperm parameters, antifolate (Pyrimethamine) activity, anti-androgenic activity, distortion of the blood-testis barrier formed by the sertoli cells and increase reactive oxygen species (ROS). On this basis, antimalarial therapies (synthetic and medicinal plants) should be used with caution, especially during pregnancy. Also, reproductive toxicities of new antimalarial drugs being launched into the marked should be screened to ascertain their safety.

Keywords: Infertility, Antimalarial drugs, Experimental animals, Reproductive toxicity.

Received: 28-03-2016 **Revised:** 30-06-2016 **Accepted:** 04-07-2016

1. Introduction

1.1 Background

Malaria, a disease caused by different strains of the protozoan parasites of the genus *Plasmodium* remains one of the most devastating human parasitic infections. It is transmitted through the bite of infected mosquitoes. However, malaria caused by *Plasmodium vivax*, *Plasmodium malariae*, and *Plasmodium ovale* are less fatal. [1]

Current statistics had shown that out of about 3.4 billion people who are exposed to malaria worldwide, about 1.2 billion people are at high risk. [2] Recent WHO evaluation in September 2015 revealed 214 million cases of malaria in the year 2014, of which 438000 deaths were reported. [2] Major burden of malaria is found in Africa, where 90% of cases are caused by plasmodium falciparum. [3]

However, development of resistance by *Plasmodium* against available antimalarial drugs had necessitated the development of better antimalarial agents from both synthetic and natural sources (Table 1). [1]

Infertility, defined as failure to be pregnant following a year of unprotected sexual intercourse is one of the most important health and social problems in several parts of the world. [4] It has been estimated that 40 to 90% of male sterility is as a result of poor semen production from an unknown cause. [4]

Several factors are associated with male infertility. Among these include; cigarette smoking, poor nutrition, reactive oxygen species (ROS), radiation, heavy metals, estogens (and derivatives), infection, scrotal temperature, sperm antibodies as well as conventional and natural herbal remedies. [4] Apart from these factors, preclinical studies had revealed that chemotherapy of malaria with synthetic drugs as well as some medicinal plants is also

* *Author for correspondence*

associated with male infertility. This review was designed to unveil the reproductive toxicities posed by these antimalarial therapies.

1.2 Antimalarial Drugs

Antimalarial drugs could be classified as either single or combined therapies, as shown in the Table 1 below.

1.3 Reproductive toxicity reports on synthetic Antimalarial drugs

1.3.1 Single Antimalarial therapy

Quinine: Osinubi and co-workers had reported that Quinine (a stereoisomer of quinidine), made from the bark of the Cinchona tree, useful in the treatment of severe malaria and nocturnal leg cramps is toxic to the reproductive system. Their findings showed that quinine was toxic to testicular gonocytes and the seminiferous tubules of rats. [6] Borovoskaya and co-worker also observed that a single injection of quinine in a maximum tolerable dose to BALB/c mouse caused morphological changes in the testes and suppressed spermatogenesis. [7] Quinine was also reported to inhibit Leydig cell steriodogenesis and fertility in male rats. [9] Ukenya and co-workers also reported degenerative changes and reduced testes tubular size following administration of higher doses of quinine and artemether to Wistar rats. [10] A study carried out by Olorunshola and Baa showed that administration of quinine dihydrochloride (5 and 10 mg/kg) intraperitonially to adult albino rats for 4 days caused changes in reproductive organs and serum testosterone level.

Chloroquine: Chloroquine, a lysomotropic agent which inhibits the degradation of internalized human chorionic gonadotropin (hCG) in leydig had been shown to; reduce fertility in male rats, [21] inhibit testosterone secretion in hCG-stimulated testis of pubertal rats, [11] reduce sperm motility as well as number of fetuses of cohabited females rats, [12] inhibits leydig cell steroidogenesis and fertility in male, [9] and also disrupt spermatogenesis accompanied by a decline in serum testosterone level in the rats.[13]

Piperaquine phosphate: Embryofetal investigation in rabbit and rat showed that Piperaquine phosphate (5 – 20 mg/kg doses) caused delayed delivery. [14]

Proguanil: According to Akinsomisoye and Raji, toxicity study of Proguanil at 2.9 mg/kg body weight daily for 5 days and 6 weeks respectively revealed duration dependent significant reduction in body weights, organ

Table 1. Classification of antimalarial drugs

	Category	Examples
Single antimalarial agents	Cinchona alkaloid	Quinine and Quinidine
	4-aminoquinolines	Chloroquine, Amodiaquine and Piperaquine
	8-aminoquinolines	Primaquine and Bulaquine
	Diaminopyrimidines	Pyrimethamine
	Sulfonamides and Sulfones	Sulfadoxine, Sulfamethopyrazine and Dapsone
	Sesquiterpine lactones	Artesunate, Artemeter and Arteether
	Quinoline-methanol	Mefloquine
	Tetracyclines	Tetracycline and Doxycycline
	Amino alcohols	Halofantrine and Lumefantrine
	Mannich base	Pyronaridine
	Naphthoquinone	Atorvaquone
	Biquanides	Proguanil and Chlorproguanil
Combination Therapies	Non-artemisinins	Sulfadoxine + Pyrimethamine, Sulfadoxine + pyrimethamine + chloroquine, Sulfadoxine + pyrimethamine + amodiaquine, Sulfadoxine + pyrimethamine + mefloquine, Quinine + Tetracycline as well as Quinine + doxycycline
	Artemisinin	Artesunate + amodiaquine, Artesunate + mefloquine, Artemether + lumefantrine, Artesunate + sulfadoxine/pyrimethamine, Dihydroartemisinin + piperaquine, Artesinin + piperaguine + primaquine and Pyronaridine + artesunate
Other combinations		Chlorproguanil + dapsone + artesunate, Arterolane maleate + Piperaquine phosphate

Source: [1, 3, 5-6].

weights, serum testosterone and semen parameters as well as degeneration in the testis and epididymis of treated rats. [15]

Halofantrine hydrochloride: Long term administration of halofantrine hydrochloride (halfan) (5, 10 and 15 mg/kg) for a period of five (5) days revealed no adverse effect on the histological structure of the testes of adult Wistar rats at therapeutic dose. However, some degenerative changes in seminiferous tubule were noticed at higher doses. [16]

Arthemether: Study by Raji and co-workers revealed that exposure of male Wistar albino rats to artemether (po) for three (3) days caused significant reduction in progressive sperm motility, viability, sperm count as well as serum testosterone levels in dose and duration dependent manners. Untreated female rats were not pregnant after they were cohabited with treated male rats. However, these changes were restored in a recovery study. [17] Olorunshola and Baa also showed that administration of Artemether (20 mg/kg) intraperitonially to adult albino rats for 4 days caused changes in reproductive organs and serum testosterone level. [18] Dose dependent significant decrease was observed in the epididymal weight but there was no significant difference in seminal vesicle and testicular weights as well as sperm concentration and serum testosterone levels between the Artemether treated animals and control animals. They concluded that administration of Artemether at recommended doses and duration employed in this study had no adverse effects on testicular function and serum testosterone level. [18]

Artesunate: Long term (6-weeks) administration of artesunate caused significant reduction in; sperm characteristics, serum follicle stimulating hormone (FSH), luteinizing hormone (LH) and testosterone levels as well as visible lesion in the testes and epididymis. Dose and duration dependent changes in sertoli cell viability and ds-DNA integrity was observed in *in-vitro* studies. However, these changes were reversible after a recovery studies. [19] ACTs also caused decrease in total sperm count, motility, serum testosterone levels with varying effects on LH and FSH as well as increases in abnormal sperm cells (morphology). [20]

Pyrimethamine: Pyrimethamine, a prophylactic antimalarial drug has been shown to cause spermatogenic arrest and male infertility in mice. [21]

1.3.2 Combined Antimalarial therapy

Sulfadoxine/Pyrimethamine: Administration of sulfadoxine/pyrimethamine (22.5 mg/kg) intraperitonially to adult albino rats for 4 days showed no significant change in seminal vesicle and testicular weights as well as sperm concentration and serum testosterone levels of animals. [18]

Arthemeter- Lumefantrine: Study by Marakinyo and co-workers revealed that treatment with combination of Artemether-Lumefantrine (4:24 mg/kg, 8:48 mg/kg) for 3 (three) and 6 (six) days revealed no alteration in reproductive parametes. [32] This finding was contrasted by that of Tijani and co-workers, whose study revealed reduction in mean sperm count, motility and viability in rats when compared to controls. [22]

Dihydroartemisinin, Piperaquine Phosphate (P-Alaxin)

Study by Kareem and co-workers on reproductive toxicity of P-Alaxin (15.4 mg/kg, p.o) for three days in male adult Wistar rats revealed reproductive impairment characterized by decreased sperm motility, viability, count, as well as decrease in testosterone level. [23]

1.4 Some antimalarial medicinal plants with reproductive toxicity

Some antimalarial medicinal plants had been reported to alter reproductive functions [24]. These include; reversible suppressive effect of *Azadirachta indica* on male fertility [25], antiinfirtility effects of *Phyllanthus amarus* [24], as well as that of *Alstonia boonei* [26] in Wistar rats.

1.5 Mechanism of action of antimalarial drugs induced reproductive toxicity

Antimalarial drugs had been proposed to have different mechanisms of reproductive toxicities (Table 2). Such mechanism(s) include; antifolate activity as well as direct inhibition of serum and plasma testosterone, LH and FSH by pyrimethamine, [27] as well as aqueous extract of *Phyllanthus amarus*. [24]

Depletion of androgen at the targets levels, especially in the caudal epididymis by Chloroquine. [12] as well as P-alaxin. [19], distortion of the blood-testis barrier formed by the sertoli cells by proguanil and artesunate. [28], generation of reactive oxygen species (ROS) by

artemisinin derivatives [28] [29], and decrease in weights of reproductive organs. [10]

Table 2. Summary of mechanism of antimalarial drugs induced reproductive toxicities

Mechanism of reproductive toxicity	Class of drugs	Reference
Antifolate activity.	Pyrimethamine	[27]
Inhibition/reduction of reproductive hormones.	Pyrimethamine, Oral artemisinin derivative	[17]
Impairment in the development of spermatozoa.	Quinine	[7]
Depletion/ inhibition of androgen at the targets levels.	Chloroquine, P-alaxin	[23]
Distortion of the blood-testis barrier	Proguanil, Artesunate	[15, 19]
Oxidative stress through the stimulation of protein kinase C activity	Dihydroartemisinin, Artesunate, Artesiane (Artemether-lumefantrine)	[10, 20, 29]
Decrease in reproductive hormones	*Phyllanthus amarus*, Co-artesiane.	[24]
Decrease in weights of reproductive organs	Co-artesiane	[10]

1.6 Conclusion and recommendations

Although several factors are associated with infertility, it is very obvious that synthetic and herbal antimalarial agents also pose infertility. Among the agents investigated, sulfadoxine/pyrimethamine was not reported to be associated with reproductive toxicity. From this present evaluation, it is very essential to educate patients and healthcare practitioners on the reproductive disorders posed by antimalaria therapies. Also supplements that could ameliorate or prevent these toxicities should be included in antimalaria therapy. Reproductive toxicity profile of new antimalarial drugs being launched into the marked should be carried out to ascertain their safety.

2. Conflict of Interest

None Declared

3. References

1. Patil CY, Katare SS, Baig MS, Doifode SD. Fixed Dose Combination of Arterolane and Piperaquine: A Newer Prospect in Antimalarial Therapy. Ann Med Health Sci Res 2014; 4(4): 466–471.
2. WHO. World Malaria Report 2014. Geneva, Switzerland http://www.who.int/malaria/publications/world_malaria_report_2014/report/en/ (Accessed on January 5th, 2016).
3. Mebrahtu E. Antimalarial Drug Resistance: In the Past, Current Status and Future Perspectives. BJPT 2015; 6(1): 1-15.
4. Olayemi FO. A review on some causes of male infertility. Afr. J. Biotechnol 2010 9(20): 2834-2842.
5. Central Drugs Standard Control Organization (CDSCO). List of Drug Approved for Marketing in India. 2011. [Last accessed on January, 6th, 2016]. Available from: http://www.cdsco.nic.in/NEW%20DRUG%20UPDATE.doc
6. http://www.slideshare.net/nasertadvi/antimalarial-drugs-15555784. Acessed, march 14th, 2016.
7. Osinubi AA, Noronha CC, Okanlawon AO. Attenuation of quinine-induced testicular toxicity by ascorbic acid in rat: a stereological approach. Afri. J. Med. Med. Sci. 2005; 34: 213-219.
8. Borovoskaya TG, Gol'dberg ED, Abramova EV, Fomina TI, Tkachenko SB. Effect of quinine on the morphology of mouse testes. Bull. Exp. Biol. Med 2000; 130 (10): 994-996.
9. Sairam MR. In: Mckevas KW (ed). Structure and function of gonadotrophins, Plenum, New York. 1978; pp. 275-294.
10. Ukwenya VGA, Sodunke AST, Falunle JB. Acute administration of co-artesiane induces oxidative stress in the testis of adult male Wistar rats. Biosci. Res. Commun 2010; 22(5): 259-264.
11. Nduka EU, Dada OA. Inhibition of gonadotropin and prostaglandin stimulation of testicular steroidogenesis in malnourished rats. J. Androl 1984; 16: 406-409.
12. Adeeko AO, Dada OA. Chloroquine reduces the fertilizing capacity of epididymal sperm in rats. Afr. J. Med. Sci 1998 27: 63-68.
13. Okanlawon AO, Ashiru OA. Sterological estimation of seminiferous tubular dysfunction in chloroquine treated rats. Afr. J. Med. Med. Sci 1998 27: 101 -106.
14. Longo M, Pace S, Messina M, Ferraris L, Brughera M, Ubben D, Mazuè G. Reprod ToxicolElmsford, N.Y. 2012; 34(4):584-97.
15. Akinsomisoye SO, Raji Y. Prolonged administration of proguanil induces reproductive toxicity in male rats. J Toxicol Sci. 2011; 36(5):587-99.
16. Adamu LH, Taura MG, Abdu IT, Asuku AY, Datti S, Sadeek AA. Effect of long term administration of halofantrine hydrochloride (halfan) on the morphology and histology of the testes of adult Wistar rat. IOSR-PHR 2013; 3:(6); 15-19.
17. Raji Y, Osonuga IO, Akinsomisoye OS, Osonuga OA, Mewoyeka OO. Gonadotoxicity evaluation of oral artemisinin derivative in male rats. J. Med. Med. Sci 2005; 5(4): 303-306.
18. Olorunshola KV, Baa Y. Comparative Effect of Three Antimalarials (Quinine, Arthemeter and Fansider) on Some Reproductive Organs and Serum Testosterone Level in Male Wistar Rats. BJPT 2014; 5(2): 55-58.
19. Akinsomisoye OS, Raji Y. Long-Term Administration of Artesunate Induces Reproductive Toxicity in Male Rats. J Reprod Infertil. 2011; 12(4):249-260.

20. Obianime AW, Aprioku, JS. "Comparative study of Artesunate, ACTs, and their combinants on the spermatic parameters of the male guinea pig". Niger J Physiol Sci. 2009; 24(1):1-6.
21. Trager W, Polonsky P. Antimalarial activity of quassinoids against chloroquine-resistant *Plasmodium falciparum in-vitro*. Am. J. Trop. Med. Hyg. 1981; 30: 531 -537.
22. Marakinyo AO, Oludare GO, Ojulara S, Afolabi AO. Effect of short term administration of Arthemeter-Lumefantrine on testicular function and antioxidant defence in rats. RJMMS 2009; 4(2): 165-170.
23. Kareem FA, Osonuga IO, Akindele RA, Kukoyi BI, Taiwo EO, Inegbeneboh D. Antifertility Effects of P-Alaxin in Male Adult Wistar Rats. JNSR 2015; 5: 19; 5-8.
24. Ogbomade RS, Chike CPR, Adienbo OM. Evaluation of anti-infirtility effect of aqueous extract of *Phyllanthus amarus* in male Wistar rats. The experiment 2014; 27(3); 1874-1879.
25. Sathiyaraj K, Sivaraj A, Kumar PV, Devi K, Kumar BS. Spermicidal Activity of Azadirachta indica (Neem) Aqueous Leaf Extract on Male Albino Rats. Int J PharmTech Res 2010; 2:(1):588-591.
26. Oze R, Akubugwo E, Orisakwe E, AKA P. Reproductive Impairment Associated with the Ethanolic Extract of *Alstonia Boonei* (De wild) stems bark in male rats. The Int. J. of 3rd World Medicine 2007; 6:1.
27. Cosentino MJ, Pakyz RE, Fried J. Pyrimethamine: An approach to the development of a male contraceptive. Proc. Nat. Acad. Sci. USA. 1990; 87: 1431-1435.
28. Celino FT, Yamaguchi-Shimizu S, Miura C, Miura T. Proliferating spermatogonia are susceptible to reactive oxygen species attack in Japanese eel (Anguilla japonica). Biol Rep 2012; 87(70):1-9.
29. Tijani AS, Ukwenya VO, Sodunke GA, Fakunle JB. Acute administration of co-artesiane® induces oxidative stress in the testes of adult male Wistar rats. Biosci. Res. Commun 2010; 22 :(5); 259-265.