



Review Paper

Small Bite - Big Threats: Assessment of Pernicious Repercussion of Antimalarial Drugs

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Available online at: www.isca.in, www.isca.me

Received 7th July 2014, revised 23rd August 2014, accepted 20th September 2014

Abstract

Malaria is one of the most grievous public health problems worldwide. Most of the regions falling in tropical and subtropical areas receiving high rainfall are facing this threat and it is major cause of mortality in these regions. This deadly disease has promulgated into most of the Asian nations which are on the threshold of development. It has been observed that Antimalarial drugs that are prescribed for treatment of malaria do produce symptoms of toxicity because of over dosage or drug reactions consequent upon administration of Antimalarials. Various Antimalarial drugs such as Mefloquine, Halofantrine, Artether, Artemether etc. are known to have caused clinical manifestations such as Neuropsychiatric toxicity, Neurotoxicity, Cardio respiratory collapse and death. The present study reviews the articles stating the clinical findings in the cases of antimalarial drugs toxicity.

Keywords: Mefloquine, Halofantrine, Artether, Artemether.

Introduction

Malaria is a deadly parasitic disease spread by the bite of female anopheles mosquitoes. The disease is endemic mostly in tropical regions receiving high rainfall as the temperature and weather conditions are conducive for the burgeon of mosquitoes. The species of protozoa known to cause harm are plasmodium Falciparum, vivax, Ovale and Malariae. The WHO factsheet on malaria estimates about 3.4 billion population at risk of malaria¹. In 2012, around 6,27,000 deaths were estimated from this deadly disease.

Drug resistance to chloroquine in P. Falciparum was reported in India for the first time from Assam in 1973. Since then the cases of resistance towards malarial drugs have increased manifold causing fatality. Efforts are being taken worldwide to reduce the causation and mortality but the fact remains that this disease affects large mass of population and numbers of poisoning cases are reported due to over dosage or drug reactions consequent upon administration of malaria.

The genesis of this review is based on survey was a survey administered in hospitals of Mahamaya Nagar, Uttar Pradesh, India wherein it total number of malaria cases reported, mortality rate, complications due to the disease, were recorded. A total of 100 cases were studied in two hospitals of the district, and ill effects on human physiology were noted. In majority of the cases renal problems, hepatomegaly, muscle cramps was the major finding. Based on these observations, research articles on the toxicity of

antimalarial drugs were reviewed, compiled and presented in the table 1.

The toxicity of Anti malarial drugs sets an unusual and interesting problem for the clinician as well as the scientists². The Toxic effects associated with Malaria can be due to the disease as well as the prophylaxis. High mortality rate is reported if diseased is not medicated but at the same time threat of toxicity due to drug is also noteworthy³. Recurrent inimical effects of antimalarial drugs vary in range. Staining of dentition, disturbances in gastrointestinal tract effect on mental status of a person as psychosis, depression, nausea, allergic reactions, ulceration, and psoriasis are some examples. Grievous effects are cardiac toxicity, toxic effects on neurons, nephrons, muscles, cells that could prove to be virulent. According to chemical structure, Antimalarial Drugs can be classified as i. Aryl amino alcohols: Quinine, quinidine (cinchona alkaloids), mefloquine, and halofantrine. ii. 4-aminoquinolines: Chloroquine, amodiaquine. iii. Folate synthesis inhibitors: Type 1 - competitive inhibitors of dihydropteroate synthase - sulphones, sulphonamides Type 2 - inhibit dihydrofolate reductase - biguanides like proguanil and chloroproguanil; diaminopyrimidine like pyrimethamine iv. 8-aminoquinolines: Primaquine, WR238, 605 v. Antimicrobials: Tetracycline, doxycycline, clindamycin, azithromycin, fluoroquinolones vi. Peroxides: Artemisinin (Qinghaosu) derivatives and analogues - artemether, arteether, artesunate, artelinic acid vii. Naphthoquinones: Atovaquone viii. Iron chelating agents: Desferrioxamine⁴. Toxic effects of various drugs have been listed below in table-2.

Table-1
Cases of Malaria reported in hospital of Mahamaya Nagar, India

Name of Hospital	Number of cases reported	Toxicity
K. A. V. Memorial Hospital	63	Splenomegaly, renal dysfunction, hypotension, hypertension, muscle cramps
Khetan Charitable Hospital	37	Drug induced abortion, hepatomegaly, dimness of vision

Table-2
Toxicity of various Antimalarials drugs

Drugs	Half life	LD-50	Toxicity
Amodiaquine	5.2 ± 1.7 min	Mouse = 225mg/kg, intraperitoneal	Cardiac arrest, respiratory arrest, broadened QRS Complex, ventricular fibrillation ⁵
		Mouse= 550 mg/kg Oral	
Lumefantrine	4- 5 days		QT Prolongation, Splenomegaly, hepatomegaly, angiodema
Halofantrine	6-10 days		Troubled breathing
Artemether	Artemether, 1.6 +/- 0.7 and 2.2 +/- 1.9 hr	Mouse = 895 mg/kg intravenous	
		Mouse = 296 mg/kg intramuscular	
		Rat = 597mg/kg intramuscular	
Quinacrine	5 -14 days	Mouse = 1000 mg/kg Oral	Seizures, hypotension, cardiac arrhythmias, and cardiovascular collapse
		Rat = 900 mg/kg Oral	
Atovaquone	2.2- 3.2 days	< 825 mg/kg/day	Methamoglobinemia

Cardiotoxicity

As cardiac system is one of the system that forms the tripod of life, so any toxic effect on cardiac system is of paramount importance. Fatal cardiac arrhythmias and prolonged QT intervals are some of the usual seen effects of the toxicity on cardiac system. The first case of drug associated death was reported in 1993, until then halofantrine was the choice of medical practitioners. After this numerous studies have reported and confirmed fatal arrhythmias⁶. Quinidine and halofantrine which are known to induce class III effect of ventricular repolarisation. Being reported to be associated with lethal QT prolongation; cardiovascular collapse⁷. The concern raised out from this almost withdrew halofantrine from market⁸. Almost all the drugs available in market possess side effects which may be minimal to severe in their effect. Mild change in heart rate is known to be induced by amodiaquine, excessive prolongation of QT interval leading to Torsade de Pointes by halofantrine. A research article describes the cellular mechanism associated with therapy which inhibition of ion channel (e.g., human ether-a-go-go related gene channel), which slows down the process of repolarisation and engender environment for arrhythmia⁹. A research study conducted on dogs showed that Artemisinin and its derivatives as artemether, artemotil have also been found to be associated with severe effects. A series of electrocardiograms and calculated QT wave interval checkup will help better administration of artesunate with lesser possibility of side effect¹⁰.

Neurotoxicity

Neurotoxic effects are yet another toxic effect exhibited by the drugs that are used in malaria prophylaxis. The neuropathology exhibited is noteworthy and eventuate in critical parts of brain defiling brain stem nuclei peculiarly those parts which are involved in hearing and balance^{11, 12}. Quinine compounds like chloroquine have been reported to cause retinal dysfunction, seizures and even coma has been reported in some patients¹³. A Research study of arteether multiple dose conducted on dogs for eight days to study the pharmacokinetics presented clinical neurological effects and progressive cardio respiratory leading to death collapse in five out of six animals. Gait disturbances, loss of spinal reflex, lesser pain response and evident loss in brain stem and reflexes shown by eye are some neurological problems associated with administration of Antimalarial drugs¹⁴. Mefloquine is usually found to be generally well tolerated by patients¹⁵.

Embryotoxicity

A Study reported embryo deaths and malformations during organogenesis by administration of artemisinin compounds¹⁶. To study embryofetal development test were conducted on (ICH compliant animals) rats and rabbits. The animals were treated with artesunate and combination of drug therapy. The effect behold were sizeable loss of embryo, apparent abortions and resorptions¹⁷. Another study aimed to assess fertility and development of embryos showed artemisinin compound to be

toxic to the foetus, retarded ossification and induced septal defects in ventricles of heart¹⁸.

Conclusion

It would rather be inappropriate if one talk about toxicity of antimalarial drugs and restricts the space only for Cardiotoxicity, neurotoxicity or Embryotoxicity. Antimalarial drugs affect the whole human body to a great extent. The toxic effects of drugs used in malaria prophylaxis starts from muscle cramps, seizures, retinal changes, neuropsychiatric disorders, and agranulocytosis and extend up to death. Drugs currently used in the treatment of Malaria are more prone to cause toxic effects that may be fatal. There is an urgent need to discover a drug that would be free from severe toxicity to help fight this giant problem worldwide. A study has suggested that protein of parasite particularly proteases play a prime role in metabolic pathways¹⁹. A recently discovered compound from the amino pyridine class, code named MMV390048, had been on headlines few days back and had been known to possess potent activity against multiple points in the lifecycle of malarial parasite's. This novel Antimalarial drug has been tested in vitro and known to possess antiplasmodial activity against chloroquine drug resistant and susceptible strain. Synthesis and structure-activity studies have been identified for number of promising compounds with peculiar antiplasmodial action²⁰. Various numerical algorithms and perturbation methods have been worked out by scientists to find exact solution to non linear problems as malaria²¹. In 21st century science and technology has grown up to such an extent wherein there is no room for approximation²².

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