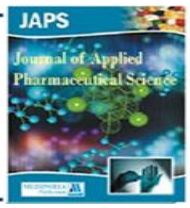
Journal of Applied Pharmaceutical Science 01 (08); 2011: 235-238

Journal of Applied Pharmaceutical Science

Available online at www.japsonline.com



ISSN: 2231-3354
Received on: 11-10-2011
Revised on: 17:10:2011
Accepted on: 24-10-2011

Over prescribing and resistance to chloroquine

Gandhi AM, Patel PP, Desai CK, Desai MK and Dikshit RK

Gandhi AM, Desai CK, Desai MK
Department of Pharmacology, B.J. Medical college, Ahmedabad, India.

Patel PP
Department of Pharmacology, B.J. Medical college, Ahmedabad, India.

Dikshit RK
Department of Pharmacology, B.J. Medical college, Ahmedabad , India.

For Correspondence
Dr Anuradha M Gandhi
Professor
Department of Pharmacology
B J Medical College
Ahmedabad – 380 0 16

ABSTRACT

Malaria is a major health concern in the developing world including India. Overdiagnosis and overprescribing of malaria may lead to increase morbidity, mortality and increases risk of resistance to antimalarial drugs and hence increase the economical burden to health care system. The present study was carried out to determine the actual cases of malaria and extent of chloroquine resistance at Civil Hospital Ahmedabad, a tertiary care teaching hospital in Gujarat, India. After Institutional Ethics Committee approval, adult patients of either gender, presenting with a history of fever at the Out Patient Department (OPD), diagnosed to be suffering from malaria and prescribed chloroquine were included in the study. Peripheral thick blood smear test and OptiMAL-rapid diagnostic test (RDT) were carried out. RDT was performed in these patients on day 0 before the start of chloroquine treatment and after completion of the 3 day chloroquine treatment. They were again subjected to RDT on day 4. The positive cases on RDTon day 4 were considered as resistant to chloroquine. During the study period of 12 months, out of the 250 clinically suspected cases of malaria who were prescribed chloroquine, 80 (31%) cases (35 cases of *P. vivax* and the 45 of *P. falciparum*) were positive for malaria (by the peripheral smear and the Rapid Diagnostic Test (RDT) OptiMAL test). Thirty out of the 35 cases of *P. vivax* malaria, responded to the three- day chloroquine treatment. Out of the 45 cases of *P. falciparum* malaria, 30 responded to chloroquine while 15 patients (35%) continued to be OptiMAL positive on 4th day and required change of treatment. It suggests that an early diagnosis, definitive treatment and avoiding overprescribing could delay drug resistance and reduce the morbidity and mortality due the disease.

Keywords: Malaria, chloroquine, overprescribing, resistance.

INTRODUCTION

The outcome of treatment in malaria depends on the right diagnosis, selection of the right drug and its efficacy, correctness of the advice given to the patient and compliance of the patient (NIMR and NVBDCP, 2011). Chloroquine (CQ) is the first drug of choice for among the available antimalarial drugs [2](National drug policy on malaria, 2008) and widely used as self-medication for presumptive treatment of malaria despite the existence of parasite resistance to the drug (Picot et al, 1997). Resistance to antimalarial drugs is on the rise and has become a major factor in deciding the choice of antimalarial drugs. For instance, as per estimates in the past decade, 50% of the strains of *P.falciparum* are resistant to chloroquine (Garg, 1999) and resistant strains of *P. vivax* are also increasing in different parts of India (Kochar, 2007). A presumptive approach alone may result in overdiagnosis of malaria. Empirical treatment based on this approach may also result in unnecessary and irrational drug use with a consequent increased risk of morbidity, mortality, resistance to antimalarial drugs and increased cost of therapy (Plowe, 2003). It thus becomes imperative to detect the extent of presumptive diagnosis of malaria study was therefore conducted at Civil Hospital, Ahmedabad, a tertiary care teaching hospital in Gujarat, India, with an objective

to determine the actual cases of malaria out of such clinically diagnosed cases and to determine the extent of chloroquine resistance in this population.

METHODS

The study protocol was approved by the Institutional Ethics Committee (IEC) of Civil Hospital, Ahmedabad (CHA). Adult patients of either gender, above the age of 18 years and presenting with a history of fever at the Out Patient Department (OPD) were screened for the study. All those patients who are clinically diagnosed to be suffering from malaria and prescribed chloroquine were included in the study. Patients who had taken prior treatment for malaria and those with a history of vomiting were excluded from the study. Pregnant and lactating women, patients with a history of hypersensitivity to antimalarial drugs and those suffering from major illnesses like hypertension or severe diabetes mellitus were also excluded from the study (OptiMAL –IT kit was supplied by Doctor & Company, Ahmedabad : Morepan Laboratories, New Delhi, Manufractured by DiaMed AG Diagnostics and Medical Products, Switzerland).

Patients were informed about the aims and methods of the study and a written consent was obtained. Detailed history, clinical examination and treatment given were recorded in a case record form (CRF). Peripheral thick blood smear test and OptiMAL-rapid diagnostic test (RDT) were carried out for malaria in all patients that were included in the study. RDT was performed in these patients on day 0 before the start of chloroquine treatment.

The cases that showed positive microscopic examination and +ve RDT for malaria on day 0 were considered as true/actual cases of malaria either *P. vivax* or *P. falciparum*. These patients were advised to return on day 4 after the completion of the 3 day chloroquine treatment. They were again subjected to RDT on day 4. The positive cases on RDT on day 4 were considered as resistant to chloroquine.

RESULTS

During the study period, 250 cases of fever and clinically suspected cases of malaria, who were prescribed chloroquine were studied. Out of these, 80 (31%) patients showed a positive peripheral smear as well as positive RDT (OptiMAL test) for either *P. vivax* or *P. falciparum* malaria. Two false positive and one false negative cases were reported (cases where peripheral smear was positive for malaria parasites and RDT was negative were considered as false negative and vice versa). Therefore it was observed that 170 (68%) cases of fever presumptively diagnosed with malaria, were not actually suffering from this infection yet they were prescribed chloroquine. (Figure 1). Out of the 80 positive malaria cases, 35 cases were suffering from *P. vivax* malaria (44%) and the remaining 45 patients were suffering from *P. falciparum* (56%) (Table 1) Out of 35 cases of *P. vivax* malaria, 30 patients responded to chloroquine treatment while 5 patients (14%) were still positive on RDT after three days chloroquine treatment. They required alternate antimalarial drugs and were referred to the medicine consultant. Thirty out of 45 confirmed

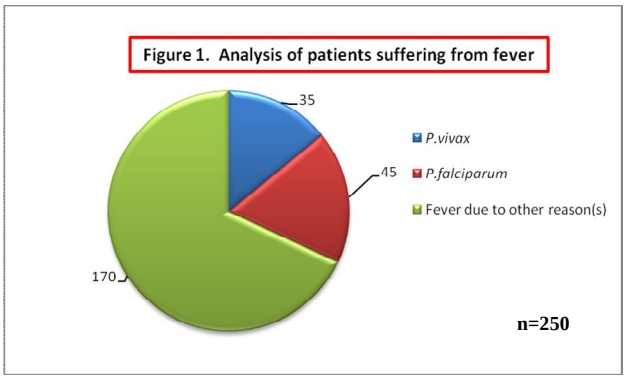


Table 1: Chloroquine sensitivity in patients suffering from malaria.

Type of malaria ►	*P. vivax* malaria n=35	*P. falciparum* malaria n=45
Chloroquine sensitive	30	30
Chloroquine resistant	05	15
Incidence of chloroquine resistance	14.29%	33.33%

DISCUSSION

Outcome of treatment of malaria depends on the efficacy of the drug, right diagnosis, the treatment given and compliance of patient while presumptive use of antimalarial drugs may increase parasite resistance. Confirming the clinical diagnosis with microscopy or Rapid Diagnostic Tests (RDTs) may prevent overuse of antimalarial drugs and decrease the risk of drug-resistance (ICMR, 2002).

In the present study, 250 patients of fever were prescribed chloroquine on the basis of a presumptive clinical diagnosis. However, only 80 cases were positive either for *P. vivax* or *P.falciparum* malaria on microscopy and RDT (OptiMAL) while 170 cases (67.86%) showed a negative peripheral smear and negative RDT test for malaria.

We further observed that out of 80 cases detected to be positive for malaria by peripheral smear and RDT (OptiMAL) tests, 35 (44 %) were of *P.vivax* and 45 (56%) were of *P. falciparum* malaria. Chloroquine was effective in 30 cases (86%) of *P. vivax* & 30 cases (67%) of *P. falciparum* origin. Resistance was therefore observed in 5 patients (14%) and 15 cases of (33%) *P.vivax* and *P.falciparum* of malaria respectively. There is therefore an evidence based of treatment on presumptive diagnosis alone, which may contribute to antimalarial drug resistance.

Treatment based on presumptive clinical diagnosis alone is an accepted approach for management of most cases of malaria in areas with high rates of transmission e.g. in rural and remote areas of the healthcare system where laboratory facilities for definitive diagnosis may not be available. Patients in endemic areas are familiar with the symptoms and they frequently self-diagnose malaria and practice self medication with chloroquine and other antimalarial drugs. These drugs are easily available from pharmacies in India. Treatment based on presumptive clinical diagnosis alone may result in unnecessary and irrational drug use. In addition, overdiagnosis and overprescribing of malaria may lead to increase morbidity, mortality and increases risk of resistance to

antimalarial drugs and an increased economical burden to health care system of the country. Thus, the clinical diagnosis would benefit from laboratory confirmation by microscopy/Rapid Diagnostic Tests(RDTs) (Plowe, 2003) .

Therapeutic efficacy and / or parasitological resistance may be measured by in vivo test. (Plowe, 2003) However, standard in vivo tests are expensive and time-consuming while in vitro methods for measuring drug resistance are not practical and have a limited scope. All available tests either do not give quick results to influence the therapeutic decisions or nor do they give results that are not interpretable in terms of individual patient treatment (ICMR, 2002) . Alternatively, non-microscopic methods, rapid dipstick methods (like OptiMAL) based on the immunochromatographic detection of Plasmodium lactate dehydrogenase (pLDH) have the capacity to detect and distinguish infections caused by *P. falciparum* and *P. vivax* species (Ferro *et al*, 2002) .

OptiMAL is the first RDT, approved on June 13, 2007 by the U.S. Food and Drug Administration (FDA) for use by hospital and commercial laboratories. This RDT utilizes a dipstick coated with monoclonal antibodies against the intracellular metabolic enzyme parasite lactate dehydrogenase (pLDH) and detects pLDH produced by viable parasites only. Its ability to follow its decline in sequential samples from that patients during treatment may be useful in evaluating clinical cases. (Palmer CJ e al, 1998, WHO, 2000) Thus, we have used this RDT as a tool for monitoring of antimalarial treatment. This diagnostic tests may provide rapid confirmatory diagnosis of malaria even at the peripheral levels of the health care system and can be performed by health workers with minimal training. This method can detect vivax and falciparum malaria. As it detects plasmodium lactate dehydrogenase (pLDH) of viable parasites, decline of viable parasites can be reflected in sequential samples from the patients during treatment. Thus, this method can also be used for monitoring of chloroquine therapy. (Palmer *et al*, 1998, WHO, 2000)**.**

Antimalarial drugs are used empirically and prescribing chloroquine to any case of fever is a common practice (Khan, 1993). This causes unnecessary expense to the patient and risks avoidable adverse effects as well as selection of resistant strains. In addition to that, their is a widespread use of chloroquine as selfmedication and inadequate dose or dosage schedule are prescribed at the health centres (Pfeiffer *et al*, 2008, McCombie, 2002). The cost of an RDT in developing countries is more than microscopic peripheral smear examination.However, prompt and accurate diagnosis will not only improve malaria treatment, but possibly reduce morbidity due to other febrile illnesses. The cost effectiveness of RDTs may depend upon many factors e.g. prevalence of malaria, cost of RDT, cost of anti-malarial treatment, and the cost of treatment of other febrile illnesses when malaria has been ruled out. RDTs may become more cost effective as the price of anti-malarials increase (Chansuda *et al*, 2007; WHO, 2006)**.**

As per recommendation by National treatment guidelines on malaria (2010), all fever cases suspected to be malaria should be investigated by microscopy or RDT and presumptive treatment with chloroquine should not be given.

Hence, We conclude that early diagnosis, treatment and reduction in overprescribing based on presumptive symptoms alone may delay the progress of drug resistance and reduce in overall morbidity and mortality due to malaria. Rapid diagnostic tests can be useful in monitoring and management of malaria. This may reduce the unnecessary use of antimalarial drugs and also reduce risk of complications of *P. falciparum* malaria particularly in endemic areas.

ACKNOWLEDGEMENT

We are thankful to Department of Medicine and Department of Microbiology for helping us in diagnosis and enrolling patients. We are also thankful to Government of Gujarat (India) for giving us funds for our study.

REFERENCES

Chansuda Wongsrichanalai, Mazie J. Barcus, Sinuon Muth, Awalludin Sutamihardja, Walther H. Wernsdorfer.A Review of Malaria Diagnostic Tools: Microscopy and Rapid Diagnostic Test (RDT). Available from: http://www.ncbi.nlm.nih.gov/books/NBK1695/ (Accessed on 07/03/2011)

Clinical and public health implications of antimalarial drug resistance, ICMR Workshop in Clinical Pharmacology (2002).

Ferro BE, Gonz·lez IJ, Carvajal FD et al. Performance of OptiMAL in the diagnosis of *Plasmodium vivax* and *Plasmodium falciparum* Infections in a Malaria Referral Center in Colombia. Rio de Janeiro. *Mem. Inst. Oswaldo Cruz*. 2002; 97(5): 731-735.

Garg, MR, Gogtay NJ, Kshirsagar NA. Resurgence of malaria in mumbai is escalating chloroquine resistance a cause. J Assoc Physicians India.1999 ; 47: 377-379

Guidelines for diagnosis and treatment of malaria in India. 2011. National Institute of Malaria Research and National Vector Borne Disease Control Programme. New Delhi. http://www.mrcindia.org/ Guidelines% 20for%20Diagnosis2011.pdf (Accessed on 04/10/2011).

Khan P, Noor I, Khan J. Treatment of *P Falciparum* malaria. J Post Med Inst. 1993; 7(2):23-27 Available at : www.jpmi.org.pk/cms/PDF/5%20Perviaz%20Khan.pdf (Accessed on 07/03/2011)

Kochar DK, Sirohi P, Kochar.SK. Malaria in India. Available from: http://www.apiindia.org/medicine_update_2007/109.pdf (Accessed on 08/03/2011).

McCombie SC (2002) Self-treatment for malaria: the evidence and methodological issues. Health Policy and Planning 17, 333–344.

NATIONAL DRUG POLICY ON MALARIA (2008) Directorate of National Vector Borne Disease Control Programme, Directorate General of Health Services, Ministry of Health and Family Welfare.http://www.whoindia.org/LinkFiles/Malaria_Malaria_drug-policy-08.pdf (Accessed on 31/05/2011).

NATIONAL DRUG POLICY ON MALARIA (2010) Directorate of National Vector Borne Disease Control Programme, Directorate General of Health Services, Ministry of Health and Family Welfare. http://nvbdcp.gov.in/Doc/drug-policy-2010.pdf (Accessed on 17/10/2011).

New perspectives in malaria diagnosis: Report of joint WHO/USAID informal consultation. 25-27 October, 1999 WHO 2000 Document No WHO/CDS/RBM/2000. 14; WHO/MAL/2000. 1091.

Palmer CJ, Lindo JF, Klaskala WI, et al. Evaluation of the OptiMAL test for rapid diagnosis of *Plasmodium vivax* and *Plasmodium falciparum* malaria. J Clin Microbiol 1998; 36: 203–206.

Pfeiffer K, Some F, ller OM, et al. Clinical diagnosis of malaria and the risk of chloroquine self-medication in rural health centres in Burkina Faso. Trop Med Int Health. 2008 : 13 (3); 418–426.

Picot S, Akede NA, Chaulet JF, et al. Chloroquine self-treatment and clinical outcome of cerebral malaria in children. Clin Exp Immunol; 1997 ;108(2):279-283.

Plowe CV. Monitoring antimalarial drug resistance: making the most of the tools at hand. J Exp Biol. 2003; 206:3745-3752.

WHO REPORT Cost-Effectiveness of Malaria Diagnosis in Sub-Saharan Africa: The Role of Rapid Diagnostic Tests in Rural Settings with High *Plasmodium falciparum* transmission Availabl from: http://www.wpro.who.int/NR/rdonlyres/6A5EC04701F1-485E-963C59D23C396E29/0/RDTinruralsettingswithhighPfalciparumtransmissionWHO2006.pdf .(Accessed on 07/03/2011)