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A Cross-sectional, Observational Study to Evaluate Prevalence & Severity of the Adverse Drug Reactions to Artesunate Therapy in a Tertiary Care Hospital in Mumbai

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ABSTRACT

Objectives: Anti-malarial drugs are commonly prescribed for Malaria & suspected cases of Malaria in India. Artesunate is one of the effective anti-malarial agents. The data available on ADRs with Artesunate is inadequate and not well documented in Indian population. Therefore this study was designed to evaluate Prevalence & Severity of ADRs with Artesunate therapy in India. **Materials and Methods:** Over a period of 12 weeks, 187 patients were screened, who were administered Artesunate, and out of that 150 patients were enrolled in this study. Universally accepted & standardized WHO & Naranjo's ADR Causality Assessment Scales were used for causality assessment. Modified Hartwig & Siegel Severity Assessment Scale 1992 was used to assess severity of ADRs found. **Results:** In this study, 150 patients were enrolled, out of that 10 ADRs were documented. Prevalence of ADRs with Artesunate found is 6.7%. ADRs documented were Pruritus/Itching, Gastritis/Epigastric Burning, Rash, Flatulence, Abdominal Pain, and Headache. All ADRs were fallen in 'Possible' category of causality assessment as per WHO scale & 5 in 'Possible' & 5 in 'Doubtful' categories as per Naranjo's scale. Severity was also assessed and 9 ADRs were 'Moderately severe' & 1 was 'Mild' category as per Modified Hartwig & Siegel Severity scale 1992. An unexpected outcome of this study was off-label indications of Artesunate use. **Conclusions:** It is concluded here that the Artesunate is quite safe for use. Prevalence of ADRs with Artesunate is 6.7 %. Most of the ADRs are moderate in intensity & not serious.

INTRODUCTION

Global efforts to control malaria have recently led to reduction in the overall disease burden, with mortality due to malaria estimated to have declined from 985,000 in 2000 to 660,000 deaths in 2010. Malaria continues to be a major public health problem, in spite of enhanced control efforts, mostly in Africa and parts of Asia. According to WHO World Malaria report (2012), there were an estimated 219 million cases of malaria (range 154–289 million) in 2010 globally. For Indian scenario, it is mention that, about 1,310,367 cases were presumed & confirmed & 753 deaths occurred in India due to Malaria in 2011. The incidence rate of malaria in India was about 0.11 % in 2011[1] In Maharashtra, in 2012, 38003 positive malaria cases found & 56 deaths were reported. In 2013, up to month of August, from Maharashtra state 28442 positive malaria cases & 43 deaths due to malaria got reported.[2] Malaria and poverty are connected. In the countries where malaria has an impact on public health, it is also severely hampering economic development.[3]

As a consequence of increasing resistance of the malarial parasite to previously effective monotherapies including chloroquine and sulphadoxine-pyrimethamine, the World Health Organization (WHO) held a technical consultation in 2001 endorsing the potential of artemisinin-based combination therapy (ACT) for drug-resistant malaria.[4] Antimalarial combination therapy is the simultaneous use of two or more blood schizonticidal drugs with independent modes of action and thus unrelated biochemical targets in the parasite.[5]

In India, National Vector Borne Disease Control Program is well established. The objective of a national antimalarial treatment policy in India is to enable the population at risk of malaria infection to have access to safe, good quality, effective, affordable and acceptable antimalarial drugs.[6] By 2009, most malaria-endemic countries including India had introduced ACT in their national drug policy, as first-line treatment for uncomplicated Plasmodium falciparum malaria.

The ACT recommended in the National Programme of India is Artesunate (4 mg/kg body weight) daily for 3 days and Sulfadoxine (25 mg/kg body weight) -Pyrimethamine (1.25 mg/kg body weight) on Day 0.[7] Injectable artesunate is a life-saving therapy in severe

Plasmodium falciparum malaria, providing a significant reduction of mortality.[8][9] It is also one of the cost-effective & affordable antimalarial agents.[10]

Artesunate- General Information

Artesunate is an antimalarial agent. It is isolated from a herb Artemisia annua that has traditionally been used in china for the treatment of malaria. Artesunate and its active metabolite di-hydro artemisinin are potent blood schizonticides, active against the ring stage of the parasite. Artesunate is ideal for the treatment of severe malaria, including cerebral malaria. It is also active against chloroquine and mefloquine resistant strains of P. falciparum. It is unstable in neutral solution and is therefore only available for injections as Artesunic acid.

The injectable formulation must be prepared immediately before use in 5% (w/v) sodium bicarbonate solution to produce the salt sodium Artesunate.

Indications of Artesunate

Treatment of severe falciparum malaria in areas where there is evidence of quinine resistance.

Expected Adverse Drug Reactions of Artesunate

Drug induced fever can occur. Neurotoxicity has been observed in animal studies but not in humans. In view of the uncertainty about the toxic effects, caution should be exercised when more than 3 days treatment is given. Cardiotoxicity has been observed following administration of high doses. Possible drug related adverse effects include dizziness, itching, vomiting, abdominal pain, flatulence, headache, body ache, diarrhea, tinnitus and increased hair loss, macular rash, reduction in neutrophil counts and convulsions. Occasional skin rash and pruritus has been observed with Artesunate.[11]

Adverse Drug Reactions

Adverse drug reactions have been creating headlines since the thalidomide tragedy. After the publication of the US Institute of Medicine report "To err is human: building a safer health system", international attention to patient safety has been growing significantly.[12]

According to World Health Organization (WHO) "An adverse drug reaction is any response to a drug which is noxious and unintended and occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or the modification of physiological function". [13]

Food and Drug Administration (FDA) defines a serious adverse event as one in which the patient outcome is death, or life threatening, hospitalization, disability, congenital anomaly or required intervention to prevent permanent impairment or damage. [14] According to ICH GCP, Adverse drug reaction (ADR) regarding marketed medicinal products: A response to a drug that is noxious and unintended and that occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. [15]

ADRs are a major universal problem and are one of the leading causes of mortality and morbidity in health care facilities globally. The incidence of ADR varies with studies. According to a study carried out at a private tertiary care hospital in South India, the incidence of ADRs was found to be 1.8%, out of which 12% of suspected ADRs were severe and 49% ADRs were moderate in severity. [16] A study by Arulmani et al. (2008) in India carried out in a secondary care hospital reported an overall 9.8% incidence of ADRs, of which 3.4% of ADRs were associated with hospital admissions. [17] Another study carried out in a tertiary care referral center in South India showed that admissions due to ADRs accounted for 0.7% of total admissions and deaths due to ADRs accounted for 1.8% of total ADRs. [18]

Pharmacovigilance deals with the vital mechanism for evaluating and monitoring the safety of medicines in clinical use. It is a division of patient care. It aims at getting the best outcome of treatment with medicines. No one wants to harm patients, but unfortunately, because of many different factors, any medicine will sometimes do this.

The Pharmacovigilance Program of India (PvPI) was implemented a few years back. As the newer drugs are striking the Indian market, the need for ADR monitoring is growing more than ever before. Therefore, monitoring of the adverse effects particularly those of serious nature is obligatory.

The primary objective of this study was to evaluate prevalence & severity of ADRs in patients treated with Artesunate in medicine wards of KEM Hospital, Mumbai.

Review of literature

Mubi M et al (2013) in their research survey about Malaria in Tanzania concluded that Anti-malarial prescription to patients with negative test results and those not tested is still practiced in Tanzania despite universal malaria testing policy of fever patients. The use of malaria diagnostics was also associated with higher prescription of antibiotics among patients with negative results. Strategies to address health system factors and health worker perceptions associated with these practices are needed.[19] Duparc S et al (2013) stated that Artesunate-Pyronaridine is a useful new ACT and should be a valuable addition to anti-malarial.[20]

Kreeftmeijer-Vegter AR et al (2013) Artesunate is the only available treatment in few countries of Europe for severe malaria via named patient programme.[21] Belhekar MN et al (2012) concluded in their research study that ACT was commonly used in the treatment of malaria. Results of their analysis suggest that all the ADRs were of moderate intensity and no serious ADR was observed.[11] Lubell Y (2011) with their analysis shows that artesunate is effective, cost-effective and affordable, which stands as evidence to support its use in children with severe malaria in Africa.[10]

Study Rationale

Though intravenous Artesunate injection is considered well tolerated, there is need to monitor ADRs associated with its use. It is always preferable to review already known or proven data time by time & in different settings. Inappropriate treatment, incorrect dosing, drug-drug interaction, administration in populations suffering from or being treated against concomitant diseases like HIV/AIDS, tuberculosis, malnutrition and anemia can all impact negatively on drug safety and efficacy.[22] [23]

Data for these scenarios is inadequate for Artesunate therapy.

So we proposed this study to evaluate prevalence & severity of the ADRs in patients treated with Artesunate in medicine wards of KEM Hospital, Mumbai.

Aim

Evaluation of prevalence & severity of the Adverse Drug Reactions to Artesunate therapy

Objectives

Primary objectives:

Evaluation of prevalence & severity of the Adverse Drug Reactions to Artesunate therapy

Study Design

It was a Cross-sectional, Observational study.

Inclusion Criteria

1) Patient treated with Artesunate in medicine wards of KEM Hospital, Mumbai.
2) Age group between 18 to 65 years, both males & females.
3) Willingness to give written informed consent.

Study site

Medicine wards of KEM Hospital, Mumbai

Study Duration

3 months (12 weeks)

Methodology

Study was conducted in compliance with the protocol, ICH-GCP, ICMR, Schedule 'Y' guidelines & Indian regulatory requirements.

After approval from IEC, study was initiated. Patients from medicine ward who were treated with Artesunate injection intravenously were identified & screening log was filled. Then they were asked for Written Informed Consent. Patient information sheet was given to them. Then after getting written informed consent, enrolled participant was interviewed by co-investigator & demographic data, diagnosis, past medical history, history of present illness, physical & systemic examinations, relevant laboratory tests, concomitant medications, reason for Artesunate use, dosing information of Artesunate was recorded on CRF. The ADRs experienced by patients from study population & documented by treating

physician, were documented in CRF which was taken as it is in the format of Suspected ADR reporting form of PvPI.

Total 187 patients were screened according to inclusion criteria, out of which 150 were enrolled in this study. Data collected was then classified according to gender differentiation, prevalence of ADRs, Causality & Severity of ADRs, and indications for use of Artesunate.

Universally accepted standard scales were used to assess causality & severity of ADRs. For causality assessment 2 scales were used i.e. WHO ADR Causality Assessment scale [24] and Naranjo's Causality Assessment scale [25]. Modified Hartwig & Siegel ADR Severity Assessment Scale 1992 [26] were used to classify ADRs according to their severity.

The results obtained were analyzed using descriptive statistical method.

RESULTS

Table No. 1: No. of Patients Screened & Enrolled

Criteria	No. of patients
Enrolled	150
Not enrolled (Screen failure)	37
Total Screened	187

Total 187 patients were screened according to inclusion criteria, out of which 150 patients were enrolled in study.

Figure No.1: No. of Patients Screened & Enrolled

Table No. 2: Reasons for Screen Failure

Reason	No. of Patients
Relatives not available at the time of consenting	14
Patient not willing for consent	12
Age above 65/ below 18 years	11

Table No.3: Gender wise Distribution of Study Population

Gender	No. of enrolled participants
Male	84
Female	66
Total	150

Total 150 patients were enrolled in this study, out of which 84 (56%) were Males and 66 (44%) were Females.

Average age of study population was 37.7 years.

Table No. 4: Diagnosis wise Distribution of Study Population Treated with Artesunate

Indications / Diagnosis	No. of participants
Acute Febrile Illnesses	107
P. Vivex Malaria	15
Meningitis	8
Anemia	3
Sepsis	3
Dengue fever	2
Other	12

Out of 150 study population treated with Artesunate, 107 (71%) were diagnosed with different types of acute febrile illnesses, 15 (10%) were positive for P.Vivex Malaria, 8 (5%) were diagnosed for Meningitis, 3 (2%) of Anemia, 3 (2%) diagnosed with Sepsis, 2 (1%) were diagnosed with Dengue Fever & 12 (8%) were diagnosed with other conditions.

The term 'Acute Febrile Illnesses' includes Acute febrile illness, Fever, Fever with chills, PUO, Acute febrile illness with Acute kidney injury, Acute febrile illness with Acute Gastritis/ Gastroenteritis, Acute febrile illness with Thrombocytopenia/ Bicytopenia.

Table No. 5: No. of Treatment Days Completed with Artesunate wise Distribution of Study Population

Treatment days completed	No. of enrolled participants	ADRs documented
<3	51	4
≥3	99	6

Study population was distributed according to treatment days with Artesunate. 2 groups were formed, <3 & ≥3 treatment days completed.[11] Out of 150 patients, 51(34%) patients received Artesunate for < 3 days & 4 ADRs were documented from this group. 99 (66%) patients received Artesunate for 3≥ days & 6 ADRs were documented in this group.

Table No. 6: Prevalence of ADRs with Artesunate

Criteria	Males	Females	Total
ADR documented	5	5	10
No ADR documented	79	61	140
Total	84	66	150

Total 10 (6.7% out of 150 patients) ADRs were documented with Artesunate within our study population of 150 patients. Out of that 5, (50%) ADRs were in Male patients & 5 (50%) ADRs were in Female patients.

$$\text{Prevalence} = \frac{\textit{No. of occurences of the health indicator}}{\textit{Size of population in which the health indicator occurs}} \times 100$$

Prevalence of ADRs in Artesunate Therapy = 6.7 %

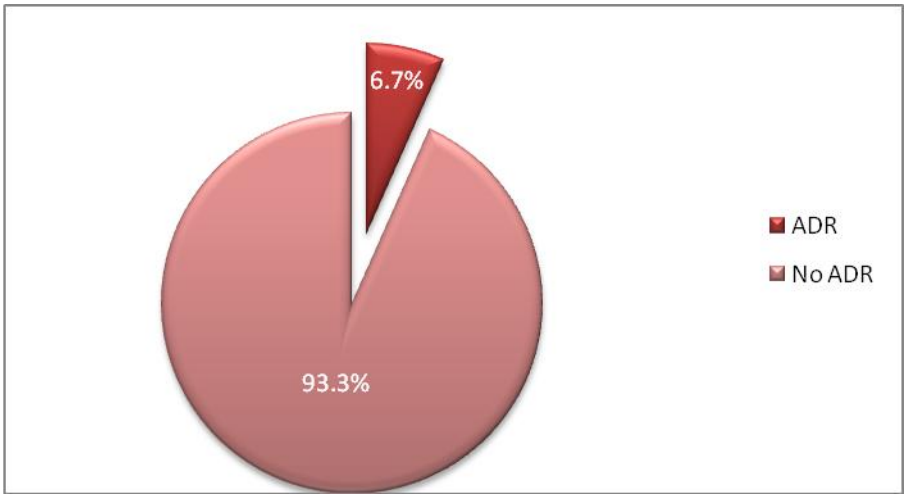

Figure No.2: Prevalence of ADRs with Artesunate

Table No. 7: Distribution of ADRs with Artesunate

ADR Term	Males	Females	Total
Rash	1	-	1
Pruritus / Itching	1	2	3
Flatulence	-	1	1
Abdominal pain	1	-	1
Gastritis / Epigastric burning	1	2	3
Headache	1	-	1
Total	5	5	10

Table No.8: System Organ Classification of ADRs

System/Organ	ADR	No. of ADRs
Gastrointestinal System	Flatulence	1
	Abdominal pain	1
	Gastritis / Epigastric burning	3
Skin / Immune system	Rash	1
	Pruritus / Itching	3
Neuropsychiatric system	Headache	1
Total		10

Table No.9: Causality Assessment According to WHO Scale

Causality	No. of ADRs
Certain	0
Probable	0
Possible	10
Unlikely	0
Unclassified	0
Unclassifiable	0

Out of total 10 ADRs documented with Artesunate, all were in the 'Possible' causality category according to WHO causality assessment scale.

Table No.10: Causality Assessment According to Naranjo's Scale

Causality Score	Causality	No. of ADRs
0	Doubtful	5
1-4	Possible	5
5-8	Probable	0
>9	Definite	0

Out of total 10 ADRs documented with Artesunate, 5 were in 'Possible' category with score 1-4. Remaining 5 were of 'Doubtful' category with score 0.

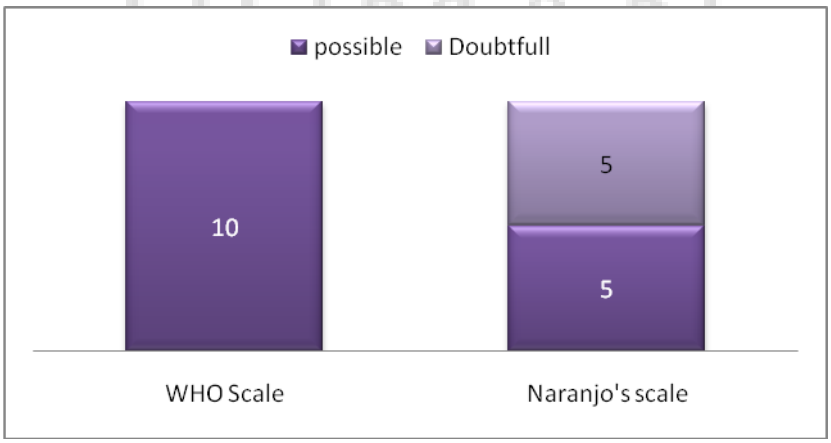

Figure No. 3: Causality Assessment of ADRs

Table No.11: Severity Assessment According to Modified Hartwig & Siegel ADR Severity Assessment Scale 1992

Severity	No. of ADRs
Mild	1
Moderate	9 (upto level 3)
Severe	0

Out of total 10 ADRs documented within the study population, 1(11%) was mild while 9 (89%) were moderate but up to level 3.

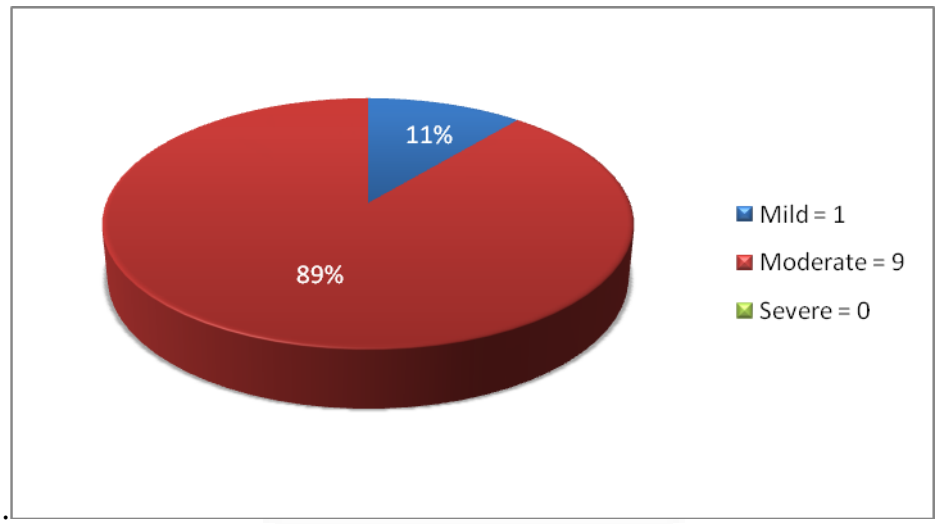

Figure No. 4: Severity Assessment According to Modified Hartwig & Siegel ADR Severity Assessment Scale 1992

DISCUSSION

Total 187 patients were screened in this study according to inclusion criteria & 150 were enrolled. The difference in occurrence of ADRs between males & females was insignificant. Hence gender does not seem be associated with occurrence or documentation of ADRs with Artesunate. Out of 150, 84 (56%) were Males & 66 (44%) were Females. The mean age of study population was 37.7 years. It was stated in literatures that 'In view of the uncertainty about the toxic effects, caution should be exercised when more than 3 days treatment is given.' [11] In this study, not significant difference was observed based upon treatment days. 6 ADRs were documented in patients treated for ≥ 3 days & 4 ADRs were documented in patients treated for <3 days. Generally, maximum 5 days treatment schedule is followed by physicians for Artesunate. Here also it was observed that treating physicians were following

similar strategy. Patients received Artesunate from 1 day till up to 5 days were got enrolled in this study.

The objective of this study was evaluation of Prevalence of ADRs with Artesunate therapy. It was found that Prevalence of ADRs with Artesunate = 6.7 %. ADRs documented in this study were expected ones. Possible Artesunate related adverse effects include dizziness, itching, Pruritus, vomiting, abdominal pain, flatulence, headache, body ache, diarrhea, tinnitus and increased hair loss, macular rash, reduction in neutrophil counts and convulsions. [11] Total 10 (6.7% out of 150 patients) ADRs were documented with Artesunate in this study. ADRs documented :- Pruritus/Itching = 3 , Gastritis/Epigastric Burning= 3 , Rash= 1 , Flatulence= 1 , Abdominal Pain= 1 , Headache= 1.

Though many ADRs are listed in literatures available, in this study, only above stated ADRs were found. We observed that all the patients were co-administered Pantoprazole & other antiemetics. This is in our opinion, has markedly reduced occurrence of severe ADRs related to gastrointestinal system. The above mentioned ADRs did not require discontinuation of Artesunate or reduction in its dose.

Causality assessment of ADRs was done using two universally accepted standard scales i.e. WHO ADR Causality Assessment scale [24] & Naranjo's ADR Causality Assessment Scale [25]. Both scales put most of the ADRs in 'Possible' category. WHO scale put all 10 ADRs in 'Possible', while Naranjo's scale put 5 in 'Possible' & 5 in 'Doubtful' categories. Here most of the ADRs followed a reasonable time sequence after drug administered and according to literature they could be possibly attributed to Artesunate. Most of the patients enrolled were treated with concomitant medications or had more than 1 concurrent illness or pathological condition or had both of these conditions simultaneously. Modified Hartwig & Siegel ADR Severity Assessment scale 1992 [26] was used to assess severity of ADRS. Most of ADRs were 'Moderately severe' but not serious. Out of 10, 9 ADRs were 'Moderate' & 1 was 'mild' in severity. All these ADRs were 'Not Serious' as per ICH-GCP definition of Serious ADRs.

These finding is in accordance with Conclusion of research study of Belhekar MN et al (2012). Results of their analysis suggest that all the ADRs with ACT including Artesunate were of moderate intensity and no serious ADR was observed. [11]

The unexpected outcome of this study was the pattern of indications for use of Artesunate. In this study, it was observed that varieties of acute febrile illnesses were treated with Artesunate. The term 'Acute Febrile Illnesses' includes Acute febrile illness, Fever, Fever with chills, PUO, Acute febrile illness with Acute kidney injury, Acute febrile illness with Acute Gastritis/ Gastroenteritis, Acute febrile illness with Thrombocytopenia/ Bicytopenia. Other indications were including P.Vivex Malaria, Meningitis, Anemia, Sepsis, Dengue Fever, Acute kidney Injury, Spleenomegaly, Altered sensorium with Hydrocephalus, Aspiration Pneumonia, Pneumonitis, CKD, CLD, GTCS, LRTI, Hepatitis with Megaloblastic anemia with LRTI, Cerebellar lesion.

CONCLUSION

It is concluded at the end of this study that Prevalence rate of ADRs with Artesunate therapy is 6.7% & ADRs are less severe & tolerable along with a suitable antacid & antiemetic cover.

RECOMMENDATIONS

This was an attempt to generate more systematic knowledge about ADRs related to Artesunate. Because of lack of resources & time, it was done on small scale. Further study with more sample size and longer duration is recommended. In future, researchers can use conclusions from this study as base for their own studies.

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