Cohort Event Monitoring Of Artemisinin Derivatives In Patients Treated For Uncomplicated Malaria In Tertiary Care Teaching Hospital.

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Aims- To study the pattern of adverse events in cohort of receiving artemisinin derivatives for patient treated for uncomplicated malaria in tertiary care teaching hospital.

Materials and Methods- Cohort event monitoring is designed to capture all AEs that occur in a defined group of patients who are exposed to a specific, newly marketed medicine during the time of routine clinical practice. This study was planned to determine the safety profile of artemisinin derivatives. Over the period of 1-year total 60 adult patients who were administered artemisinins were enrolled. Pre-treatment and post treatment questionnaire forms were used to record AEs at starting of treatment and on follow-up visits on 3rd and 7th day.

Results- Out of total number of patients 59 patients were thoroughly followed up. Total 80 AEs were recorded, and 3 patients did not show any kind of event. Gastrointestinal tract and musculoskeletal systems were most commonly involved. Most commonly observed AEs were weakness, nausea, dizziness, loss of appetite and restlessness/irritability. AEs were highly observed during 3rd day follow-up.

Statistical Analysis- Thus, after analysis it suggests that almost all AEs were mild in severity.

Conclusion- Thus, this study indicates that artemisinin was commonly used in the treatment of uncomplicated malaria and it offers representative idea of the profile of adverse events occurring due to artemisinin derivatives likely to be encountered in patients in an Indian public hospital.
INTRODUCTION:
Pharmacovigilance (PV) is the science of collecting, monitoring, researching, assessing and evaluating information from healthcare practitioners and patients on the adverse effects of medications, biological products, herbas, vaccines, medical device, traditional and complementary medicines with a view to identifying new information about hazards associated with products and preventing harm to patients.[1] There are different approaches to PV like spontaneous, passive and active. In active approach is done by detecting the adverse events(AEs) by monitoring patients records, direct questioning of the patients and through laboratory testing at predefined intervals at the beginning, during and at times after treatment.[2]

As a part of active PV cohort event monitoring (CEM) gives a chance to increase awareness of pharmacovigilance among healthcare workers and encourage an idea that pharmacovigilance falls within the scope of clinical practice. The method is designed to capture all adverse events that occur in a defined group of patients who are exposed to a specific, newly marketed medicine during the time of routine clinical practice.[3] CEM is one of the effective methods is, which is a time-limited, targeted programme and a prospective, observational, non-interventional study of adverse events associated with one or more monitored medicines. It has advantages like early detection of signals of unsuspected adverse drug reactions (ADRs) is possible, denominator information allows incidence rates of ADRs to be calculated, risks and risk factors could be assessed; comparisons between drug, pregnancy outcomes and deaths are obtained.[4]

Malaria is the most common disease in Africa and some countries in Asia with the highest number of cases. The mortality rate is 0.3–2.2% worldwide, and in cases of severe forms of malaria in regions with tropical climate, it is 11–30%.9 while in the developed world malaria occurs as imported from endemic regions.[5] As a result of increasing resistance of the malarial parasite to previously effective monotherapies including chloroquine (CQ) and sulphadoxine-pyrimethamine (SP), at present artemisinin derivatives are the conventional treatment for uncomplicated malaria.[6] Use of AL(Artemether and Lumefantrine) and artesunate + sulfadoxine-pyrimethamine (AS+SP) is part of India’s first-line treatment policy and all studies for AL in India between 2011 and 2017 found treatment failure rates to be < 10%. So, it is foremost to put this study featured for safety profile of this drug in group of patients(cohort).[7] Therefore, in the present study the adverse events occurring in the patients of uncomplicated malaria treated with artemisinin derivatives. Here CEM gives all AEs that occur in cohort receiving artemisinin derivatives by monitoring them throughout the whole treatment period and after the treatment. Only few studies like this have been done regarding safety profile of artemisinin and most of them were conducted as a national programme in African countries.[2]

MATERIALS AND METHODS
Settings- The study was conducted over a period of 1 year in a tertiary care hospital in India. Ethics Committee approval was obtained before commencing the study.

Study Population- 60 patients (40 males and 20 females) hospitalized in medical ward receiving artemisinin derivatives for treatment of uncomplicated malaria were enrolled in the study. Patients were enrolled in the study after obtaining the written informed consent.

Study design: This study was prospective, observational and longitudinal which was aimed to study the pattern of adverse events in cohort of receiving artemisinin derivatives for treatment of uncomplicated malaria in tertiary care teaching hospital.

Inclusion Criteria:
1. Patients of uncomplicated malaria on artemisinin therapy in medicine department.
2. Patients of Age ≥ 18 years.
3. Patient willing to participate.

Exclusion Criteria:
1. Complicated malaria patients
**Study procedure:**
Patients of any gender and age ≥ 18 years diagnosed with uncomplicated Malaria and receiving artemisinin derivatives as an anti-malarial therapy were recruited for the study. Diagnosis of uncomplicated malaria was made either microbiologically by identifying in thin or thick blood smear film and by rapid diagnostic test or clinically or both (according to the standard treatment guidelines) by the treating physician at medicine department and these patients were taking artemisinin derivatives as a treatment from the hospital.

The demographic details of the patient, relevant history and treatment details were duly recorded. AEs were confirmed after consultation with the treating physician or after communication with the patient and were recorded in validated AE reporting forms which were pre-treatment and post-treatment questionnaire forms. Relevant investigation details were also noted. Patients were communicated for any newly developed AEs or worsening events in physical follow up visits on 3rd and 7th day after starting artemisinin treatment or by telephonic communication. In our study all the patients have received Artesunate in injectable form for the treatment of uncomplicated malaria along with tablet primaquine for complete cure. So here all patients were given injectable artesunate at dose of 4mg/kg for 3 days if parasite persists in blood than it was given for 5 days.

Data analysis Descriptive statistics was applied by using Microsoft Excel. Patients’ data were analysed to study with following parameters:
- Demographic data
- Disease profile of the patients receiving artemisinin derivatives
- Analysis of drugs used
- Clinical manifestations of the reported AEs.

**RESULTS**
- **Demographic data**
Total 60 patients of uncomplicated malaria were enrolled in this study. In which 40 were male and 20 were female patients.
Out of total number of patients 59 patients (1 was loss to follow-up) were thoroughly followed up on 3rd day and on 7th day after starting the artemisinin treatment. According to collected data, uncomplicated malaria is more affecting the age group between ≥18-40 years. There are total 37 patients of this age group out of 60.

- **Distribution according to types of malaria**
According to this study n=47 patients were having rapid diagnostic test positive for Plasmodium Vivax. While n=13 patients were having Plasmodium Falciparum.

![Figure 1 Distribution according to malaria types](image-url)
Adverse events (AEs) Profile of artesunate (Table.1)

In this study total 60 patients were enrolled and were given artesunate for the treatment of uncomplicated malaria. There was 1 loss to follow-up, so total 59 patients were monitored for any adverse events after starting treatments artesunate. Patients were observed on 1st day of treatment and then 3rd and 7th day of treatment.

Total 80 events were recorded in 59 patients during monitoring and regular follow-ups. Here 3 (5.1%) patients did not show up any type of adverse events.

<table>
<thead>
<tr>
<th>System organ classification</th>
<th>Events</th>
<th>Percentage %</th>
<th>Number Total= 80</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIT</td>
<td>Nausea</td>
<td>10 %</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Loss of appetite</td>
<td>7.5 %</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Tastelessness</td>
<td>6.25 %</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>3.75 %</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea</td>
<td>3.75 %</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>2.5 %</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Bitter taste</td>
<td>1.25 %</td>
<td>1</td>
</tr>
<tr>
<td>MSS</td>
<td>Weakness</td>
<td>20 %</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Body ache</td>
<td>1.25 %</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Joint pain (knee)</td>
<td>1.25 %</td>
<td>1</td>
</tr>
<tr>
<td>CNS/Psychiatry</td>
<td>Restlessness/ irritability</td>
<td>8.75 %</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>3.75 %</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Insomnia</td>
<td>1.25 %</td>
<td>1</td>
</tr>
<tr>
<td>ANS</td>
<td>Dizziness</td>
<td>8.75 %</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Sweating</td>
<td>3.75 %</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Drowsiness</td>
<td>2.5 %</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Syncope</td>
<td>1.25 %</td>
<td>1</td>
</tr>
<tr>
<td>General</td>
<td>Chills and rigor</td>
<td>5 %</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Fever</td>
<td>1.25 %</td>
<td>1</td>
</tr>
<tr>
<td>Skin</td>
<td>Itching</td>
<td>2.5 %</td>
<td>2</td>
</tr>
<tr>
<td>ENT</td>
<td>Tinnitus</td>
<td>1.25 %</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Dry cough</td>
<td>2.5 %</td>
<td>2</td>
</tr>
</tbody>
</table>

(GIT- Gastro-intestinal tract, MSS- Musculoskeletal system, CNS- Central Nervous system, ANS- Autonomic nervous system, ENT- Ear, Nose, Throat)
After collecting data most observed adverse event was weakness. It was 20% of the total AEs and observed in 16 patients. Second most common observed AE was nausea (10%) in 8 patients. Nausea was the commonly occurred event related to gastro-intestinal tract. Other commonly seen adverse events were dizziness, restlessness/ irritability, loss of appetite. Although, weakness is most commonly observed but after distributing all AEs according to system-organ wise then most commonly recorded adverse events were related to gastro-intestinal tract in total 35% of total AEs. 18 patients had AEs related to musculoskeletal system which were around 22.5% of the total adverse events.

**Age-wise distribution of occurrence of AEs**

Most commonly observed event in age group of ≥18-40 years was weakness. This was around 22.25% of the total events. In this age group, GIT was the most commonly involved system in relation to the adverse events. Nausea and loss of appetite were the frequently seen AEs related to GIT system.

In this age group weakness and dizziness were recorded most commonly around 17.85 % and 14.28 %. Also, most commonly involved system was GIT.

**Gender-wise distribution of occurrence of AEs**

There were total 20 females in all monitored patients. After 2nd follow up total 30 AEs were recorded in this group. It contributes 37.5 % of all the events. In female, there were 6 events (20 % of the overall AEs) were recorded of weakness. But loss of appetite was the common event related to GIT. Loss of appetite contributes 13.33 % of all events.

Total 50 events were seen in male group. It contributes 62.5% of all AEs. In this group 39 patient were enrolled and 2 patients did not show any events. Most commonly observed event in male was weakness. It was 20% of all AEs, which is highly observed event in almost all the groups. Dizziness (12%) was more recorded in males compare to female group. While chills and rigor was less seen compare to female group (only 2%). After dividing all AEs to system-organ wise, it is noticed that GIT related events were commonly observed than other system.

All adverse events were observed in duration of the beginning of the treatment with artesunate (1st day) to 1st follow up (3rd day). But in 2nd follow up (7th day), no any adverse event was observed.
Table 2 Adverse events recorded during 1st and 2nd follow-up.

<table>
<thead>
<tr>
<th>Duration</th>
<th>AEs observed (Number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st day to 3rd day (1st follow-up)</td>
<td>80 events</td>
</tr>
<tr>
<td>4th day to 7th day (2nd follow-up)</td>
<td>0 event</td>
</tr>
</tbody>
</table>

- **Severity of adverse events.** (Figure 2)
  Severity of the events were confirmed by attending physician. 1 (1.25%) out of 80 events was severe and it was high grade fever. Hence, artesunate have no or very less relation with severe events because in this study remaining 79 events were mild.

- **Recovery status on 7th day (2nd follow up) of the events.**
  On 2nd follow up, no any patients had any kind of AE. So, all recorded events were within day 1 to 3rd day (1st Follow up). All 80 adverse events were recovered from beginning of the treatment to 7 days. So, recovery rate was 100%.

**DISCUSSION**

Early diagnosis and quick treatment with effective antimalarial drugs are the two important components of malaria control and elimination. After the discovery of artemisinin (ART) by Professor Tu Youyou, these medicines have continuously gained significance as a substitute drug, for their high efficacy level against plasmodium as there has been increased prevalence of resistance to previous antimalarial drugs (chloroquine-CQ, sulfadoxine-pyrimethamine-SP) reported from various areas. The malaria therapy nowadays includes ACT as 1st- and 2nd-line treatment in most endemic nations which includes artemisinin combination (or one of its derivatives) with other drug(s) (or two other antimalarials) referred to as partner drugs. The drug combinations in the ACT not only have different mechanism leading to their enhanced efficacy but also, the chances of developing of drug resistance to each component drugs are lower.[8]

Artemisinin and its derivatives are extraordinarily well tolerated. Large-scale safety monitoring or pharmacovigilance is often talked about in the context of antimalarial drugs, but it is hard, and it is not
The pattern of adverse events has been looked reported by patients who were treated with artemisinin derivatives more precisely treated with artesunate for a presumptive diagnosis of malaria. Recorded events and their rates are listed in result. This 12 months prospective observational study was conducted in patients taking artemisinin derivatives alone or with other anti-malaria drug being registered at medicine department, tertiary care teaching hospital from February 2020 to February 2021 for AEs. CEM was chosen for monitoring safety profile. Most patients begin to experience adverse events by day 1 after medication, and this worsens and peaks by day 2 and day 3. Thereafter, the symptoms tend to subside or completely resolve. Close monitoring of patients within this time frame is thus imperative to prevent the occurrence of severe AEs or ADRs, improve adherence as well as improve documentation of events. Total 60 patients were observed from which 56 patients developed AEs whereas remaining 4 either didn’t develop any AEs or were lost to follow up. So here total 56 (94.9%) patients out of 59 patients had experienced. This incidence rate is quite similar to other studies. Analysis of AEs in patients receiving artemisinin derivatives revealed that here 100% of the patients have received artesunate as a treatment for uncomplicated malaria and primaquine for radical cure. While Peter Usman Bassi et al., patients had received artesunate/amodiaquine (AA) or artemether/ lumefantrine (AL) Mahesh N. Belhekar et al., patients had received artesunate with either doxycycline, mefloquine, sulfadoxine-Pyrimethamine. In present study adverse events were more in females. Reasons for these sex differences in adverse reactions might be due to differences between men & women in body mass index, fat composition, hormonal changes, and the effect of these changes on drug metabolism. Total 30 AEs were recorded in 19 female patients in this study and 1 female did not have any kind of AE during the treatment with artesunate. While 50 AEs were recorded from 37 males (total- 39 males) and 2 patients did not have any events. So here many patients had complained more than 1 AE, which is accordance to other studies. In Belhekar M.N. et al., The difference in the occurrence of adverse drug events between male and female patients was statistically insignificant, hence gender does not seem to be associated with the reporting or occurrence of ADR. But in our study female had more experienced AEs compare to males. Sex-related differences in the use of medicines also contribute to the ADR risk profile for women, given that they use oral contraceptives, iron and other supplements during pregnancy, hormones, and other products for menopausal women. According to Ndagije HB et al., Women had an 80% higher risk of developing ADRs than men, similar to other studies that reported a greater risk of between 50 and 70% for females. Also, in our study Females had developed more AEs compare to males. This finding means that there should be more monitoring of ADRs for women and more sensitisation about these issues should be done. Ndagije HB et al., here it was found that patients in urban areas were more likely to report ADRs to antimalarial treatment than those in the rural areas. Vida Ami Kukula et al., patients were enrolled from urban and rural both the areas. Such comparison cannot be made in our study. According to this study 78.33% (n=47) patients were having rapid diagnostic test positive for Plasmodium Vivax. While 21.67% (n=13) patients were having Plasmodium Falciparum. P. vivax infection is more common in other studies too. The most common system involved in relation to recorded AEs with treatment of artesunate was GIT (35%) comprising of nausea, loss of appetite, tastelessness, vomiting, diarrhoea, abdominal pain. Nausea (10%) was recorded highest compared to other GIT related events. This shows small relevance with studies of Peter Usman Bassi et al. and Belhekar M.N. et al. Here some
study shows high incidence rate of ADRs related to GIT.\[6\] While Vida Ami Kukula et al. had recorded more neurological adverse events which is contrast to our study.\[9,11\] The muscular-skeletal system, autonomic and central nervous system also contributes to the major portion in burden of recorded AEs. Weakness (20%) was the major individual observed while doing CEM in patients receiving artesunate. This events shows parallel relation with other studies in which CEM was used to monitor safety of artemisinin derivatives.\[12,13,14\] It was observed that restlessness or irritability and dizziness were also common in the patients. Though they were 8.75 % of total events. Samuel Chatio et al. have conducted this type of study and results suggested that weakness and dizziness were more commonly observed than other events in the patients. While in present study GIT related events were more common.\[15\]

Here in Oluwaseun Egunsola et al., headache was the highly reported events related to CNS.\[16\] Even study with artemether shows compare to more incidence.\[17,18\] But in our study headache was less recorded compare to dizziness. Fever (1.25%) as an adverse event was very less in number. Chills and rigor was noticed after starting treatment. Most of the study shows the parallel result with these two events.\[9,11\]

Total 56 patients has reported AEs during study time. Most of them around 37 patients (61.67%) were falling into age group of ≥18-40 years. So, this group had higher incidence rate of AEs. While Peter Usman Bassi et al., most of the patients were enrolled in age group < 25 years of age.\[9\] So, most of all the AEs were recorded in this group. Total 49 AEs were recorded out of 37 patients.

Now comparing this event occurrence by gender of the sample, it was found that there were more AEs observed compare to male group. Heather P. Whitley et al. and Soldin OP et al. have explained the reason behind this in the study.\[19,20\] According to present study, GIT related AEs were most common, and weakness (20%) was remained highest observed event like other groups. In our study loss of appetite (13.33%) was more observed compare to nausea. This event was observed in other studied too.\[21\] Joint pain in knee was recorded in one patient of this group. Which is not frequently seen AE in other studies.\[9,11\] There was not any pregnant patient enrolled in present study. So, comparison and event monitoring cannot be done.

In male group total 39 patients were enrolled and out of which 37 patients had experienced 50 events out of the total events. Which comprises 62.5 % of all AEs. Weakness is remained most common AE and GIT related AEs were frequently seen in this group. Dizziness (12 %) was more observed compare to female group.

Severity assessment shows that most of the all AEs were mild in nature and don’t only one event was recorded as a severe. Mild events were 98.75 % and remaining were severe in nature. But most of all the events were observed in day 1 like other studies.\[9\] They were resolved with or without the treatment in next 2-3 days.

In order to optimize adherence and hence efficacy, clinicians must focus on preventing adverse effects whenever possible, and distinguish those that are self-limited from those that are potentially serious. Considering the findings in this study there is pivotal role of CEM of artemisinin derivatives.

**CONCLUSION** -

After receiving all the data, statistical analysis was done. All the events were recorded in 3rd day follow-up, but not on 7th day follow-up. Majority of the patients were fallen into age group of ≥18-40 years. So, majority of AEs were come from this group. Overall, GIT related events were most common in all the groups contributing 35 % of the total events.

This suggest that artesunate has good level of safety profile among the enrolled patients. This study gives overall idea of an adverse events of artesunate which can be useful for clinicians and policy makers to provide standard treatment guidelines of it. Thus, the recognition of these
adverse events and their management can ensure optimal care of the patient.

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