Introduction to pharmacovigilance and study of Adverse drug reaction of antimalarial drug

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Abstract:

Pharmacovigilance plays a crucial role in monitoring adverse drug reactions (ADRs) associated with antimalarial drugs, particularly given the ongoing public health challenges posed by malaria in tropical and subtropical areas. Although antimalarial medications are essential for both the treatment and prevention of malaria, their use can lead to various ADRs that affect treatment efficacy and patient safety. This study reviews the ADRs linked to commonly utilized antimalarial drugs, including chloroquine, quinine, primaquine, mefloquine, sulfadoxine-pyrimethamine, and artemisinin-based combination therapies (ACTs).Data were sourced from published literature, World Health Organization (WHO) reports, and pharmacovigilance databases. The analysis reveals that chloroquine is commonly associated with gastrointestinal disturbances and retinal toxicity, while quinine can notably cause cinchonism and hypoglycemia. Primaquine poses a risk of hemolytic anemia in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Generally, ACTs exhibit favorable safety profiles, although mild neurological and gastrointestinal effects have been noted. Additionally, some medications, like sulfadoxine-pyrimethamine, can lead to severe cutaneous reactions.Furthermore, the study highlights the urgent need for robust pharmacovigilance systems and emphasizes the importance of early detection and regular reporting of ADRs to ensure the safe administration of antimalarial drugs. Strengthening ADR monitoring mechanisms is critical for reducing drug-related morbidity and enhancing patient outcomes in regions where malaria is endemic.

Keywords: Pharmacovigilance, pharmacy, pharmacist, adverse drug reaction reporting, health system, rational use of medicine, pharmacotherapy, antimalarial drugs

Introduction:

Pharmacovigilance [PV] is also called the safety of medicines and help to avoid further catastrophes. The world health organization [WHO] recommends its member countries to devise an effective pharmacovigilance system to deal with the identification, reporting and monitoring of adverse drug reaction [ADRs] the pharmacovigilance system is aimed to promote and protect public health by ensuring the availability of essential medicines in the market and reducing the burden of ADRs. What is Pharmacovigilance Pharmakon [Greek] Medicinal Substance Vigilia [Latin] To Keep Watch WHO

definition: The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems. Malaria continues to be one of the most serious infectious diseases worldwide, particularly in tropical and subtropical regions such as India, Africa, and Southeast Asia. It is caused by Plasmodium species, P. falciparum, P. vivax, P. malaria and P. ovule and transmitted by the bite of infected Anopheles mosquitoes. According to the World Health Organization (WHO), millions of malaria cases are reported annually, making it a major public health challenge. The cornerstone of malaria control is the effective use of antimalarial drugs. Commonly used antimalarial medications include chloroquine, primaquine, quinine, mefloquine, artemisinin-based combination therapies (ACTs), and silodosin–pyrimethamine. Although these drugs are effective in treating malaria, they are also associated with adverse drug reactions (ADRs), which may range from mild gastrointestinal discomfort to severe neurological.

A number of studies, reports, and scientific reviews have highlighted the importance of pharmacovigilance in monitoring the safety of antimalarial drugs. These studies describe the adverse drug reactions (ADRs), mechanisms responsible for toxicity, and the need for strong surveillance systems in malaria-endemic countries.

1. Chloroquine – ADR Profile Chloroquine has been extensively studied since its discovery. Various studies report that gastrointestinal disturbances, pruritus, and headaches are the most common ADRs. Long-term use is associated with retinal toxicity, which may lead to irreversible vision loss (Hobbs et al., 2009). Several reports have also shown cardiac toxicity such as QT prolongation in overdoses. Clinical research emphasizes the necessity of regular eye examinations for long-term users.
2. Quinine – Cinchonas and Severe ADRs Quinine has been known to produce a characteristic toxicity known as cinchonas, documented in multiple clinical studies. Symptoms include tinnitus, blurred vision, dizziness, and nausea. Severe reactions such as hypoglycaemia, particularly in pregnant women, have been commonly reported (WHO Malaria Report). Rare but severe ADRs like Blackwater fever involve intravascular haemolysis and have been described in African case studies. Case reports also indicate arrhythmias, requiring ECG monitoring for high doses.
3. Primaquine – Haemolysis and G6PD Deficiency Primaquine toxicity is well studied due to its oxidative properties: It causes haemolytic anaemia in individuals with G6PD deficiency (Beutler, 1991). Studies emphasize screening for G6PD deficiency before initiating therapy. Reports also mention methemoglobinemia, abdominal discomfort, and cyanosis. WHO strongly recommends pre-treatment G6PD testing to prevent severe ADRs.
4. Artemisinin Derivatives (ACTs) – Safe but Mild ADRs Artemisinin-based combination therapies (ACTs) are widely used due to better safety profiles. Literature reports: Mild ADRs such as dizziness, headache, nausea, and weakness. Rare neurological effects at high doses in animal studies. Delayed

haemolysis after IV artesunate has been documented in some patients (Donor et al., 2010). However, overall ACTs are considered the safest among antimalarial classes.

5. Sulfadoxine Pyrimethamine (SP) – Severe Dermatological ADRs SP is known for potentially serious ADRs: Common: nausea, vomiting, mild rash Severe: Stevens–Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) reported in several case studies and WHO alerts. Haematological ADRs such as megaloblastic anaemia due to folate inhibition have been documented.
6. Mefloquine – Neuropsychiatric ADRs Numerous clinical studies describe mefloquine induced psychiatric disturbances: Nightmares, vivid dreams, anxiety, depression. Severe: hallucinations, psychosis, suicidal ideation Several randomized trials confirm the association, leading to caution in individuals with mental health disorders.

Pharmacovigilance Studies on Antimalarial Drugs Many pharmacovigilance-based studies highlight the need for improved ADR reporting in malaria-endemic countries: WHO Global Surveillance Reports Underreporting of antimalarial ADRs remains a major challenge.

Pharmacovigilance strengthens early detection of harmful drug reactions. Indian PvPI (Pharmacovigilance Program of India) Data Reports from ADR Monitoring Centres show rising cases of ADRs due to chloroquine, SP, and primaquine. PvPI recommends routine training of healthcare workers in ADR reporting.

International Findings Studies from Africa and Southeast Asia emphasize the importance of active surveillance for ACT safety. Drug resistance trends require more vigilant monitoring.

Importance of Monitoring ADRs Across literature, the following points are consistently highlighted: ADRs affect patient compliance, leading to incomplete treatment Serious ADRs can result in hospitalization or death if not detected early. Strong pharmacovigilance prevents irrational use, ensures safe prescribing, and supports national.

Need of pharmacovigilance

The forceful marketing of new drug products by pharmaceutical companies and the consequential rapid disclosure over a short period of time of large numbers of patients to them necessitate the formation of a system for global assessment of drug safety concerns. These actions need an effective and efficient pharmacovigilance system that has been realized more than ever to make sure safe use of drugs.

There may be a need to monitor the effects of drugs during the clinical trials and after it in market. Adverse events can even happen during the clinical trials and after its launch in the market. Monitor the quality of drugs. Identify the health risks involved in the administration of certain drugs. Prevent harm to people. Research the efficacy of drugs. Pharmacovigilance is needed to protect public health by monitoring the safety of medicines after they are approved. This continuous safety surveillance is crucial for detecting, assessing, and preventing adverse drug reactions that may not have been apparent in clinical trials. It provides information for regulatory decisions, ensures the rational use of drugs, and helps protect patients from potential harm.

Key Points: Detecting adverse drug reactions: Pharmaceuticals can have unintended side effects that are only discovered after widespread use in diverse populations. Pharmacovigilance provides a system to find these reactions early.

Protecting patient safety: Monitoring helps ensure medications remain safe for different groups of people, including the elderly, children, and pregnant women. It also helps to identify issues like drug interactions or incorrect use.

Informing regulatory decisions: The data gathered is essential for regulatory bodies to make informed choices about a drug's use, such as updating labels, restricting its use, or even withdrawing it from the market. Improving drug development: Insights from post market surveillance can help improve drug formulations and usage guidelines for future development.

Reducing healthcare costs: By preventing or mitigating adverse drug events, pharmacovigilance can help avoid hospitalizations and other complications associated with medication related problems, which ultimately saves costs.

Ensuring rational and informed use: It provides healthcare providers with the information they need to make data-driven decisions about prescribing, and helps educate patients about the potential side effects of their medications.

Monitoring in real-world conditions: It allows for the monitoring of a drug's effectiveness and safety under actual, real-life conditions outside of the controlled environment of a clinical trial.

Historical Background of Pharmacovigilance

The history of pharmacovigilance reflects the evolution of drug usage and the increasing focus on drug safety. Initially, drugs, primarily derived from natural sources, were evaluated through empirical observation, with adverse effects often seen as unavoidable due to limited scientific understanding. The 19th and early 20th centuries saw a rapid increase in synthesized chemical entities, leading to broader drug usage and a higher occurrence of adverse drug reactions (ADRs). Among the earliest documented instances of drug-related harm was the use of chloroform as an anesthetic in the mid-19th century, associated with sudden cardiac deaths. However, these incidents were typically recorded as isolated cases, lacking a structured monitoring system. This inadequacy in drug safety evaluation only became clear following significant drug-related disasters.

A pivotal moment in pharmacovigilance history was the thalidomide catastrophe of the late 1950s and early 1960s. Thalidomide, which was prescribed to pregnant women to alleviate morning sickness, resulted in severe congenital malformations for innumerable newborns globally. This event underscored the critical need for monitoring drug safety both pre-approval and post-marketing, leading regulatory agencies worldwide to reinforce drug approval mechanisms and to prioritize the detection, evaluation, and prevention of ADRs.

In the aftermath of the thalidomide incident, the World Health Organization (WHO) initiated efforts to foster international collaboration in drug safety. In 1968, the WHO established the Programme for

International Drug Monitoring (PIDM), which became a cornerstone of contemporary pharmacovigilance. This initiative focused on collecting, analyzing, and disseminating reports of ADRs across different nations. The Uppsala Monitoring Centre (UMC) in Sweden was subsequently appointed as the global coordinating center for managing international ADR data.

Pharmacovigilance has substantially evolved, transitioning from basic case reporting to a robust scientific field dedicated to the detection, assessment, understanding, and prevention of adverse effects or any drug-related issues. Its scope has broadened to encompass synthetic drugs, vaccines, biological products, herbal medicines, and medical devices. Today, pharmacovigilance is essential to ensure patient safety and enhance public health outcomes.

Evolution of Adverse Drug Reaction Monitoring

The concept of adverse drug reactions (ADRs) has become increasingly significant as clinicians identified unexpected and at times severe effects associated with commonly administered medications. ADRs are characterized as harmful and unintended responses to drugs that occur at the typical doses used for prevention, diagnosis, or treatment. Historically, early systems for reporting ADRs were informal, relying heavily on individual clinicians' observations.

The evolution of regulatory science has led to the creation of structured ADR reporting systems. Spontaneous reporting systems emerged as crucial tools in pharmacovigilance, allowing healthcare professionals and, subsequently, patients to report suspected ADRs. These systems played a vital role in identifying rare, serious, and delayed adverse reactions that often went unnoticed during preclinical studies or clinical trials. The establishment of national pharmacovigilance centers in various countries has significantly enhanced drug safety surveillance.

In India, the drive towards pharmacovigilance accelerated with the initiation of the National Pharmacovigilance Programme in 2004, which was subsequently revamped and renamed the Pharmacovigilance Programme of India (PvPI) in 2010. This program, coordinated by the Indian Pharmacopoeia Commission, aims to monitor ADRs, promote the safe use of medications, and contribute to the WHO-maintained global drug safety database.

Historical Use of Antimalarial Drugs

Malaria is a longstanding infectious disease, with references tracing back to ancient cultures, including those of China, Egypt, and India. The treatment of malaria has evolved from traditional herbal remedies to more advanced methods, notably the discovery of quinine from the Cinchona tree's bark in the 17th century, which, despite its effectiveness, was linked to adverse effects known as cinchonism—characterized by symptoms such as tinnitus, headache, nausea, and visual disturbances.

The 20th century marked the advent of synthetic antimalarial drugs like chloroquine, primaquine, and mefloquine. Chloroquine emerged as a primary treatment option due to its effectiveness, affordability, and tolerability. Nevertheless, its prolonged use has been associated with adverse drug reactions (ADRs),

encompassing gastrointestinal issues, skin reactions, retinopathy, and potential cardiotoxicity during extended treatment, necessitating vigilant monitoring of antimalarial medication safety.

Primaquine raised concerns regarding hemolytic anemia among patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, highlighting the influence of individual patient factors on the incidence of ADRs and underscoring the need for comprehensive patient monitoring and pharmacovigilance. Likewise, mefloquine was recognized for its neuropsychiatric adverse effects, leading to constraints on its clinical application. These findings collectively stress the ongoing need for awareness and management of drug safety in malaria treatment.

Role of Pharmacovigilance in Antimalarial Drug Safety

The emergence of drug resistance in malaria and the introduction of effective antimalarial therapies, particularly artemisinin-based combination therapies (ACTs), have heightened the significance of pharmacovigilance. Although ACTs are acknowledged for their high efficacy, they are not devoid of adverse effects, which can include gastrointestinal symptoms, dizziness, and rare instances of severe hypersensitivity reactions. Continuous monitoring of these therapies is imperative to guarantee their safe application, particularly among vulnerable groups such as children and pregnant women.

Pharmacovigilance systems are integral in the identification, evaluation, and prevention of adverse drug reactions (ADRs) linked to antimalarial medications. Various methodologies for data collection, such as spontaneous reporting, cohort event monitoring, and active surveillance, empower regulatory authorities to revise treatment guidelines, issue safety advisories, and, when necessary, restrict or withdraw the use of unapproved medicines. The investigation of ADRs related to antimalarial drugs has substantially enhanced treatment outcomes and has played a significant role in mitigating malaria-related morbidity and mortality.

Study of Antimalarial Drugs: Antimalarial drugs are used for the treatment and prevention of malaria infection. Malaria is caused by four species of the plasmodium genus they are: P. falciparum

- P. vivax
- P. ovale
- P. malariae

Malaria is a mosquito-borne infectious disease caused by a protozoa species. The word malaria originates from Italian terminology mal + aria = bad air because protozoa of the plasmodium species are transmitted by mosquitoes. Malaria is a disease you get from being bitten by a mosquito. Some mosquitoes carry tiny parasites. They can infect you with the parasites when they bite you. Malaria can cause severe illness and death if left untreated. Kids under 5 are more likely to get life-threatening illness. Malaria is most common in tropical areas where it's hot and humid. Most cases happen in Africa. It's rare in the U.S. See a healthcare provider right away if you live in or have traveled to an area where malaria spreads and you have symptoms. This is true even if you've taken medications to prevent malaria during your trip. Malaria is a disease caused by a parasite. The parasite is spread to humans through the bites of infected mosquitoes. People who have malaria usually feel very sick with a high fever and shaking chills. While the disease is uncommon in temperate climates, malaria is still common in tropical and subtropical

countries. Each year nearly 290 million people are infected with malaria, and more than 400,000 people die of the disease. To reduce malaria infections, world health programs distribute preventive drugs and insecticide-treated bed nets to protect people from mosquito bites. The World Health Organization has recommended a malaria vaccine for use in children who live in countries with high numbers of malaria cases. Protective clothing, bed nets and insecticides can protect you while traveling. You also can take preventive medicine before, during and after a trip to a high-risk area. Many malaria parasites have developed resistance to common drugs used to treat the disease.

Causes and Transmission Malaria in humans is caused by five species of the Plasmodium parasite: P. falciparum, P. vivax, P. ovule, P. malariae, and P. knowlesi. P. falciparum is the deadliest species and is responsible for the majority of malaria-related deaths globally. P. vivax is the most widespread and can cause relapses months or years after the initial infection because it can lie dormant in the liver. Malaria is primarily transmitted through the bites of infected female Anopheles mosquitoes, typically from dusk to dawn. Parasites are injected into the bloodstream, travel to the liver to multiply, and then infect red blood cells, causing symptoms when the cells burst. Transmission can also occur through blood transfusions, organ transplants, and from mother to child. Complications Untreated malaria, especially P. falciparum, can lead to severe complications such as cerebral malaria, severe anemia, organ failure, and low blood sugar. Certain groups, including young children and pregnant women, face a higher risk of severe illness. Diagnosis and Treatment Diagnosis involves identifying the parasite in blood samples using methods like microscopy, rapid diagnostic tests (RDTs), or molecular tests. Treatment depends on various factors and utilizes antimalarial drugs. Severe malaria requires immediate intravenous treatment.

Conclusion:

India's pharmaceutical industry ranks as the third largest globally in terms of volume and 14th in value, emerging as a significant clinical trial hub. A robust pharmacovigilance structure is crucial to protect citizens from potential harm and adverse effects linked to new drug molecules. Although India has implemented a pharmacovigilance program aligned with WHO guidelines through the CDSCO, achieving desired outcomes remains a challenge. Increased awareness and training for medical professionals and the public, alongside well-defined policies for reporting adverse drug reactions (ADRs), can foster an effective pharmacovigilance system in collaboration with government bodies, pharmaceutical companies, healthcare professionals, regulatory authorities, and patients.

Malaria continues to pose a serious public health threat in tropical and subtropical areas, necessitating a deep understanding of the parasite's life cycle, clinical symptoms, diagnostic approaches, and preventive measures. Antimalarial treatments, particularly Artemisinin-based Combination Therapies (ACTs), have significantly enhanced treatment success. Additional medications like primaquine and tafenoquine are vital for achieving a radical cure and preventing relapse.

Sustaining pharmacovigilance, monitoring drug resistance, and ensuring the safe application of antimalarial drugs are essential for preserving treatment efficacy. Effective malaria control involves not

only drug administration but also vector management, timely diagnosis, and public education. Monitoring adverse reactions, which can range from mild to severe, is critical for maintaining patient safety and the efficacy of antimalarial treatments.

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