



Adverse Event Monitoring of Artemisinin Combination Therapy in Nigeria: The Challenges and Limitations of the Study

*Surveillance des manifestations indésirables de la thérapie combinée artémésinine au Nigeria:
Les défis et les limites de l'étude*

K. A. Oshikoya

ABSTRACT

Artemisinin combination therapies (ACTs) are first line anti-malarial drugs in malaria endemic regions of the world as recommended by the World Health Organization. ACTs are relatively new in Nigeria and there is little experience with their use. The pharmacovigilance of ACT drugs has been advocated in African countries so as to establish their safety in the African population. There is an on-going adverse event monitoring of the ACT drugs in Nigeria and a preliminary result has been published by the National Agency for Food and Drug Administration and Control. This commentary aims to discuss the challenges and limitations of the on-going pharmacovigilance of ACT drugs in Nigeria and proffer useful suggestions on how to overcome the problems. *WAJM* 2010; 29(4): 221–224.

RÉSUMÉ

*Polythérapies artémésinine (ACT) sont en première ligne des médicaments antipaludiques dans les régions d'endémie du paludisme dans le monde tel que recommandé par l'Organisation mondiale de la Santé. Les ACT sont relativement nouveaux au Nigeria et il ya peu d'expérience à leur utilisation. La pharmacovigilance des médicaments ACT a été préconisée dans les pays africains de manière à établir leur sécurité dans la population africaine. Il ya un suivi permanent des effets indésirables des médicaments ACT au Nigeria et un résultat préliminaire a été publié par l'Agence nationale pour Food and Drug Administration et de contrôle. Ce commentaire vise à examiner les défis et les limites de la pharmacovigilance en cours de médicaments ACT au Nigeria et proposer des suggestions utiles sur la façon de surmonter les problèmes. *WAJM* 2010; 29 (4): 221-224.*

INTRODUCTION

The artemisinin combination therapy (ACT) drugs are relatively new in Nigeria and there is little experience with them in Africa. The safety of ACT drugs, like in other African countries, has not been established in the population of Nigerians. However, there is an on-going debate on the need to establish systems for pharmacovigilance of ACT drugs in African countries.¹

The World Health Organization (WHO), in conjunction with the National Agency for Food and Drug Administration and Control (NAFDAC), the National Malaria Control Centre (NMCP), the Society for Family Health (SFH) and the Yakubu Gowon Centre (YGC), have embarked on adverse event monitoring of ACT drugs in the six-geopolitical zones of Nigeria. This is a noble course that calls for both local and international applause. Some pharmacovigilance experts have expressed concerns about the feasibility of adverse event monitoring of ACT drugs in Africa and have suggested ways of overcoming the challenges^{2,3} but from the preliminary results published by the NAFDAC,^{4,5} the design and methods of monitoring the ACT adverse events appear to leave so much to doubt. When doubt exists, the results of such study may not be acceptable internationally. The authenticity of the final results of the on-going study is likely to be based on probability of the number of adverse events that are likely to be reported and the approach to the study. Ralph Edwards, the director of the Uppsala Monitoring Centre, has once noted during his reflections on the development of pharmacovigilance, that efforts made to get to the point of performing a study of pharmacovigilance, supported by laboratory evidences, are of great values in adverse event reporting.⁶

The challenges that may face adverse event monitoring of ACT drugs in Africa have been previously discussed by Talisuna *et al.*⁴ However, the challenges may vary from one African country to another. This commentary is therefore aimed at outlining the practical challenges and limitations that may jeopardise the results of on-going adverse event monitoring of ACT drugs in Nigeria.

Approach to the Study

Given the considerable dearth of local expertise in pharmacovigilance in Nigeria, the few available ones should be involved in this type of study, more so when the study is based on a national survey. A very good way to harness Nigeria-based pharmacovigilance experts is to advertise the pharmacovigilance study in the media, including local medical journals, for individuals to respond to. Alternatively, the steering committee of the study could make online searches for these experts who have made scholarly contributions to pharmacovigilance in Nigeria, through academic publications and invite them to contribute. I am aware of a pharmacovigilance research group at the Lagos State University Teaching Hospital, Ikeja,⁷ who were not represented in the on-going study. Their invaluable contributions are actually missing in the design of the study, especially on how to overcome the special challenges of assessing adverse events in children.

In general, pharmacovigilance is a multidisciplinary issue that involves disciplines such as basic and clinical pharmacology, clinical medicine, toxicology, epidemiology and genetics.⁸ Unfortunately, expertises in these disciplines are few in Nigeria and this may probably explain the use of focus persons in the selected study centres. A pharmacovigilance team overseeing the study in each of the centres should be headed by a pharmacovigilance expert who is a health care professional with deep experience in both direct patient care and hospital-based pharmacovigilance researches, which will aid the team to produce the highest-quality safety data. It is not convincing that a 4-day training given to the focus persons was enough to make them experts in pharmacovigilance or make them competent to accurately assess the causality between the reported adverse events and the ACT drugs.

Setting of the Study

The study was commenced in sites spread across the 6 geopolitical zones in Nigeria which include the University College Hospital, Ibadan; Federal Medical Centre, Gombe; the Ahmadu Bello University Teaching Hospital, Zaria; the

University of Uyo Teaching Hospital, Uyo; National Institute for Pharmaceutical Research and Development (NIPRD), Abuja; and the University of Nigeria Teaching Hospital, Enugu. The purpose of these geopolitical spread is to widely represent all the tribes in Nigeria in the study and to increase the power of the study, in terms of the number of participants. Patients are likely to present more to public (teaching, district and general) hospitals than private clinics. To the best of my knowledge, the NIPRD clinic is expected to care for their staff and relations; therefore ethnic representation of the patients recruited from this study centre is likely to be biased and the influence of pharmacogenetics on adverse events of ACT drugs may be masked in homogenous population of patients. Perhaps, a general hospital in Abuja or the National Hospital, Abuja, would have been a more appropriate centre.

The study was claimed to be observationally prospective, yet patients were given ACT drugs to use at home and asked to either record adverse events on their own or come back to report the events at the study centres. This method is rather ambiguous, unreliable and unimaginable in a study of this magnitude. It is proper to admit the patients throughout the period of the study, thus supporting the fact that the study should have been performed in hospitals instead of clinics. Hospital admission would ensure that the ACT drugs are taken by the patients under supervision according to the instructions of the manufacturers. This will also eliminate the possibility of non-compliance by the patients and allow prompt treatment of severe and fatal adverse events. An observational study requires that the researchers or the designated health care professionals, whose judgement can be trusted, witness the adverse events and document such events in the appropriate manners. One wonders how the illiterate patients were able to describe or record the adverse events they experienced.

Cohort Selection

Children are not small adults⁹ and should be studied differently from adults. The toxicity of drugs in children can be

different from those seen in adults. Some drugs are known to cause different adverse events in the childhood population compared to the adult population.¹⁰ Children, under the age of 16 years, experienced a unique adverse drug event from adults, in the development of Reye's syndrome.¹¹ The restriction of the use of salicylates in children has resulted in a dramatic reduction in incidence of Reye's syndrome. The development of the organ systems and the enzymes systems within children, which metabolise and eliminate drugs, occurs throughout childhood; meaning that the pharmacokinetics and pharmacodynamics are different from those of the adults.¹² Children frequently die from malaria more than adults; therefore outcome measures of severe and fatal adverse events of the ACT drugs that are appropriate for adults may be inappropriate in paediatric studies.

Patients with HIV/AIDS, pregnant women, and children with protein-energy malnutrition (PEM) are special and should be studied as specific cohorts. Prevalence of malaria is high in these patients;¹³⁻¹⁵ therefore they are likely to use ACT drugs more frequently than other patients. The ACT drugs are metabolised in pathways similar to those of anti retroviral drugs, thus the two groups of drugs can adversely interact¹⁶ and may result in exaggerated adverse event reporting of ACT drugs.

Pregnancy comes with many physiological changes which may have some effect on metabolism and pharmacokinetics of drugs.¹⁷ There is evidence that the pharmacokinetics of several antimalarial drugs, including artesunate, is altered in pregnancy and doses used in the general population are not adequate in pregnancy.¹⁸⁻²⁰ Modifying the dose of ACT drugs in pregnancy is likely to increase incidence of adverse events to these drugs.

Children with PEM are known to metabolise antimalarial drugs very poorly.^{21, 22} Given the fact that the metabolism of ACT drugs has not been studied in these children, they may be at risk of ACT drug toxicity; therefore, these children need to be studied as a separate cohort.

Definitions in Pharmacovigilance

The on-going ACT adverse event monitoring is not the same as adverse drug reaction (ADR) monitoring. It is important to recognise the distinction between an adverse event and ADR. Adverse event is any undesirable medical occurrence that develops after the administration of a drug, regardless of the suspected relationship between the drug product and event, while an ADR is an event with an established causal relationship.²³ These definitions highlight some of the practical challenges related to the detection of adverse events and the determination of the severity of events to a specific component of the ACT drugs. The focus persons at the point of data collection are required to detect adverse events, which are often difficult to distinguish from common symptoms of malaria.²⁴ Once an adverse event has been detected, the maximum severity of the event needs to be established. Although, standardised guidelines have been provided by the WHO^{23, 25} but the grading may be subjective and cause inter-rater grading error. A consensus has to be reached with a pharmacovigilance expert in grading the severity of the event so as to minimise grading errors.

Classification of the relationship of an adverse event to a product is another challenge. Determining if an event has been caused by a given product or is related to other concomitantly administered drugs, malaria, or other illnesses, is also difficult and often subjective. In addition, defining the period of "reasonable temporal association" between an event and prior treatment is problematic when considering combination therapies that include partner drugs with long elimination half-lives. Assigning a causal relationship and determining if an event is unexpected is even more difficult when multiple drugs have been administered together,⁴ especially in children.^{7, 26}

ACT Drugs Studied and Influence of Counterfeit/Fake Drugs

Only artemether with lumefantrine (AL) and artesunate with amodiaquine (AA) were studied, yet other groups of ACT drugs like artesunate with mefloquine, artesunate with piperazine,

and artesunate with atovaquone are abundant in the markets and are widely prescribed or self-medicated. Unless, drug use policy in Nigeria strictly bans the use of other groups of ACT drugs and the ones in the market completely mobbed up, adverse events of the other ACT drugs will have to be equally monitored.

Antimalarial drugs are among the self-medicated drugs in Nigeria.²⁶ This is made worse by categorising ACT drugs as over the counter drugs. Counterfeit and fake ACT drugs are now proliferating in the markets as a result of poverty.²⁷ Adverse events are likely to result from the adulterated components of ACT drugs which may likely give a false positive result.

Monitoring Method

Two broad approaches for pharmacovigilance are used in developed countries, including passive spontaneous reporting systems, and systems utilising pharmaco-epidemiological methods.⁴ Post-marketing surveillance of the ACT drugs will involve continuous reporting of their adverse events and re-evaluation of their risks and benefits. This method is cheap, simple, and able to detect rare events. It also provides the opportunity to continuously monitor safety of the drugs. However, spontaneous reporting of adverse events is under-mined by under-reporting²⁸ and difficulty of establishing a causal relationship between the events and ACT drugs. The method is currently non-existent in Nigeria and other African countries. Perhaps, this may explain the use of pharmaco-epidemiological method in the on-going study.

Laboratory investigations are very essential in drug safety monitoring but are likely to be performed in the ongoing study only on patients with severe and fatal adverse events. Parents are likely to be the one to report for their children the adverse events of the ACT drugs. Children may not be able to express what they feel when experiencing subtle adverse events which are not recognisable by their parents; therefore serial laboratory investigations performed before, during and after the ACT drug administration may be able to reveal such events.

Acute fulminant hepatitis has been reported following the use of artesunate and amodiaquine combination drug in adults [29]. Therefore, monitoring with laboratory investigations will be necessary for early signal detection of hepatic adverse events of ACT drugs. The Lumefantrine component of one of the ACT drugs studied has the potential to cause cardiac adverse events; therefore electrocardiography monitoring may be required. Similarly, neurologic adverse events have been reported to ACT drugs in animal studies; thus neurological evaluation may be necessary in the ongoing study.

Other Challenges

Other challenges facing the ongoing study include not knowing what events the patients should report and one not sure if all adverse events or only adverse drug reactions should be reported. It is not yet clear how the study intends to assess the risk factors for ACT adverse events, and establish possible interactions between ACT drugs and other orthodox and herbal medicines since this will require complex pharmacokinetics and pharmacodynamic studies.

Conclusion

Pharmacovigilance for ACT drugs is challenging in Nigeria but feasible if approached with sincerity. Transparency in the recruitment of expertise for studies involving drug safety must always be ensured. Children and special group of patients should be studied as specific cohorts in drug safety issues since 'one size does not usually fit all.'

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