mémoire en vue de l'obtention du Master Biologie Santé, mention Complexes Pathogènes Tropicaux

Development of Tools and Methods for Monitoring Safety of Artemisinin based Combination Treatments in Africa

Date: 22.July.2005

By: Malek A. Abu Serhan

Jury members:	Pr. Denis MALVY	Président
	Dr. Pascal MILLET	Juge
	Dr. Jean-Louis KOECK	Juge
	Dr. Françoise HARAMBURU	Juge
	Pr. Djavad MOSSALAYI	Juge

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Abbreviations

ACTs : Artemisinin Based Combination Treatments

ADRs : Adverse Drug Reactions

AQ : Amodiaquine

AS : Artesunate

Hb : Hemoglobin

HIV/AIDS : Human Immunodeficiency Virus/ Acquired Immuno-Deficiency Syndrome

P. falciparum : Plasmodium falciparum

SEA : South East Asia

TB : Tuberculosis

WHO : World Health Organization

Summary:

ACTs (Artemisinin based Combination Treatments) have been newly adopted as first line treatment for malaria in many African countries that lack a pharmacovigilance in place. Monitoring safety of these drugs is crucial for safe and rational use, and this monitoring could be achieved by implementing simple tools and methods suitable for health workers at peripheral level especially. Best knowledge of ACTs adverse reactions and designing a comprehensive and simple reporting form are essential for monitoring safety of these drugs.

Among these proposed tools, checklist of adverse reactions of ACTs could be successful and easy way to report for safety problems of ACTs, also attaching illustration for some medical terms for non physician health workers along with the case report form would be promoting factor for reporting process.

Introduction:

60% to 70% of all malaria cases in the world occur in Africa south of the Sahara [1] and an estimated 1 to 2 million people in Africa die from malaria each year; most of these are children under 5 years. [1, 2, 3] Majority of mortality and morbidity occurs outside health facilities.

Anti malarial drug resistance has become one of the greatest challenges in malaria treatment, and this forced many countries to change their national policies guidelines [3, 4], mainly toward ACTs therapy.

ACTs have enormous potential in malaria therapy, since the combination enhances efficacy and delays development of resistance. [5, 6, 8] Therefore, since 2001 WHO has recommended ACTs as first line for treatment of acute uncomplicated malaria in countries experiencing resistance to conventional monotherapies. [3, 7, 8, 9]

Since 2001 a total of 51 countries have adopted one of ACTs as first line or second line treatment of malaria, 34 of them are in Africa ([10] and a total of 23 of these African countries are now using ACTs for treatment of malaria. [11]

WHO currently recommends the following therapeutic options for treatment of uncomplicated malaria:

- artemether-lumefantrine
- artesunate + amodiaquine
- artesunate + sulfadoxine-pyrimethamine SP (in areas where SP efficacy remains high)
- artesunate + mefloquine (in areas with low to moderate transmission)

Artesunate + amodiaquine is the main used combination in African countries that have adopted ACTs for treatment of malaria.

Artesunate (AS) plus amodiaquine (AQ) combination has been adopted for the treatment of uncomplicated falciparum malaria in many African countries. [7] Some studies done in Africa has shown that this combination has superior efficacy and curative rate over conventional monotherapies in most of these countries, all these clinical trials have been done in African children using a dosage of 4mg/kg/d AS + 10mg/kg/d AQ for 3 days, they have found that this combination is efficacious in curing malaria infection by rapid elimination of parasitemia and clearance of fever in addition to preventing recrudescence. [12- 16]

Although efficacy and safety of ACTs are well documented in South East Asia (SEA)[17]; there is limited information about the safety of ACTs outside SEA. Since ACTs are newly marketed in Africa there is limited safety information there about them.

In most malaria endemic countries, particularly in Africa, there is no pharmacovigilance program in place. In addition there is very limited information available on Adverse Drug Reactions (ADRs) in developing countries, where there is no spontaneous reporting culture in many of these countries; time constraints on health professionals and absence of reporting systems are two main factors. [18] Also, this problem is caused by lack ofproper drug regulation including ADRs reporting, large number of substandard products circulating in their market, lack of independent information and the irrational use of drugs. [17]

Therefore, there is urgent need to monitor safety in new populations in malaria areas in Africa, and thus, pharmacovigilance is important in African countries that adopted ACTs as treatment for malaria and to maintain monitoring of their adverse reactions especially where co morbid conditions such as HIV/AIDS, malnutrition and TB are common. Actually, introduction of ACTs offers an opportunity for African countries to put drug safety monitoring in place.

Backed by the WHO Roll Back Malaria department and other international cooperating partners, five African countries, which are in the process of introducing ACTs (Burundi, Democratic Republic of the Congo, Mozambique, Zambia and Zanzibar), have drawn up action plans to introduce pharmacovigilance in their health sector. [17]

Observational epidemiological studies can be used to evaluate safety of these drugs but they are expensive and take long time during which people may get harmed. [19]

Therefore, it is important to set up a Pharmacovigilance system since information collected during the pre-marketing phase is incomplete; these information are incomplete due to:

- Tests in animals are insufficiently predictive of human safety
- Patients in clinical trials are selected and limited in number, and conditions of use different from those in clinical practice
- Short duration of clinical trials, so rare adverse reactions might not be observed
- Information about rare but serious ADRs, chronic toxicity and drug interaction is often lacking.
- Missing information about sub groups, such as women and malnourished individuals

Pharmacovigilance is needed in every country as well, because there are differences between countries in the occurrence of ADRs, because the following points are different among them:

- Drug production
- Distribution and use
- Genetics, diet, traditions
- Pharmaceutical quality and storage quality. [20, 21]

African countries that may have little or no safety monitoring infrastructure, simple techniques can be used to promote and facilitate reporting of adverse events of ACTs to a responsible body of experts.

Objectives:

1. **General:** the rational and safe use of ACTs**.**

2. **Specific:**

    - Development of tools and methods for monitoring the safety of ACTs in African countries**.**

    - Designing a reporting form for ADRs of ACTs in Africa

Method:

Fro reviewing reported adverse reactions artesunate and amodiaquine and adverse reactions of their combination, we performed a search in the Medline database using the following key words: artesunate, amodiaquine, artesunate-amodiaquine, toxicity, adverse reactions, case report, safety and side effects, the objective of the review is not to do an extensive search but rather to focus on safety and adverse reactions of the two drugs and their combination, therefore studies that focused on efficacy and were not done to evaluate safety were excluded. Also the search was focused on studies that have been done in Africa, since the occurrence of adverse reactions is different from country to country.

We proposed a reporting form for adverse reactions of ACTs, and tools to promote the process of reporting such as checklist method, in which adverse reactions of ACTs are listed in the reporting form for easier reporting and detecting.

Results:

Knowledge of adverse reactions of ACTs in advance will facilitate the process of reporting and monitoring.

For health workers to be familiar with what they should expect and so to avoid misdiagnosis, and to be able to link between an event and drug administration, e.g. amodiaquine causes neutropenia which can't be seen or detected without blood tests, however neutropenia causes an increase in the susceptibility to bacterial infections, but health workers will not be able to link between an increased susceptibility to bacterial infections and amodiaquine administration unless if they know in advance that amodiaquine might cause neutropenia.

Health workers will be aware and able to some extent to diagnose such reactions and discriminate them from reactions of other medicines or related to certain diseases, although this is not easy often.

Therefore we go briefly through ADRs of amodiaquine, artesunate and their combination; that were collected in experimental and clinical studies or presented as case reports.

Reported adverse reactions:

One of the newly marketed combinations that have been adopted in many African countries is artesunate/amodiaquine combination therapy (Arsucam®), which is the cheapest among ACTs and has found to be very efficacious for treatment of uncomplicated malaria infection.

1. Amodiaquine (AQ):

1.1 Mode of action

Before discussing the drug adverse reactions it is important to explain briefly the mechanism of action of amodiaquine, since this is much related to the adverse reaction occurrence and might explain how they occur.

AQ is one of the 4-amino quinolines that seem to act by concentration of the drug in the digestive vacuole of the intraerythrocytic parasite. It has been demonstrated that AQ bind to heme and inhibit its polymerization in vitro. [23, 24] therefore it is probable that AQ act by inhibition of heme polymerization of the parasite leading to accumulation of soluble heme toxic for the parasite. [22]

1.2 Adverse reactions

Main adverse reactions of amodiaquine are similar to that of chloroquine and the most commonly reported adverse events with amodiaquine were gastrointestinal (nausea and vomiting) and pruritus. [29]

In a randomized clinical study done to evaluate efficacy and tolerance of some anti-malarial therapies in children under 10 years in Cameron (61 children), the following side effects were reported after treatment with AQ (30mg/kg in three divided daily doses) [25] :

- Fatigue 88%
- Vomiting 16.4%
- Pruritus 13.1%
- Dizziness 8.2%
- Diarrhoea 6.6%

Another randomized study that was done to evaluate efficacy and safety of atovaquone/proguanil versus AQ (10mg/kg once daily for 3 days) for treatment of *P. falciparum* among children in Gabon (78 child), has shown that 43% of children presented with mild to moderate adverse events after treatment with AQ, such as diarrhoea 15%, cough 13%, vomiting 7% and weakness 7%. [26]

Similar events were reported in a randomized clinical trial to evaluate safety and efficacy of some antimalarial drugs for treatment of uncomplicated malaria among children (6months to 5 years) in Tanzania (118 children), events occurred after treatment with AQ (25mg/kg

divided in 3 doses for 3 days), such as anorexia in 44.1%, difficulty in breathing in 9.0% and lethargy in 36.1%. [27]

1.3 Case reports

Prophylactic AQ was banned following serious hematological adverse effects that occurred during prophylactic treatment for malaria. [28- 30] the main reported serious hematological adverse event was agranulocytosis in 1/2000.[31] AQ caused agranulocytosis when given in a dosage of 400 mg weekly with period of exposure ranging from 3 – 24 weeks. [32]

Another finding is neurological adverse events that might be caused by AQ, from January 1998 to June 2000; the authors described 35 case reports of children aged from 5 months to 15 years who presented neurological side effects after taking AQ at Yopougon teaching hospital in Abidjan, Côte d'Ivoire, such as stiffness of the neck, muscular spasm and convulsions. [33]

Also hepatitis has been reported. [29, 34, 35]

Seven cases were reported in patients who developed hepatitis after receiving AQ for malaria prophylaxis for 4 to 15 weeks. Four patients had a minor form of hepatitis and three had a severe form. [34]

Three cases were reported in patients 23, 59 and 22 weeks after beginning of treatment and who received a total dose of 16, 26 and 15 g of AQ respectively for the prophylaxis of malaria; two of them died. [35]

One case report describes a 34-year-old man who ingested more than 250 g of AQ hydrochloride (for pain) over one year, who presented with diffused conjunctival, corneal, and skin changes and also abnormal results from retinal function tests. This reveals that AQ repeated use over long period may lead to retinopathy. [37]

In general, the risk of severe reactions of AQ is estimated to be between 1in 1000 and 1 in 5000 when used as prophylaxis. [36]

2. Artesunate (AS):

2.1 Mode of action:

Artesunate is one of artemisinin derivatives that have endoperoxide in their structure which might contribute to the antimalarial activity. These peroxides are source of reactive O_2 species and free radicals that are toxic to the parasite. [38, 39]

These free radicals are reactivated by intraparasitic heme and seem to damage intracellular microorganelles and membranes of the parasite, possibly by alkylation. [38, 40]

2.2 Toxicity in animals

AS was found to induce tremor, gait disturbances and lethargy in rats when given in high doses (31mg/kg for 7consecutive days). [41] Also 300mg/kg/d of AS for 28 days caused neurological abnormalities in mice. [42, 43]

AS has been found to be toxic to rat and rabbit embryos and cause growth retardation in rats (16.7mg/kg/d in rats and 12mg/kg/d in rabbits for 12 days). [44]

2.3 Adverse reactions

In general AS is well tolerated, and in some clinical studies no adverse reactions were reported after administration of rectal AS for treatment of uncomplicated malaria in children. [45-47]

Vomiting, nausea and dizziness were all observed in patients after administration of 600mg oral AS over 6 days. [48-50]

In clinical study done for comparing of 5 days and 7 days regimens of AS for treatment of malaria in Thai patients, minor complaints were reported such as headache, dizziness and nausea (1200mg over 5days and 1600mg over 7 days). [51]

Mild side effects were also reported in a clinical study among Gabonese patients (4-15 years) such as vomiting 4/50, abdominal pain 3/50, coughing 2/50 and pruritus 2/50 after administration of AS orally (4 mg/kg once daily for 3 days) [52]

2.4 Case reports

When used in human generally AS has mild side effects; they are uncommon and restricted to transient rise in transaminase enzyme and decrease of reticulocytes numbers. [18]

There is no evidence that AS causes allergic reactions, neurological or psychiatric reactions or cardiological or dermatological toxicity when used in human.
(AS 12mg/kg over 5 or 7 days) [53]

However, case of ataxia and slurred speech was described in 1996 in a 36-year-old American after treatment of malaria with oral artesunate. [54]

3. AS/AQ combination:

3.1 Toxicity in animals:

No data are available in animals.

3.2 Adverse reactions in clinical trials:

In general, mild side effects were reported after administration of artesunate-amodiaquine combination for treatment of malaria such as weakness, headache dizziness, anorexia nausea, vomiting, abdominal pain, diarrhoea and myalgia. [55-57]

Neutropenia early occurred in 1.75% and during a multi centre comparative clinical trial in African children, using a dosage of 4mg/kg/d AS and 10mg/kg/d AQ for 3 days. [55]

In the same study early drug-induced vomiting necessitating alternative treatment occurred in 3.4% of patients on day 0 and day1 of treatment.

40 volunteers received an AS/AQ combination in Casamance/Senegal during a clinical study to evaluate safety. The following adverse reactions were reported in 37 subjects after administration of AS 4mg/kg/d and AQ 10mg/kg/d both for three days: [58]

Undesirable effects with 40 healthy volunteers

Adverse reaction	n	%	CI 95%
Headache	3	7, 5	[1,6 - 20,4]
Dizziness	13	32, 5	[18,6 - 49,1]
Fatigue	30	75	[58,8 - 87,3]
Myalgia	7	17, 5	[7,3 - 32,8]
Gastric disturbances	14	35	[20,6 - 51,7]
Pruritus	1	2, 5	[0,1 - 13,2]
Undesirable effects	37		

The gastrointestinal adverse reactions were:

- Nausea 12,5%
- Vomiting 7,5%
- Abdominal pain 7,5%
- Hunger 7,5%
- Anorexia 5%

Since acute malaria symptoms overlap with adverse drug reactions expressed by the patients, results on healthy individuals may be useful.

3.3 Case reports:

One case report described a drug-induced hepatitis in a previously healthy young woman exposed to 2 doses of AS/AQ. [59]

The following table summarizes reported adverse reactions of AS, AQ and their combination:

Drug	**Toxicity in animals**	**Reported adverse reactions (clinical studies)**	**Case reports**
AQ		• Fatigue • Vomiting • Pruritus • Dizziness • Diarrhoea • Anorexia • Difficulty in breathing • Lethargy • Cough	• Agranulocytosis • Hepatitis • Neurological adverse reactions • Retinopathy
AS	• Tremor • Gait disturbances • Lethargy • Embryonic toxicity	• Transient rise transaminase enzyme • Decrease of reticulocytes numbers • Vomiting & nausea • Abdominal pain • dizziness • Coughing • Pruritus	• Slurred speech • ataxia
AS-AQ combination	Not available	• Headache • Dizziness • Fatigue • Pruritus • Vomiting • Nausea and hunger • Neutropenia • Abdominal pain • Diarrhoea	• hepatitis

Method to promote and facilitate reporting and monitoring of ACTs safety, Checklist method:

Since most of malaria cases are seen at the peripheral hospital or dispensary health centers and posts, it is very important to insist on pharmacovigilance principals at this level and to start implementing strategies for monitoring of safety at dispensary level. Health workers are in the best position to report suspected ADRs observed in their everyday patient care. However, we have to take into consideration the limited infrastructure and resources at this level in African countries. In addition, most of health worker at this level are not physicians. So, simple techniques could be used to monitor safety and to report ADRs of ACTs at the dispensary level.

Spontaneous reporting is a simple way to monitor safety of drugs. However, it should be promoted and enhanced to assure success and continuity especially at the dispensary level. Many factors should be taken into consideration to make reporting successful and continuous at this level:

- Designing comprehensive and simple reporting form, containing all necessary information

The reporting form should have internationally known design and include four sections that should be completed

- First of all the patient information such as identification number, gender, age, weight …etc.
- Adverse event: description and date of the event, reporting date, relevant tests, patient information/history and outcomes.
- Suspected medication: name, dose, frequency and route used, duration of treatment, therapy date, if the event reappeared after the reintroduction of the treatment and concomitant medical therapy
- Reporter: name, address, specialty and occupation

The following is the proposed case report form for health workers in African countries to report adverse reactions of ACT:

A. Patient information

Name : _____ Age : _____ Weight : _____	Sex : □ Male □ Female

Relevant medical history
(e.g. allergies, pregnancy, hepatic or renal dysfunction, other diseases, alcohol use, other)

B. Adverse reaction

1. description

Severity : □ Mild □ Moderate □ Severe Localization :
Nature and characteristics :

2. Date of reaction : DD / MM / YYYY
___/ ___/_____

3. Outcome of the adverse reaction

□ Death □ Disability □ Hospitalization □ Recovered □ Recovering □ Continuing
Reaction abated after stopped use or dose reduced : □ Yes □ No □ Doesn't apply
□ Other _____

4. Relevant tests and lab. data (if available)

C. Suspected drug

Name : _____ Dose_____ Frequency_____ Route used_____
Therapy dates (dd/mm/yyyy) : from to
indication for use _____
Has the patient already been treated with this drug: yes/no If yes, when: __/__/___

Other drugs taken concomitantly
Name _____ Dose _____ Ferquency _____ Route _____
Therapy dates (dd/mm/yyyy)

D. Reporter information

Name _____ Occupation _____
Specialty _____
Address _____

Reporting could be promoted by simplifying case report form by different ways such as designing the case report form as checklist or attaching a list of ACTs adverse reactions along with the report form:

1. List of all known ADRs of ACTs and expected ones as well

The list of adverse events could be simplified as scale or checklist to motivate health worker to fill in, even some part might be filled by the patients themselves. ACTs side effects scale or checklist is one method of increasing the recognition of ACTs adverse reactions, that implemented by health workers (or patients themselves) to assess the safety of ACTs.

Ideal checklist should be simple, quick to complete and capturing all important clinical relevant data.

2. Simple illustration of the medical terms and ADRs, since most of health workers at this level are not physician and they might not be familiar with medical terms, of course understanding of ADRs stimulate reporting and help to assess observed reactions:

As an example of this illustrative attachment:

ADRs	diagnosis	Clinical picture
1. Neutropenia	below 1500 Neutrophils per mm3 (Absolute Neutrophil Count) – blood test	If below 500 Neutrophils /mm3: Increased risk of infections, e.g. otis media; tonsillitis; sore throat; mouth ulcers; gum infection and skin abscesses.
2. Diarrhoea	more than two loose or watery stools per day	Loose, watery, and frequent bowel movements Could lead to dehydration

The proposed checklist design can be as follows:

Patient name: Age: Gender:
Drug name: Treatment dates: __/__/____ to __/__/___ Dose: Route: Frequency: Reason for prescription: Has the patient already been treated with this drug: yes/no If yes, when: __/__/___
Reporter name: Specialty: Date:

Lab tests (if available)		**comments**
1. Temperature	°C	
2. Weight	Kg	
3. Neutrophil count	Cell/mm3	
4. Reticulocyte count	Cell/mm3	
5. Hb	g/dl	
6. Transaminase enzyme (AST/ALT)	U/L	

Problem	**Yes/No**	**Severity: mild, moderate or severe**	**Date**	**Comments**
Nausea				
Vomiting				
Diarrhoea				
Dizziness				
Fatigue				
Eruption				
Pruritus				
Abdominal pain				
Cough				
Fever				
Jaundice				
Headache				
Neurological : -lethargy -tremor -blurred vision				
Other, specify:				

- Motivation of health workers to report any suspected ADRs through:

    1. appreciation of their work regarding reporting
    2. continuous contact with them through email, mail and phone
    3. invitation of health workers to attend training sessions to enhance their feeling about their importance as part of the pharmacovigilance in the country

- Producing printed materials and about data collection and verification, signal detection, guidelines for filling in the reporting form and how to deal with serious adverse reactions.

Implementing tools for monitoring safety of ACTs in Africa needs many aspects to be taken into consideration. Before starting the reporting process in a country, that country should establish and set up a pharmacovigilance centre.

Location of the pharmacovigilance centre is preferred to be a governmental department. However, any department in a hospital or academic environment, working in clinical pharmacology, clinical pharmacy, clinical toxicology or epidemiology may be a suitable place or any existing structure already involved in ACTs surveillance.

Planning for setting up a pharmacovigilance centre needs several basic steps to be achieved in order to be in the right way to establish the centre;

1. Making contact with the health authorities and with local, regional and national institutions working in the field, outlining the importance of the project and its purposes.
2. Designing a reporting form; distribute it to hospital departments, family practitioners, peripheral health centers …etc. to start collection of data.
3. Producing training materials for health professionals about definitions, aims and methods of pharmacovigilance system.
4. Creating the centre: staff, accommodation, phone, database…etc.

5. Educating the pharmacovigilance staff and promoting the importance of reporting ADRs through medical journals and communication activities.
6. Establishing a system for the storage and retrieval of data (database)
7. Maintaining contact with international institutions working in pharmacovigilance, e.g. WHO department of essential drugs and medicines policy and the Uppsala monitoring centre.

After this essential step, health workers should be aware of all reported adverse reactions of ACTs in general and to focus on the used or adopted combination. For example, artesunate-amodiaquine combination is being used by many African countries and therefore health workers in these countries should be educated about reported and serious adverse reactions of this combination.

The reporting form should be as comprehensive and simple as possible, and includes the main four sections that should be present in any case report in the world. The form must include information about the patient, the suspected drug, the observed adverse reaction and the reporter information.

General guidelines for filling in the form should be available for health workers along with the case report form;

- All suspected reactions including minor ones should be reported, since ACTs are considered new drugs. Other things to be reported are: increased frequency of a given observed reaction, all ADRs associated with drug-drug, drug-food or drug-food supplement interactions. In addition, ADRs from overdose or medication errors should be reported and when there is a lack of efficacy as well, if it has not been collected during resistance assessment.

- As most of health workers at peripheral level in Africa are not physician, it is very important to know how to recognize ADRs and diagnose them properly, the following WHO approach might be helpful in assessing possible drug related ADRs: [16]

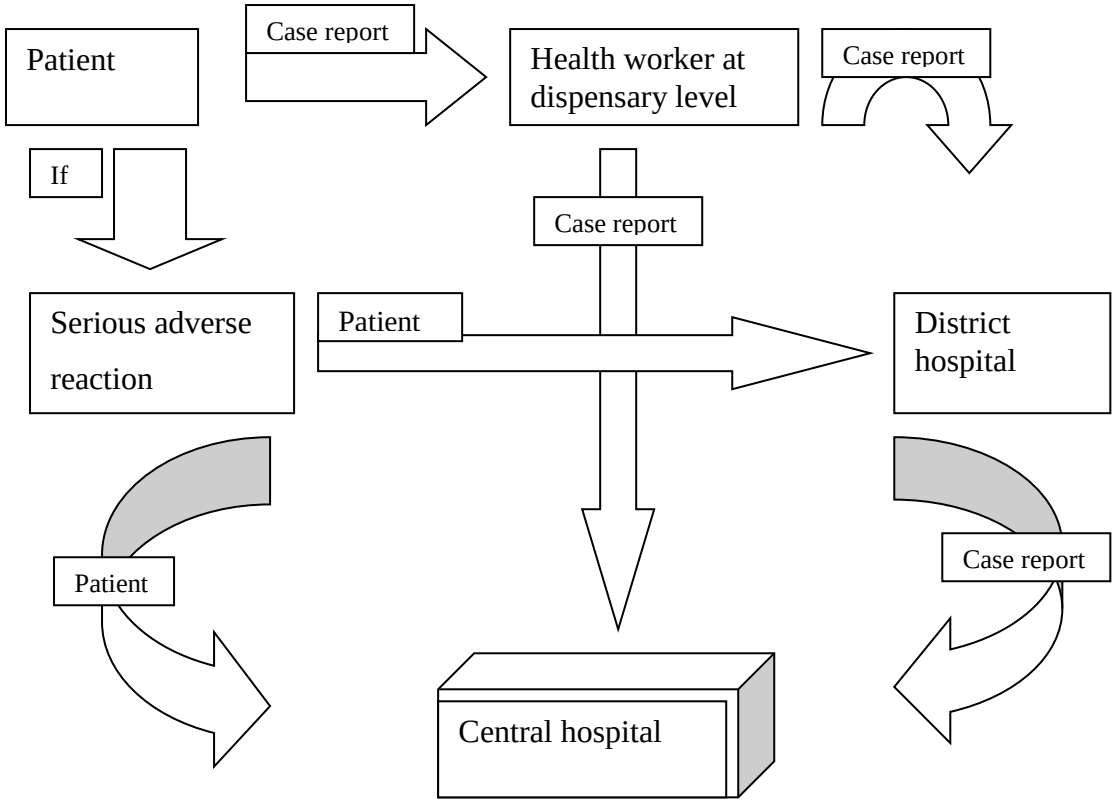
1. Ensure that the medicine actually was taken by the patient at the dose advised.
2. Verify that the onset of the ADRs was after the drug was taken.
3. Determine the time interval between the beginning of drug treatment and the onset of the event.
4. Evaluate the suspected ADRs after discontinuing or reducing the dose and monitor the patient status.
5. Analyze the alternative causes for the reaction (other medication or disease)
6. Use up-to-date literature and personal experience on drug and their ADRs and verify if there is previous reports on this reaction
7. Report any suspected ADR to the national ADRs centre.

- In the case of serious adverse reactions, health workers should send the patients immediately to the nearest hospital. Serious adverse reaction can be defined as reaction that requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformations, results in persistent or significant disability or incapacity, is life threatening or results in death. Also adverse reactions that require significant medical intervention to prevent one of these outcomes are considered as serious ones.

- All sections of the case report form should be filled in as completely as possible, using a separate form for each patient.

- The completed case report form should be sent to the national or the regional ADRs centre or to the central hospital.

The mechanical flow of the case report form from the dispensary to the central hospital or pharmacovigilance centre is explained in the following diagram:



Challenges:

Implementing pharmacovigilance and tools to monitor safety of ACTs in Africa would face many challenges.

The irrational use of ACTs and presence of a large number of untrained people who prescribe and dispense drugs, or illegal practitioners contribute to the difficulty of implementing drug safety monitoring.

Since ACTs have been newly introduced in Africa, drug safety monitoring is needed to be explained to the general public as the concept is new to them and could be misunderstood. The media could be used to promote this.

Also, we have to take into consideration the lack of materials and human resources in African countries. Therefore, the priority in most of these countries is for the prevention and control of communicable diseases rather than for setting up a system for monitoring safety of drugs.

Lack of necessary manpower is another challenge. Limited number of trained health professionals, physicians and pharmacists in Africa would impede the process of safety monitoring.

And finally the problem of under reporting, which is a common phenomenon in all countries. Correcting of under reporting is difficult because its extent is unknown and very variable.

Under reporting may delay signal detection and lead to underestimation of the problem size.

It is of great importance to know how to set up and run a pharmacovigilance centre in Africa and in every country as well.

Conclusion:

Monitoring safety of ACTs in Africa at the peripheral level can be done using simple techniques and tools. Designing comprehensive and simple case report form is essential step in the safety monitoring process. Checklist of adverse reactions of ACTs could be successful tool to promote reporting and facilitate this process especially for non physician health workers and this also can be promoted by attaching simple illustration for medical terms.

Another vital issue is the knowledge of all adverse reactions of ACTs in advance, since this knowledge will greatly promote the process of reporting and detecting adverse reactions.

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