Overview Of Pharmacovigilance Activities In Nigeria: A Renewed Call To Action.

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Abstract

Background

Modern medicines have modified the way in which diseases are managed and controlled.' However, these benefits continues to be challenged by the increasing evidence that adverse reactions to medicinesare a common, yet often preventable, cause ofillness, disability and even death.2 In some countries, adverse drug reactions (ADRs) rank among the top 10 leading causes of mortality.' Reducing the morbidity and mortality associated with ADRs require that mechanisms be put in place for evaluating and monitoring the safety of medicines. This means having in place a well-organized pharmacovigilance system. Pharmacovigilance-an umbrella term used to describe the processes for monitoring and evaluating ADRs - is akey component of effective drug regulation systems, clinical practice and public health programs.

The WHO defines Pharmacovigilance as the science and activities relating to the detection, understanding, assessment and prevention of adverse drug effects or any other possible drug - related problems. Over the years, its horizons has been expanded to accommodate herbals, traditional and complementary medicines, blood products, biological, medical devices and vaccines. Apart from adverse drug events or reactions, the scope of pharmacovigilance extends to medication errors, drug-drug interactions, lack of efficacy, counterfeit medicines, abuse and misuse of medicines. Others include use of medicines for unapproved indications, poisoning and drug related mortality.

RELEVANCE OF PHARMACOVIGILANCE

The process involved in the clinical development of medicines are restricted to controlled environment characterized by testing of medicines for short-term safety and efficacy on a limited number (500-5000) of carefully selected subjects prior to release for public consumption. This may conceal vital reactions associated with the use of newly developed medicines. It is therefore important that new medicines are monitored for their safety and effectiveness under real-life conditions post release. More information is generally needed about use in specific population groups such as the elderly, children and pregnant women.

Aims of Pharmacovigilance

- Improve patient care and safety in relation to the use of medicines
- Improve public health and safety in relation to the use of medicines
- Contribute to the assessment of medicines benefits and risks
- Contribute to the assessment of rational use and effectiveness (including cost-effectiveness) of medicines
- Promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public.

Adverse Drug Reactions

The principal purpose of pharmacovigilance is to evaluate adverse drug reactions (ADR). The WHO defines an ADR as a noxious and unintended response to a drug which occurs at doses normally used in humans for the prophylaxis, diagnosis or treatment of disease or for the modification of physiologic function.5Classical examples of ADRs are aplastic anaemia to chloramphenicol (grey-baby syndrome), Stevens-Johnson's syndrome to lamotrigine or penicillins, upper gastrointestinal haemorrhage to non-steroidal anti-inflammatory drugs, warfarin induced haemorrhage, rhabdomyolysis to statins and congenital malformations to thalidomide. A few instances of adverse drug reactions are shown pictorially in Figures 1 to 7.

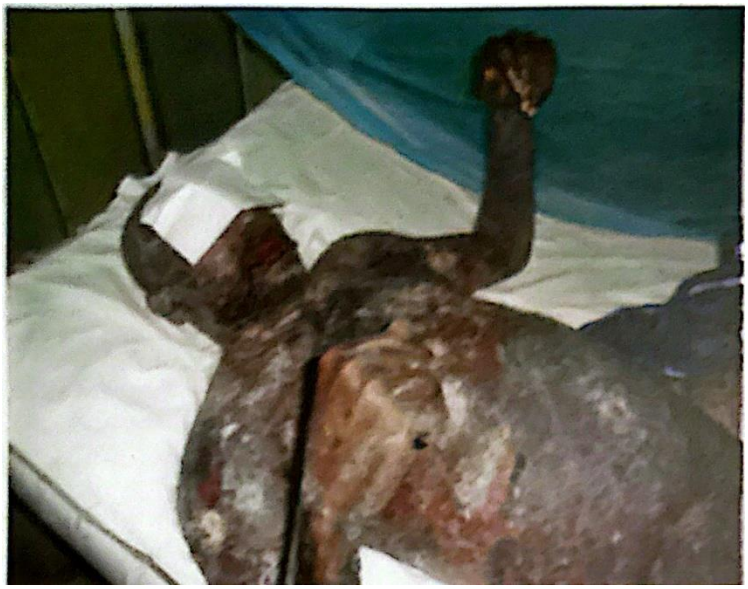

Figure 1: Penicillin induced Toxic Epidermal

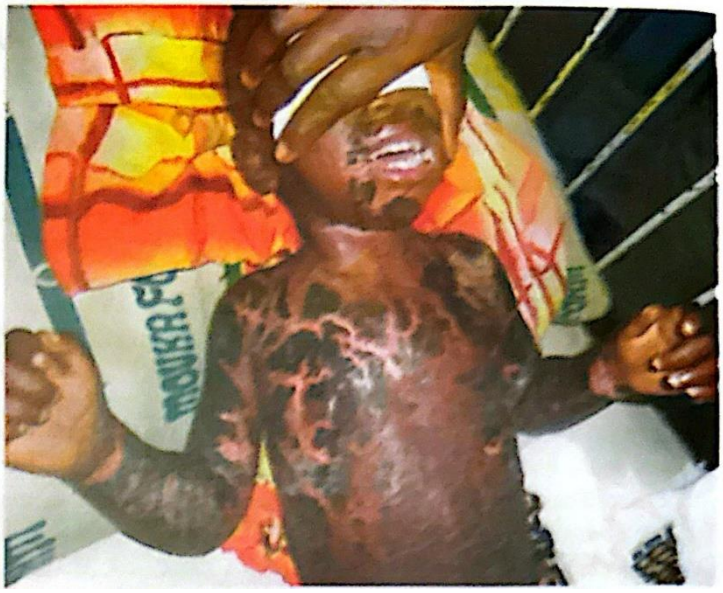

Figure 4: Herbal mixture induced cutaneous

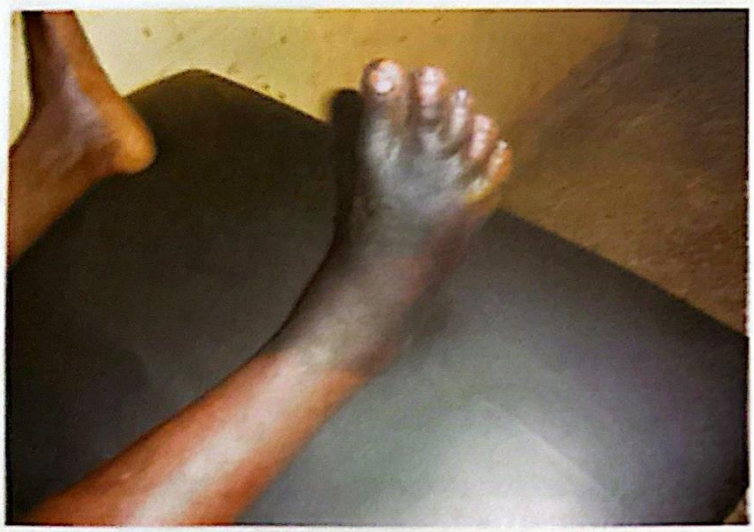

Figure 2: Warfarin induced

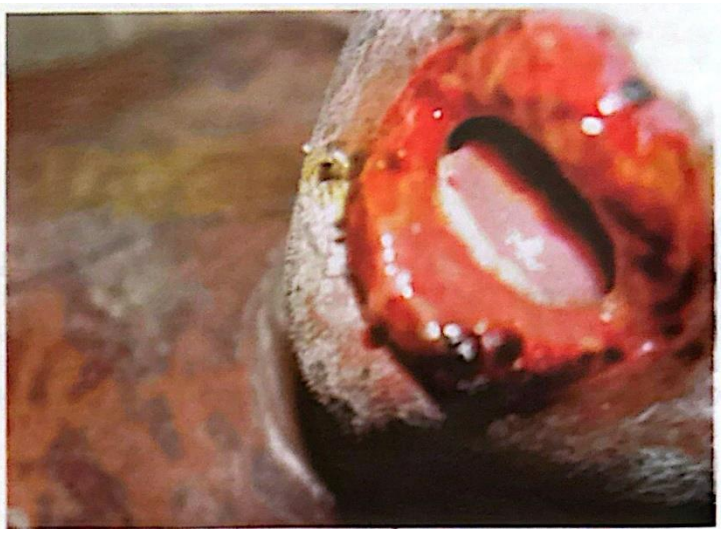

Figure 5:Carbamazepine induced Stevens-Johnson Syndrome.

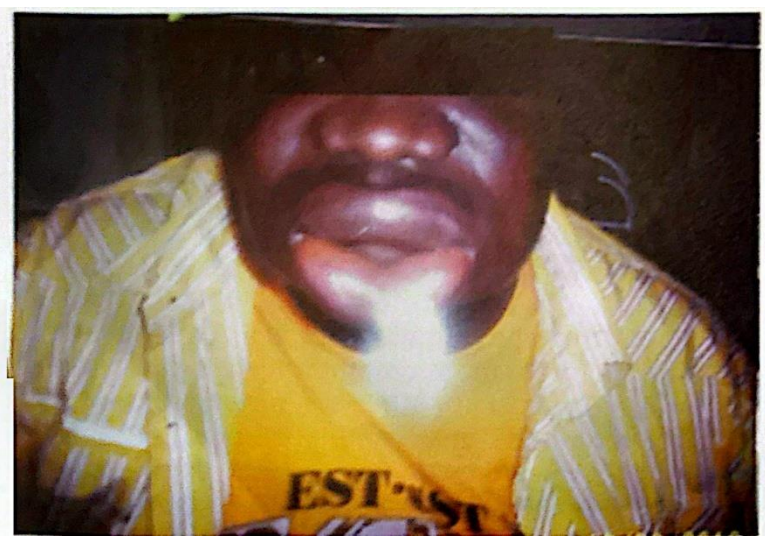

Figure3:Lisinopril-induced

Historical Perspective

The history of pharmacovigilance can be classified based on the time course of events in relation to the thalidomide tragedy of the 1960s. Accordingly, there are three main periods namely:Pre-thalidomide era,Thalidomide tragedy and Post-thalidomide era.

Pre-thalidomide era: Major events were in the USA and are chronicled as follows;

1848

The Lancet started collecting notifications of side effects after a death caused by anaesthesia

1906

US Federal Food and Drug Act requires that pharmaceuticals be "pure" and "free of any contamination"

1937

USA: 107 lethal cases after diethylene glycol was mistakenly used to solubilise sulphanilamides

1962 FDA required both safety & efficacy data

In 1952 in France, report of 100 lethal cases from use of skin preparations containing diethyl tin diodide.

Thalidomide era: Major events occurred in 1960 in Germany with reports of two grossly deformed infants born to mothers with history of thalidomide use during their antenatal period. By 1961,477 cases of phocomelia were documented in paediatric clinics across Germany. This prompted the recommendation of its

withdrawal to the regulatory authority. However, beauracratic delays of one month alone led to an additional 50-100 new cases! In the end, more than 4000 cases of phocomelia was documented.

Figure 6a: child survival of thalidomide.

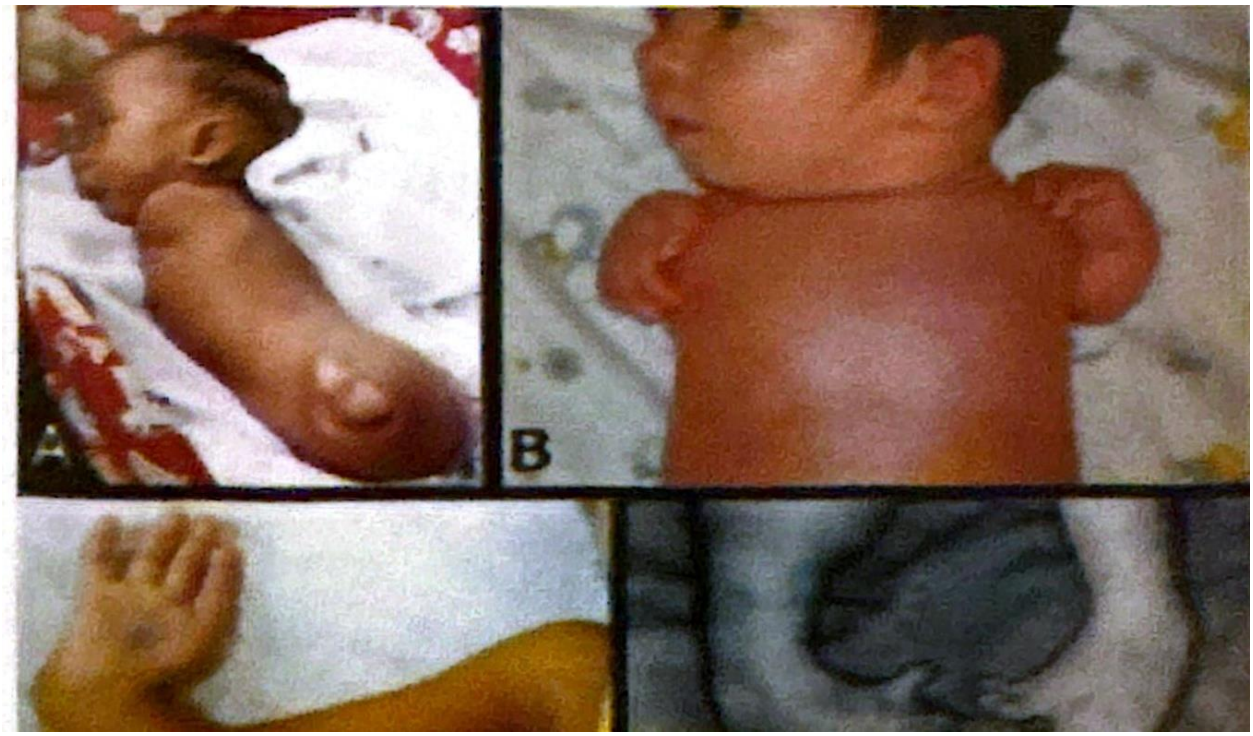

Figure 7: thalidomide birth defects.

Thalidomide (-N-Pthalimidoglutarimide) was developed in 1950 originally as a hypnosedative. It also has anti-inflammatory activity and inhibition of angiogenesis. The mechanism of action involves inhibition of the proinflammatory cytokine tumor necrosis factor alpha (TNF-ä) by enhancement of mRNAdegradation." It was marketed in 1956 in West Germany(UK 1958)as Contergan, Distaval, Kevadon, Talimol and Softenon and was widely used in the 1950s and early 1960s for the treatment of nausea and vomiting in pregnancy (hyperemesis gravidarum).However its use was limited by teratogenic effects necessitating its withdrawal from West German market in November 1961 (UK December,1961). Of the 10,000 infants with birth deformities in West Germany, only 5,000 survived. In the UK, of 600 malformed babies, 400 survived. The global estimate of total number of survivors was put at 10,000.01 Figure 3shows the trend of phocomelia in the years following introduction of thalidomide to the German pharma market.

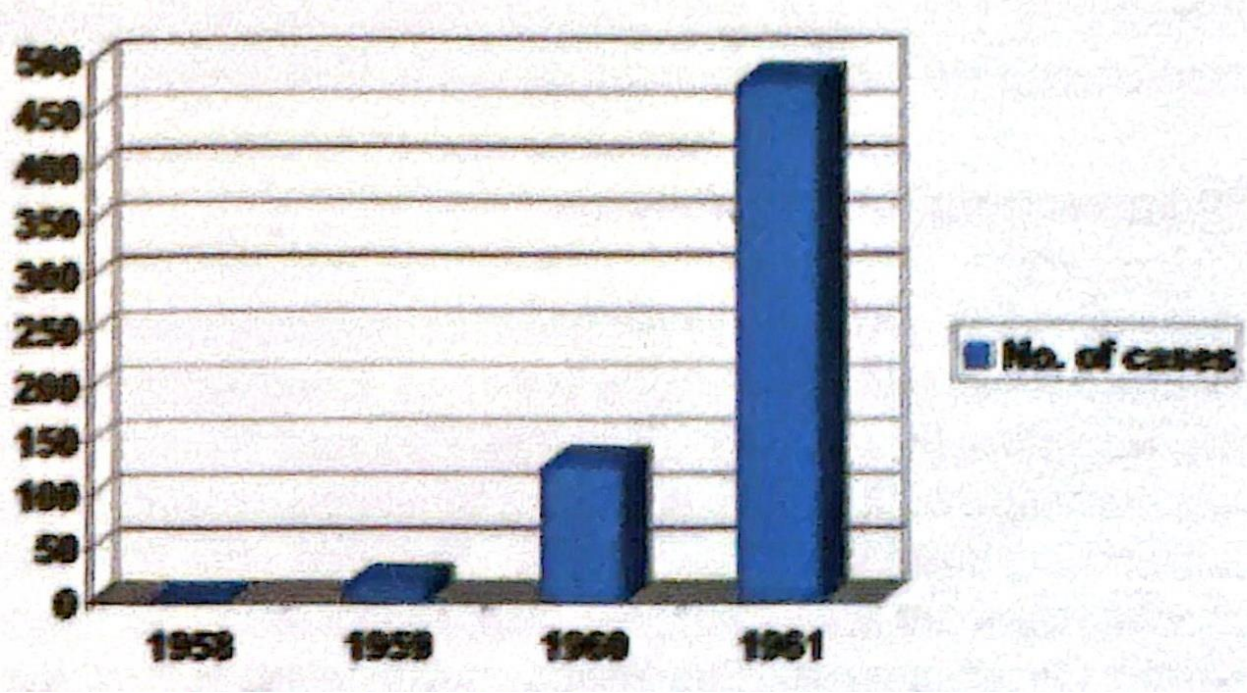

Figure 8: Trend of thalidomide birth defects

Post-thalidomide era: There began a reawakening to drug safety with emergence and strengthening of regulatory structures and control over drug use and development across countries. For example, in the UK, this led to the introduction in 1963 of the Committee on the safety of drugs; the yellow card system in 1964; and ultimately the Committee on the Safety of Medicines in 1965 by an act of parliament (Medicines Act of 1965) that prioritize safety, quality and efficacy requirements before licensing of medicines for use. This was promptly adopted by the European Union under the EC directive 6565 of 1965and the Kefauver Harris Amendmentin the US,11.12 In 1968, the WHO launched a program for International Drug Monitoring in a global collaborative effort to coordinate medicine safety and control. In Nigeria, efforts at pharmacovigilance only began in the 80s and 90s with initial unsustained efforts notably in the University of Benin Teaching Hospital (UBTH) and Ahmadu Bello University Teaching Hospital (ABUTH)in Benin City and Zaria respectively." Notable achievements then includes the one-month long training of a Federal Ministry of Health Staff at Upsalla Monitoring Committee in Sweden in 1981 with further training of NAFDAC staffs in 2003.

Following application in November 2003, Nigeria was granted associate membership of the International Drug Monitoring Program by the WHO in December 2003.Following the establishment of the National Pharmacovigilance Center in 2004, Nigeria was admitted as the 74" member of the WHO Drug Safety Monitoring Program. Since then, Nigeria has recorded significant milestone accomplishment in pharmacovigilance.

Some notable medicine related problems in Nigeria includes: The chloroquine disaster in Enugu in 1989where poorly compounded chloroquine syrup killed several children in University of Enugu Teaching Hospital (UNTH); the paracetamol tragedy of 1990 in Jos and Ibadan that involved the death of over 109 children, due to toxic ethylene glycol solvent; and most recent is the "my pikin" tragedy of 2000 that also involved the use of ethylene glycol in teething powder. Others were the anesthetic failure reported with the use of substandard epinephrine and suxamethonium during open heart surgery in 2003 and the severe anaphylaxis to locally manufactured intravenous infusions in 2002-2004.

Pharmacovigilance Systems

Collaboration among key partners in pharmacovigilance is vital if the future challenges are to be surmounted and if the discipline is to continue to develop and flourish. The key partners include government, industry, hospitals and academia, health professionals, patients, medical and pharmaceutical associations, the media and the World Health Organization. The WHO coordinates activities of drug monitoring together with its collaborating center in Upsalla, Sweden. The collaborating center is responsible for maintaining the global ADR database known as the Vigibase. The major processes of the pharmacovigilance system are data collection, data analysis and reporting. This information is then communicated to the national pharmacovigilance center where the information is interpreted for onward transmission to the WHO program for international drug monitoring at Upsalla, Sweden."

CONCLUSION

Forty years of pharmacovigilance efforts in Nigeria has led to sustained public enlightenment in the beneficial and adverse effects of medicines particularly amongst health practitioners and patients alike. This success story is however tinted by a rising trend in drug related morbidities and mortality. Hitherto absence of a comprehensive drug policy have not helped matters, as is lack of a united front by health practitioners and managers. Clearly, more work needs to be done, and stakeholders must close ranks to mitigate this scourge which has remained the third commonest cause of death due to non communicable diseases behind heart diseases, cancer and accidents.

This article is therefore an effort to further stimulate interest in the subject with a view to getting all on board to strengthen pharmacovigilance in Nigeria's health care space.

REFERENCES

1. Castro-Borrero,W.,Graves,D.,Frohman,T.C.,Flores, A. B., Hardeman, P., Logan, D.,Frohman,E.M.(2012). Current and emerging therapies in multiple sclerosis: a systematic review. Therapeutic Advances in Neurological Disorders,5(4),205-20http://doi.org/10.1177/1756285612450936

2. Pirmohamed, M., & Park,B.K.(2003).Adverse drug reactions: Back to the future. In British Journal of Clinical Pharmacology (Vol. 55, pp.486-492).http://doi.org/10.1046/j.1365-2125.2003.01847.x

3. Lazarou, J., Pomeranz, B. H., & Corey, P.N.(1998). Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA : The Journal of the American Medical Association, 279(15),1200-1205http://doi.org/10.1001/jama.279.15.1200

4. Edwards, I. R. (2012). Pharmacovigilance.British Journal of Clinical Pharmacology.http://doi.org/10.1111/j.1365-2125.2012.04249.x

5. World Health Organisation. (1972). Definitions by WHO.

6. Nirmal, S. A., Pal, S. C., Mandal, S. C., &Mandal, S. C. (2014). Pharmacovigilance of herbal medicines. Pharma Times, 46(10),19-22.http://doi.org/10.3233/JRS-150643

7. Durand,D.,Grene-Lerouge,N.,Cardona,F.,&Maison, P. (2014). [Pharmacovigilance and medication errors]. Soins,(784), 37-39.Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24839683

8. Friedman,L.M.,Furberg,C.D.,& Demets,D.L.(2010).Fundamentals of clinical trials.http://doi.org/10.1007/978-1-4419-1586-3

9. Paravar, T., & Lee, D. J. (2008). Thalidomide:mechanisms of action.International Reviews of Immunology, 27(3), 111135.http://doi.org/792566355[pii] 10.1080/0883010801911339

10. Botting, J. (2002). The history of thalidomide.Drug News & Perspectives, 15(9), 604.http://doi.org/10.1358/dnp.2002.15.9.840066

11. Kim,J. H., & Scialli, A. R. (2011). Thalidomide:The Tragedy of Birth Defects and the Effective Treatment of Disease. Toxicological Sciences,122(1),16.http://doi.org/10.1093/toxsci/kfr088

12. Tantibanchachai, B. (2000). US Regulatory Response to Thalidomide (1950-2000). In Embryo Project (pp.17).

13. Isah,A. O., Pal, S. N., Olsson, S., Dodoo, A., &Bencheikh, R. S. (2012). Specific features of medicines safety and pharmacovigilance in Africa, Therapeutic

Advances in Drug Safety,3(1),
2534.http://doi.org/10.1177/2042098611425695

14. Isah, A. O. (2013). Drug safety in emerging countriesa perspective from nigeria. Clinical
Therapeutics,35(8),e118.http://doi.org/10.1016/j.clinthera.2013.07.365

15. Opadeyi, A., Fourrier-Réglat, A., & Isah,A.O.(2016). Pharmacovigilance in Nigeria: An Overview. Pharmaceutical Medicine, 30(2),8794.
http://doi.org/10.1007/s40290-015-0133-3

16. WHO. (2004). Pharmacovigilance: ensuring the safe use of medicines. World Health.Retrieved from
http://pvtoolkit.org/toolkit/readers/pv_ensuring_safe_medicine_use.pdf

17. Olson, C. (2012). Pharmaceutical Management:
Pharmacovigilance.Managemnet Sciences for Health.http://apps.who.int
/medicinedocs /documents/s19612en/s19612en.pdf