International Journal of Pharmaceutical Science Invention
ISSN (Online): 2319 – 6718, ISSN (Print): 2319 – 670X
www.ijpsi.org Volume 2 Issue 1 ǁ January 2013 ǁ PP.05-11

Spontaneous reporting of paediatric adverse drug reactions in a Nigerian tertiary health centre – any relationship to severity?

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ABSTRACT: *Nigeria is the most populous country in Africa but little information exists about Adverse Drug reactions (ADRs) in children. This study investigated the spontaneous reporting of paediatric ADRs by health workers in a tertiary hospital. Reports about ADRs received by the pharmacovigilance unit of Ahmadu Bello University Teaching Hospital, Zaria from 2008 to 2012 were analyzed. Only 36(6.9%) of522 reports were of children. Doctors made 22(61.1%) reports, pharmacists 13(36.1%) and nurses 1(2.8 %). ADRs affected mainly kidneys and mucoepithelial surfaces. Nineteen (52.8%) ADRs were severe. Commonest drugs implicated were "My pikin" [an over-the-counter teething mixture in 18(50%)] cases, antibiotics 8(22.2%) and antimalarials 3(8.3%). There were no reports about antituberculous drugs or traditional medications. Only 5(0.06%) of 7,702admittedchildren were reported to develop ADRs. Sixteen (44.4%) children died (after taking "My pikin"). Following reports about "My pikin", the National Agency for Food and Drug Administration and Control issued a public alert withdrawing its use, Thus reporting helped prevent fatalities. Reporting of paediatric ADRs was poor unless the ADR was severe. Health workers must be sensitized to report allADRs irrespective of severity. Research is needed into the effect of training different types of health workers including informal health workers.*

Keywords— *Adverse Drug reactions, Africa, Children, Health workers, Nigeria.*

I. INTRODUCTION

Adverse Drug reactions (ADRs) are a major cause of morbidity and mortality worldwide and lead to increased healthcare costs, decreased adherence to treatment and loss of confidence in health systems [1-3]. Children are more vulnerable to ADRs than adults and may develop permanent disability or die as a result of them [3-6]. Thus it is vital that they are monitored for ADRs. Spontaneous reporting of ADRs by health workers is an important aspect of monitoring safety of medicines as the health workers are able to observe patients' response to medicines. However, there is limited information about ADRs in children from developing countries especially sub Saharan Africa [2, 6]. Most studies about paediatric ADRs originate from North America and Europe where disease patterns, drug usage and population characteristics differ from those of developing countries [2-6].

Nigeria is the most populous country in Africa and has a large emerging pharmaceutical market [2]. Efforts by the government to establish a medicine monitoring program had previously met with little successdue to a lack of awareness and consensus among stakeholders about the importance of monitoring ADRs [2]. In 2004, the Federal government, recognizing the need for efficient pharmacovigilance established the National PharmacovigilanceCentre (NPC). The aim of the NPC is to create awareness of and encourage reporting of ADRs. Health workers all over the country were sensitized through a series of workshops and encouraged to send reports to hospitals and zonal PV centres. These reports are sent to a central coordinating body in the National Agency for Food and Drug Administration and Control (NAFDAC). However by early 2012, the NPC had received only 10,000 reports which translates to approximately eight reports per million population per year [7]. This is far below the WHO international target of 100 per million per country [2]. Further, there are few reports of paediatric ADR sdespite widespread use of medicines in children. The aim of this study was to investigate the spontaneous reporting of paediatric ADRs by health workers in a tertiary hospital in Northern Nigeria. Specifically, to determine the type and severity of ADRs reported, drugs suspected of causing ADRs and the type of person making the report. It is hoped that this information would add to knowledge about ADRs and contribute to improved drug safety in children.

II. MATERIALS AND METHODS

2.1 Background

The study was conducted in Ahmadu Bello University Teaching Hospital Zaria (ABUTH), a tertiary health centre situated in Kaduna state, Northern Nigeria, 280 kilometres from Abuja, the Federal capital.

ABUTH is a 500 bedgovernment hospital providing clinical care for Kaduna and the surrounding states. Paediatric cases referred to ABUTH include neonates, children needing intensive care, nephrology, oncology, neurology, haematology and surgery. There is also a clinic specializing in treatment of HIV positive adults and children and prevention of mother-to-child transmission of HIV. The hospital is a training centre for doctors, pharmacists, nurses and other health workers and is centre for research. The hospital pharmacovigilance unit was established in 2008 and workshops were held to sensitize health workers about spontaneous reporting of ADRs.

2.2 Methodology

This is a retrospective auditof reports of ADRs received by the pharmacovigilance unit (PV) in children aged less than 18 years from2008 to 2012.Clinical records of patients (where available) were also reviewed. Reports were recorded on standard yellow reporting forms supplied by the National Pharmacovigilance Centre (NPC) of Nigeria.Data extracted included age and gender of the patient, comorbid illnesses, and the profession of the person making the report. Other information included details of the ADR, information about medicines suspected to have caused the ADR (doses given, reason for use, route and frequency of administration) and concomitant medicines used.

2.3 Data Analysis

Data was analyzed using SPSS version 16. Frequency distributions of the different variables were calculated and cross tabulations done. Variables analyzed included characteristics of the children, the ADRs and drugs suspected to have caused the ADRs. Suspect drugs were classified into therapeutic groups. Rates of ADR related admissions and ADR occurrence during hospital stay were calculated as percentage of the paediatric in-patient population during the study period. Patient outcome (as recorded on the yellow reporting forms) was classified as recovered fully, recovered with disability, congenital abnormality, life threatening, death and others. The severity of ADRs was assessed using the modified scale by Hartwig [8] outlined below;
Mild: Self-limiting reactions which resolved over time without treatment and did not contribute to prolongation of length of admission.

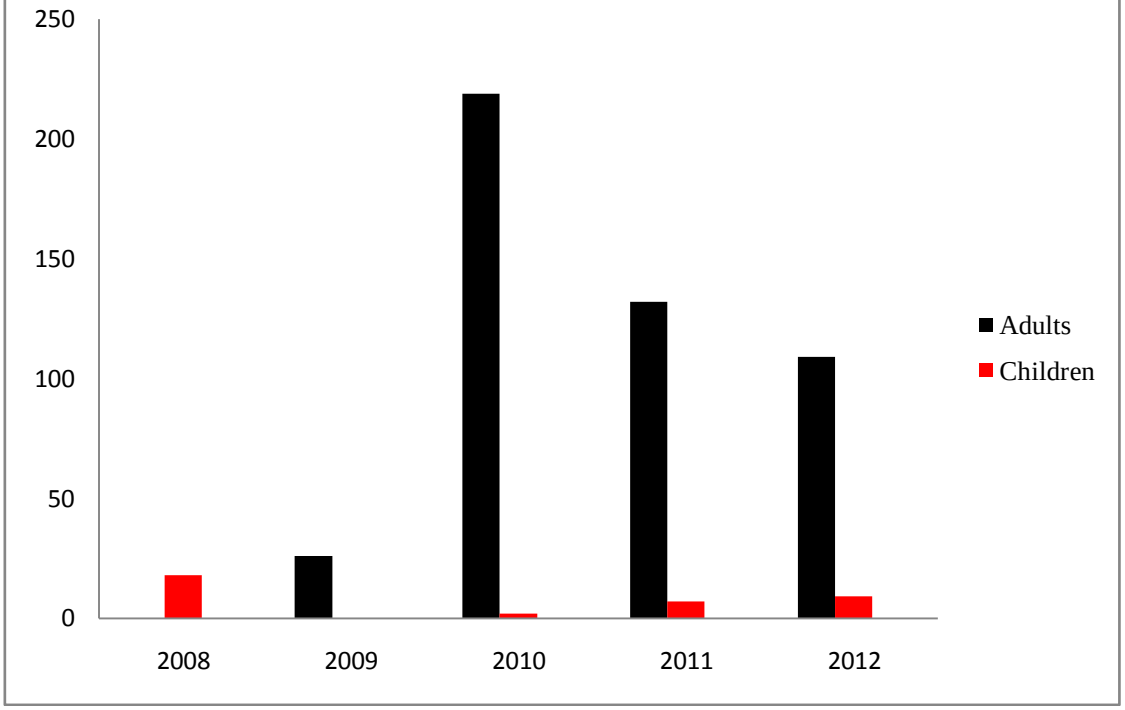
Moderate: reactions that required therapeutic intervention and hospitalization prolonged by 1 day but resolved in less than 24 hours or change in drug therapy or specific treatment to prevent a further outcome.
Severe: reactions that were life threatening, producing disability and those that prolonged hospital stay or led to hospitalization, required intensive medical care, or led to the death of the patient.

III. RESULTS

3.1 Reports Received

The PV unit received a total of 522 reports during the study period but only 36(6.9%) were of ADRs in children. Most 18(52.9%) paediatric ADRs were reported in 2008, after which the number decreased dramatically and then decreased (Fig 1). There were 7,702 children admitted during the period but only 5(0.06%) were reported to have developed ADRs during their hospital stay while ADRs were the cause of admission of 18(0.23%) children. The majority 17(94.4%) of the children admitted because of the ADRs were referred from other government hospitals or private hospitals.

FIG 1
Number of reported Adverse Drug Reactions in adults and children per year



3.2 Drugs Associated With adrs

Fourteen drugs were suspected to have caused the ADRs (TABLE 1). Two drugs had no NAFDAC number implying that they were not registered in the country and one otherdrug had expired. The greatest number of ADRs was associated with an over-the-counter teething mixture called "*My pikin*", composed of paracetamol and diphenhydramine hydrochloride. The drug was registered with NAFDAC and had been on sale for over 2 years. It was discovered reported that some batches had been contaminated with Diethylene glycol [9]. "*My pikin*" was the cause of almost all the severe ADRs.The other major groups of drugs associated with ADRs were antibiotics (most commonly ciproxin) and antimalarials (all Artemesinin Combination Therapy). There was one report of an ADR caused by an antiretroviral (Nevirapine), and another by a cytotoxic (Vincristine). There were no reports of ADRs caused by antituberculous drugs, anticonvulsants, or traditional medications. Reasons for using the drugs were– treatment of teething problems in 13(36.1%) children; infections-9(25%); prophylactic (prevention of teething problems and hyperuricaemia) - 6(16.7%); malaria - 3(8.3%); hypertension - 1(2.8%); tetanus -1(2.8%), cancer1(2.8%)and pain - 1(2.8%). Most 21(58.3%) drugs were not prescribed. Drugs were administered orally in 27(75%) patients, intravenously in 7(19.4%) and intramuscularly in 2(5.6%). In 2(5.6%) instances an overdose had been given and in 1(2.8%) a medication error occurred. Other medicines (ranging from 1 to 6 per patient) had been used concurrently by 20(55.6%) children (TABLE 2}. This included traditional medicines used by 2 children.

Table 1 Drugs Suspected To Be Have Caused Paediatric Adverse Drug Reactions

Suspect Drug	Number of affected children	% of cases n=34
Teething mixture	18	50.0
Antibiotics	8	22.2
Antimalarials	3	8.3
(*ACTs)	1	2.8
Antitetanus serum	1	2.8
Analgesics	1	2.8
Antineoplastic	1	2.8
Antiretrovirals	1	2.8
Antiemetics	1	2.8
Diuretics	1	2.8
Allopurinol		
TOTAL	36	100.00

***ACTs - Artemisinin based combination therapy**

Table 2 Concomittant Drugs Used

Suspect Drug	Number	% of cases n=54
Antibiotics	12	22.2
Vitamins	8	14.8
Analgesics	7	13
Intravenous fluids	7	13
Diuretics	5	9.3
Antimalarials	3	5.5
Traditional	2	3.7
medications	10	18.5
*Other		
TOTAL	54	100.00

(*Other consisted of digoxin, anticonvulsants, antihypertensives, Cytotoxics, antifungal agents, micronutrients and cough syrups.)

3.3 PATTERN OF ADRs

The children's ages ranged from 12 days to 16 years. Most 25(69.4%) were less than 5 years including one was a neonate. Slightly more ADRs were reported in male 20(55.6%) children. Comorbid illnesses were malnutrition -3(8.3%) children, acute kidney injury 2(5.5%), cancer 2(5.5%) and an unspecified thyroid condition in 1(2.8%) child. ADRs affected mainly the kidneys and mucoepithelial surfaces in 18(50%) and 10(27.8%) children respectively. Other manifestations are shown in TABLE 3. ADRs were assessed to be severe in 19(52.8%), moderate in 7(19.4%), mild in 6(16.7%) and could not be determined in 4(11.1%) cases. The ADRs lasted from a few hours to 9 days.

Table 3 Clinical Manifestations Of Adverse Drug Reactions

Types of Reaction	Number (%) n=48	Suspected Drugs
Acute kidney injury (anuria)	**18(37.5)**	***My Pikin* teething mixture**
Dermatological (Rashes/blisters/ burns/ Erythema/ Uticaria)	**16(33.3)**	**Ciprofloxacin Artemeter-Lumefantrine Antitetanus Serum - ATS Cotrimoxazole, Chloramphenicol Nevirapine, Vincristine Pentazocine**
Vomiting	**4(8.3)**	**Artesunate+Amodiaquine Ciprofloxacin Allopurinol**
Fever	**3(6.3)**	**Artesunate+Amodiaquine Ciprofloxacin Hydrochlothiazide +Amiloride**
Generalized body weakness	**2(4.2)**	**Artemeter-LumefantrineArtesunate+Amodiaquine**
Dyspnoea	**1(2.1)**	**Ceftriaxone**
Shivering	**1(2.1)**	**Ceftriaxone**
Hyperactivity	**1(2.1)**	**Hydrochlothiazide +Amiloride**
Excessive drowsiness	**1(2.1)**	**Promethazine**
Body swelling	**1(2.1)**	**Chloramphenicol**

3.4 PERSONS MAKING THE REPORT

All reports were made by health professionals – doctors in 22(61.1%) cases, pharmacists 11(36.1%) and a nurse in 1(2.8%). Doctors reported almost all 18 (94.7%) of the severe cases, 3(42.9%) of the moderate cases, and 1(16.7%) mild case. Pharmacists reported all grades of severity. Two 2(5.8%) reports were made by parents - a nurse and a doctor who reported mild reactions to drugs they had given their children.

3.5 ACTION TAKEN AND OUTCOME

The drug was discontinued in 28(77.8%) children and changed in 3.Hydrocortisone was given to 4 children, an antidote to one child and promethazine to another. In 5 cases, the action taken was not stated. Some of the children who developed acute kidney injury were dialyzed. Overall 13(36.1%) patients made a full recovery, 16(44.4%) died (those who ingested "*My pikin"*), 1(2.8%) child's outcome was reported as life threatening, another as on-going while the outcome of 8 patients was not recorded. Following reports received about the ADR associated with "*My pikin*"**,** NAFDAC issued a public alert stopping its use all over the country, closed down the facility manufacturing it and withdrew the drug from retail outlets, pharmacies and hospitals [10].

IV. DISCUSSION

ADRs were reported following use of various drugs but the number of spontaneous reports received was low (i.e. there was gross underreporting). Paediatric ADRs contributed less than 10% of all reports and were mainly of severe ADRs. ADRs affected chiefly the renal and dermatological systems and almost half of reported ADRs were fatal. The main reporters were doctors and pharmacists, with little or no input from other health care workers.

The majority of ADRs was caused by an over-the-counter drug contaminated with Diethylene glycol (DEG) a known nephrotoxin [9]. Because the ADR it caused was reported, the National Agency for Food and Drug Administration and Control took measures to safeguard the health of unaffected children [10].This illustrates the importance of spontaneous reports and of taking timely action about them. However response to ADRs can be limited by underreporting. Other studies about ADRs in Nigeria have also reported low rates of ADR reporting by health professionals especially of paediatric ADRs [5, 7, 11, 12] as opposed to much higher rates recorded from other parts of the world. Different reviews and studies found varying rates of ADRs among

children ranging from 1% to 179% to for ADRs occurrence during hospital stay, and less than 1% to 28% in children admitted because of ADRs [3, 4, 13-18]. However it is difficult to compare incidence of ADRs as rates vary greatly between studies and between countries because of differences in definition and classification of ADRs, methods and length of data collection [6]. Antibiotics and antimalarials were reported to be major causes of ADRs. This is expected as they are commonly used in the treatment of childhood illness and ADRs associated with them are widely reported [3-6, 13-18]. However it is surprisingly that there were few or no reports of ADRs caused by antituberculous drugs, anticonvulsants, antiretrovirals (ARVs) and cytotoxics which are commonly used in the hospital as it is a referral centre. Yet there are reports about ADRs caused by these drugs [4, 6, 14-17]. It is also of note that no reports were made of ADRs due to traditional herbal medications though they are often given to sick children in the community.

Dermatological symptoms were the second commonest group of manifestations. This is similar to findings of other studies [3-6, 13-18], including the WHO international centre (the Uppsala Monitoring Centre) which receives reports about ADRs from different parts of the world [19]. The percentage of severe reactions in this study was high but falls within the range of other reports (1% to 61%), but mortality was much higher than that usually reported (0.05to 50 5%)[3,4, 17-19]. However the mortality was similar to that reported during the worldwide epidemics of DEG poisoning [21,22].

The study was limited in that the likelihood of causation of ADRs by the drugs was not determined. It was also outside the scope to determine reasons for underreporting. It is possible that reports about ADRs may have been submitted to other departments e.g. ADRs caused by ARVs were probably reported to the specialist HIV clinic. A study in another Nigerian hospital found that nurses recorded ADR reports in their daily report book [11]. This may explain why few reports are made to PV units by nurses in this and other Nigerian studies. Underreporting occurs all over the world and is one of the drawbacks of spontaneous reporting [2, 5, 11, 13]. Yet because spontaneous reports remain one of the main methods of generating data about ADRs, efforts must be made to improve reporting. Measures which have proved successful are sensitization of health workers and training, use of morning reports as a forum for documenting ADRs as well as newsletters and reminders [2, 3, 8,20]. In this study, as in other studies doctors and pharmacists were the health personnel who most often reported ADRs. [2-5,11, 14,16] However other health workers who also have close contact with patients (e.g. Physiotherapists, social workers, adherence counsellors and health attendants) could also be trained to ask for and report ADRs. The effectiveness of using them would need further research. Health workers in other government and private hospitals should also be trained as patients were referred by them. It should be remembered that there is a large group of informal health providers (patent medicine sellers and traditional practitioners) who supply children with drugs [23]. Consideration should be given including them in sensitization and training programs as has been done with other initiatives like the Roll Back Malaria program [24]. Doing this might improve reporting of ADRs caused by drugs commonly used in the community like over-the-counter medicines and traditional medications.

It is recommended that sensitization and training should be carried out among health workers. Training should include all cadres of health staff that have close contact with patients and could be extended to health providers in the informal health sectors. Training should stress the importance of reporting *all* types of ADRs, not just severe ones. Future research should assess the effectiveness of ADR reporting by different groups of health workers.

V. CONCLUSION

Hospital based reports can identify ADRs in children which are caused by both prescription and non-prescription drugs. However there is underreporting of paediatric ADRs unless they are severe. Thus efforts need to be made to improve reporting through sensitizing and training of workers in both the formal and informal health sectors. Training should stress the importance of reporting all suspected ADRs irrespective of severity. Future research must examine the effect of training different groups of healthcare providers. This is important because it has the potential to save children's lives.

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