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Adverse Drug Reaction in Children: A Review of Management

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Abstract: With a better understanding of the profiles of the adverse effects of different drugs taken by a patient, prompt recognition and reporting will go a long way in minimizing the incidence of Adverse Drug Reactions (ADRs). A high index of suspicion is required as ADRs may sometimes mimic some diseases. Any organ system may be affected; the most commonly affected organ systems are the skin and appendages, manifesting mostly as morbilliform eruptions. Stevens-Johnson syndrome and toxic epidermal necrolysis are the most severe dermatologic manifestations of ADRs. Good drug history is an essential part of any clinical assessment and it is very important to ask about prescription and non-prescription drugs. The non-prescription drugs should include illicit drugs (in adolescent children), herbal and homeopathic medicines. Laboratory diagnostic tests play no significant role in the diagnosis of ADRs and when required is guided by the suspected pathologic mechanism. Primary preventions of ADRs is the preferred option; there are however therapeutic approaches to established cases. Even though genetics have been known for so long to be involved in the development of ADRs, there is, as yet, no reliable means of predicting the occurrence of ADRs in susceptible children. Not until there is a breakthrough in this area, children will continue to suffer this major problem of drug therapy.

Key words: Adverse drug reactions, children, manifestation, evaluation, prevention, therapy

INTRODUCTION

Adverse Drug Reactions (ADRs) are common. They are global problems of major and important concern in health care, confronting primary care physicians on daily basis (Dorman *et al.*, 2000; Pirmohamed and Park, 2003). All drugs have the tendency to produce adverse reactions; however, the tendency is higher with some drugs in children. Antibiotics (Jonville-Bera *et al.*, 2002; Weiss *et al.*, 2002; Pirmohamed, 2005; Oliver *et al.*, 2005); glucocorticoids, tuberculostatics and immunosuppressive agents (Weiss *et al.*, 2002); anticonvulsants and vaccines (Clarkson *et al.*, 2001; Kemp *et al.*, 2006; Le *et al.*, 2006) are few of the reported drugs producing ADRs in children. Cutaneous drug allergy is a common manifestation of adverse drug reaction and poses problem to the treating physician. The reaction rate varies from 0 to 8% and is highest for antibiotics (Oliver *et al.*, 2005). Other reported adverse reactions to antibiotics include maculopapular rashes and diarrhoea from ceftriaxone and amoxicillin; vancomycin-induced shock and liver enzymes

derangement from fosfomycin. In Nigeria, high rate of antibiotics prescription and misuse and polypharmacy have been reported in both the urban and rural health facilities (Olayemi *et al.*, 2005; Oshikoya *et al.*, 2006; Nwolisa *et al.*, 2006), thus placing Nigerian children at a high risk of ADRs.

Managing ADRs, when recognized early, may not be a problem to the physicians but recognizing when drugs may be culprits in adverse outcomes and ADRs is a serious problem amongst physicians and it is of concern. Often times, they are interpreted as another symptom of illness, requiring treatment with more drugs. Management of adverse drug reactions in children is not significantly different from the management in adults except for the subtle differences in their risk factors. In this review, the manipulative risk factors that could be used to prevent ADRs are discussed with emphasis on the ones that are peculiar to children.

The key to appropriate management are prevention, prompt recognition and early institution of supportive therapy-indeed, this may be life-saving. In addition, this

review also aimed at discussing the appropriate ways to recognize and treat adverse drug reactions.

CLINICAL MANIFESTATION

Adverse drug reactions are great mimics of some diseases (Routledge, 1998) and may present, like in adults, with involvement of any organ system, including systemic reactions such as anaphylaxis. Multiple ADRs can be shown to one or more drugs and may cause a variety of symptoms and changes in laboratory values. Drug reactions may be caused by the metabolic and immunologic response of the skin (Reid and Casillas, 2003). The most commonly affected organ systems involved in an ADR are the skin and appendages, followed by the gastrointestinal system: the reaction may also be generalized (Morales-Olivas *et al.*, 2002; Schirm *et al.*, 2004; Fattahi *et al.*, 2005). Involvement of other organ system is less common. The most common dermatologic manifestation of ADRs is morbilliform eruptions (Reid and Casillas, 2003; Morales-Olivas *et al.*, 2002; Martinez-Mir *et al.*, 1999). Typically, an erythematous, maculopapular lesion appears within one to three weeks after drug exposure, originates from the trunk and eventually spreads to the limbs. Urticaria is typically a manifestation of a truly allergic, type I reaction but it may appear with type III or pseudo allergic reactions as well. Severe non-allergic, hypersensitivity cutaneous reactions (i.e., erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis) represent bullous skin diseases that require prompt recognition because of their association with significant morbidity and mortality. Eczematous lesions are most commonly associated with topical medications and usually represent contact dermatitis, which is classified as type IV reaction to a drug exposure.

The general criteria for the diagnosis of allergic ADRs include consistency of the patient's symptomatology with an immunologic drug reaction; administration of a known drug capable of causing allergy; temporal sequence of drug administration and appearance of symptoms consistent with a drug reaction; exclusion of other causes of allergic symptoms; and supportive laboratory data in keeping with immunologic mechanism to explain the drug reaction.

CLINICAL EVALUATION

Evaluation of any patient that developed adverse drug reaction is the same irrespective of the age or gender. Evaluation must begin with a precise and detailed

history (Vervloet and Durham, 1998; Pirmohamed and Park, 1999), including clinical symptoms and their timing and duration in relation to drug exposure. The initial history should include a recording of all prescription and non prescription drugs, especially illicit drugs (in adolescents), herbal and homeopathic medicines (Pirmohamed, 2005) taken within the last month, including dates of administration and dosage. Unless the patient has been previously sensitized to a drug, the interval between initiation of therapy and the onset of reaction is rarely less than one week or more than one month. Patients or their parents should be asked about previous drug exposures and reactions.

Physical examination may provide further information to support ADRs. A modest initial step is an evaluation of signs and symptoms of an immediate generalized reaction, because this is the most severe life-threatening form of ADRs (Reid and Casillas, 2003).

A detailed skin examination is essential to distinguish between the various types of skin lesions, because this may provide substantial clues to the possible immune-mediated mechanism of the drug reaction. A classic drug rash is the most common skin manifestation. It presents as an exanthematous or morbilliform eruption originating on the trunk; urticaria is IgE antibody-mediated and results from direct mast cell stimulation; purpura is from vasculitis or drug-induced thrombocytopenia; maculopapular lesions with distribution on the fingers, toes, or soles may result from serum sickness; eczematous rash in sun-exposed areas from Photoallergic reaction; Solitary circumscribed erythematous raised lesion from fixed drug eruption; and papulovesicular, scaly lesion from contact dermatitis. Fever is a common manifestation of drug allergy and should be remembered in children with fever of unknown origin.

LABORATORY EVALUATION

Laboratory diagnostic tests are not helpful in the diagnosis of ADRs. However, they are useful in evaluating haematological, biochemical or immunologic markers that confirm activation of a particular immunopathologic pathway to explain the suspected adverse drug effect. Laboratory evaluation is guided by the suspected pathologic mechanism (Ten Holder *et al.*, 2002).

THERAPY

The most ideal way to manage ADRs is to prevent its occurrence in predictable cases. However, if it has occurred, therapeutic measures become necessary.

Preventive measures: (Pirmohamed, 2005; British National Formulary, 2004; MCA and CSM, 2002).

Never use any drug unless there is a good indication: Drugs are often prescribed because both doctors and patients have to view prescriptions as the essential outcome of the visit (Fraser, 1985). Majority of doctor-patient encounters in general practice in Ireland resulted in a prescription for drug treatment (Pont *et al.*, 2004) which ideally is not supposed to be so. Prescribing non-indicated drugs is not only irrational but places the patient at risk for developing ADRs.

Always anticipate adverse reactions when new drugs are used: Have a high index of suspicion that an ADR may have occurred if untoward effects are seen with recently initiated or changed drug therapy. Many years back in Nigeria, *Streptococcus pneumoniae* causing meningitis in children was sensitive to ampicillin; its use has been associated with morbilliform rash that was detected early as a result of anticipation of this adverse reaction (Njokanma *et al.*, 1994b).

Take a good medication history: Allergy and idiosyncrasy are important cause of ADRs. Ask if the person had previous reactions. There may also be a family history of ADRs that share a common characteristic indicative of an inherited disorder. Genetic factors are important contributors to the incidence and severity of ADRs (Impicciatore, 2003; Jaja, 2003a,b, Kling, 2003, Lutucuta *et al.*, 2001; Maitland-van der Zee *et al.*, 2002). Infact it has been reported to contribute to an estimated 50% of ADRs (Classen *et al.*, 1997) and account for 20-95% of drug response variability (Kalow *et al.*, 1998).

The knowledge that specific gene mutations can cause ADRs is not new. What is relatively new is the ability now to interrogate on a genome wide scale the genetic determinants of ADRs especially in children.

Ask if the person is already taking other drugs including self-medication and herbal drugs; interactions may occur: ADRs due to drug interactions may be due to drug effects on metabolic pathways, enzyme induction (increased metabolism) or enzyme inhibition (decreased drug clearance). In the Chinese population, besides genetic differences, environmental factors such as concomitant use of traditional Chinese medicine and allopathic medication may influence the perceived incidence of ADRs (Macpherson *et al.*, 2001; Chen *et al.*, 2001; Bensoussan *et al.*, 2000). Little is known about the role of herbal medication in the development of ADRs, however it has just been reported in the United Kingdom

(UK) that some herbal medicines produced in Africa, marketed in the U.K, are liable to produce ADRs (MHRA, 2005). Since the use of herbal medicine is prevalent in Africa it is not impossible that its concomitant use is contributory to the risk of developing ADRs as hypothesized in the Chinese.

Age and hepatic or renal impairment may alter the metabolism or excretion of drugs, so that much smaller doses may be needed: Infants and very young children are at high risk of developing adverse drug reactions than adults because their capacity to metabolize drugs is not fully developed (Krammer *et al.*, 1985; Knight, 1994). Genetic factors may also be responsible for variations in metabolism. As a result of high resistance of the organisms causing neonatal septicaemia in Nigeria to the older antibiotics, newer antibiotics are used which are not totally free of adverse effects (Njokanma *et al.*, 1994a).

The potential for ADRs increases with the number of medications prescribed: There is a significant association between the numbers of medications received by children and the risk of ADRs. The higher the number of drugs consumed the higher the prevalence of ADRs (Fattahi *et al.*, 2005). It also has been noted that patients with an ADR were taking significantly more medications than were patients without an ADR (Fattahi *et al.*, 2005; Wilkins, 2002). Polypharmacy has been shown to be an important factor that predisposes patients to ADRs (Impicciatore *et al.*, 2001; Pirmohamed, 2005; Oshikoya *et al.*, 2006) and is similarly found in the adult patients (Fattinger *et al.*, 2000). Therefore prescribe as few drugs as possible and give clear instructions to children or their parents who are likely to misunderstand complicated instructions.

If serious adverse events are liable to occur warn the patient: In one US study on adult patients, two thirds of patients reported the desire to be informed of all possible adverse effects of their medications, regardless of how uncommon they were (Bongard *et al.*, 2002). In this same study, most patients felt that physicians were never justified in withholding information from patients. Patients' knowledge of the risks associated with their medications is frequently inaccurate and at best inconsistent. Patients feel they should be informed of potential ADRs regardless of how infrequently they occur (Ziegler *et al.*, 2001). The doctor-patient relationship is less likely to be adversely affected in the event of a serious ADR if the patient is aware of the potential for that particular ADR. Increased patient education may reduce the incidence of ADRs (Murray *et al.*, 2006).

Always remember that ADRs can mimic other diseases:

Therefore consider ADRs as a strong differential in a child with fever of unknown origin

Preventing medication errors: Pediatrics pose a unique set of risks of medication errors, predominantly because of the need for dosage calculations, which are individually based on the patient's weight, age or body surface area and their condition. For example, Selbst *et al.* (1990) reported a case of a 10 month old baby who received a 10 times overdose of intravenous theophylline as a result of drug dosage miscalculation.

Various useful suggestions to prevent medication errors in children have been advised by the American Academy of Pediatrics Committee on Drugs and Committee on Hospital Cares (Stucky, 2003), Institute for Safe Medication Practices (ISMP) and Pediatric Pharmacy Advocacy Group (PPAG) (Levine *et al.*, 2001). In addition, Walsh *et al.* (2005) has also reported on strategies that are currently used to avoid pediatric medication errors; these include the use of computerized physician order entry, changing doctor's habits in prescribing, pharmacy dispensing and nurse administration. In addition, preventing medication errors from drug dosage calculation and hospital environment have been highlighted by Wong and Ghaleb (2006).

Report all cases of ADRs to the Medicines Health care Products Regulatory Agency in the country where it was experienced on a yellow card as per reporting criteria:

Until now, the basis of drug safety monitoring has largely remained spontaneous ADR reporting. This method is, nevertheless, limited mainly by under reporting (Fletcher, 1991; Institute of Medicine (US), 2000), which does not allow medical care assessment of ADRs' real impact. Most hospitals identify an ADR by spontaneous or stimulated reporting. Another approach is computerized detection (Cox *et al.*, 2001; Bates *et al.*, 2003; Couffignal *et al.*, 2000; Bagheri *et al.*, 2000; Dugue *et al.*, 2004).

No source of ADR identification (spontaneous reporting or computerized detection) is really exhaustive. Nevertheless, simultaneous use of these sources had been shown to improve detection of ADRs (Weiss *et al.*, 2002; Bäckström *et al.*, 2004; Dormann *et al.*, 2000). Capture-recapture is a newly reported method of estimating the real impact of ADRs in hospital (Lapyre-Mestre *et al.*, 2006). Its principle consists of combining data provided by several sources coming from the same population. After identification of matches between sources, the capture-recapture method allows estimation of the number non-identified cases by any of the sources. Thus, the total number of cases in population and

sensitivity of each source can be deduced. In the study of Lapyre-Mestre *et al.* (2006) information was sourced from the Programme de Medicalization des Systems d'Information (PMSI) database and the French Pharmacovigilance database. The validity of this method is yet to be put to test by other researchers before its wide use becomes acceptable.

Prescription of drugs based on evidenced based medicine:

there should always be a strong indication for every drug prescribed. This can only be achieved by practicing evidence-based medicine. Sulphadoxine + pyrimethamine still remains the most frequently prescribed antimalarial used amongst children in Nigeria despite the reported high resistance and change in the national guideline for malaria treatment in Nigeria (Oshikoya 2006a,b). The sulpha group of this drug carries the risk of fixed drug eruption and Stevens Johnson syndrome.

THERAPEUTIC MEASURES

Some therapeutic measures may be used to prevent development of adverse reaction to some drugs. Histaglobulin has been reported useful in preventing multiple drug-induced skin reactions (Mohanty *et al.*, 2006). Histaglobulin is histamine-added human gamma-globulin, a product of the Serum Institute of India. It is indicated for the treatment of atopic dermatitis (Jolles *et al.*, 2000), allergic rhinitis and other chronic allergic states (Kaur *et al.*, 2003). In both allergic rhinitis and urticaria, histamine is the primary mediator and it plays a major role in Type I allergic skin reaction induced by various drugs. Many drugs, such as ACE-inhibitors, antiepileptics, sulphonylureas, sulphonamides and non-steroidal antiinflammatory drugs (NSAIDs) have cutaneous drug allergy as their side effect. In case of specific indications, these drugs can be used under the coverage of histaglobulin. Histaglobulin administered subcutaneously induces production of antibody against the histamine-immunoglobulin complex, which binds and inactivates histamine released during allergy. Repeated doses of histaglobulin increase this antibody titre.

Similarly pre-treatment of children with either H₁ (diphenhydramine) or H₂ (cimetidine) antihistamines before intravenous vancomycin is administered prevents shock; a common adverse reaction to rapid intravenous vancomycin administration (Renz *et al.*, 1998).

The most important measure in managing ADRs once it has occurred is to discontinue the offending medication. The continued use of the offending drug may be justified if the risk of not treating the underlying disease is greater than the risk of continuing the drug and if no suitable

alternative exists. Otherwise, alternative medications with unrelated chemical structures should be substituted. The clinical consequences of medication cessation or substitution should be closely monitored. In the majority of patients, symptoms will resolve within two weeks if the ADRs are the allergic type.

Additional therapy for allergic drug reactions is largely supportive and symptomatic. Systemic corticosteroids and antihistamines may speed recovery in severe cases of drug allergy. Topical corticosteroids and oral anti-histamines may improve dermatologic symptoms. The severe ADRs of Stevens-Johnson syndrome and toxic epidermal necrolysis require additional intensive therapy (Craven, 2000).

COMPLICATIONS AND PROGNOSIS

Complications can cover a whole spectrum of events, from very mild to life-threatening reactions that require hospitalization. These events may be disabling, incapacitating, or produce congenital abnormalities in later generations.

When the reaction is type A, dose reduction or stopping the drug will generally lead to resolution of the symptoms. A few, mainly type B reactions, if not identified early can have prolonged, permanent, or even fatal consequences.

FUTURE OF ADVERSE DRUG REACTIONS

The future development in ADRs lies in the exploration of its genetic determinant in every child. Individual predisposition to ADRs is, at least partly, genetically determined (Pirmohammed and Pak, 2001). The role of genetics is being further explored by Bruce Carleton and Michael Hayden in Canada (Thomson, 2005). Through their Genotype-Specific Approaches to Therapy in Childhood (GATC) Programme, they aim to explain the differential safety profile of drugs to individuals. They also want to develop diagnostic tests to determine a child's genetic fingerprint. Once the risk of a child developing an ADR can be predicted, personalized drug recommendations can be made for some commonly used drugs.

CONCLUSIONS

The key to appropriate management of adverse drug reactions is prevention and prompt recognition. However, prevention is the best way to avert ADRs. The greatest hope lies in the future of predicting ADRs by genetic determination before drug recommendations in children.

Meanwhile, knowledge of the adverse effect profiles of the different medicines the patient may be taking is important to minimize ADRs. This can be obtained from reference textbooks and/or drug information centers where literature searches could be carried out. Every physician should cultivate the habit of reporting ADRs for a drug reported today saves so many lives tomorrow.

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