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REVIEW ARTICLE

Adverse Drug Reactions in Children: Types, Incidence, and Risk Factors

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Summary

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Background: Adverse drug reactions (ADRs) are common in children but there appears to be a lack of understanding of the condition by some physicians.

Objectives: To alert paediatric physicians to the existence and occurrence of ADRs by classifying them, reporting their incidences all over the world, and identifying their risk factors in children.

Methods: A MEDLINE search, using *Index Medicus* and *PubMed*, for recently published systematic reviews, meta-analysis studies and original researches on ADRs in adults and children was carried out. The search involved both inpatients that developed ADRs while on admission and those admitted as a result of ADRs. Abstracts from all searches were read to determine their relevance, and in most cases, the original article was sourced to provide further information.

Results: The search yielded many relevant articles containing reviews, systematic and meta-analysis studies, original researches on in-patients who developed ADRs and many who were admitted for ADRs.

Conclusion: ADRs are global problems affecting children in both developing and developed countries. A higher level of clinical suspicion and vigilance, good knowledge of the predisposing factors, and proper monitoring of at-risk drugs in patients at-risk, may help prevent many ADRs, thus reducing its global incidence.

Introduction

ADVERSE drug reactions (ADRs) constitute a global problem of major and important concern in health care.[1-3] They confront primary care physicians on daily basis.[4] They are defined in various ways, but according to the World Health Organization (WHO), ADR is defined as any response to a drug that is noxious and unintended which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for modification of physiological function.[5,6] Thus, this definition excludes adverse events caused by errors in drug administration or non-compliance and tends to avoid overestimating the ADR rate. Drugs involved in ADRs include prescription, non-prescription, biological and herbal drug products. ADRs rank as one of the leading causes of death and illnesses in the developed world;[7] however, there is paucity of information about its incidence in developing countries, especially those in Africa. It is probable that so many adverse drug reactions go unrecognised and unreported. Indeed it has been estimated that about 95 percent of ADRs go unreported worldwide.[8,9] The problem with under-reporting is that physicians may not recognise when drugs are probably the culprits in adverse outcomes and ADRs are often interpreted as further symptoms of illnesses, which require treatment with more drugs.

A wide range of drugs has been reported as being involved in ADRs in children. These include antibiotics[10-12] (the most commonly prescribed determines the prevalence of the ADRs seen); non-steroidal anti-inflammatory drugs (NSAIDs),[12,13] opiates,[14] glucocorticoids, tuberculostatics, immunosuppressive agents,[11] anticonvulsants and vaccines.[15,16] The use of drugs in children is of considerable public interest, yet there is limited published information available. This review is therefore aimed at reviewing the available literature

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on adverse drug reactions in children with the main objective of alerting paediatric health care providers of the not-so-rare events of ADRs which constitute a major problem of drug therapy.

Classifications

Adverse drug reactions, otherwise regarded as drug toxic effects, are classified according to the predictability of the observed reactions.[17] This classification was proposed in 1977 by Rawlins and Thompson as type A and type B.[18] Both types constitute major categories of ADRs and although reported ADRs include both types in most instances, a majority of reactions are of type A. Three further minor categories of ADRs have since been proposed, namely types C, D, and E.[19]

1. **Type A reactions:**[17,19-21] These constitute the great majority of ADRs, are usually the consequences of a drug's main pharmacological effect, are low therapeutic index and are therefore predictable. They are dose related and usually mild, although they may be serious or even fatal. Usually they may be due to incorrect dosage (too much or for too long) for the individual patient, drug-drug interactions (disordered pharmacokinetics), side effects (nephrotoxicity of aminoglycosides) or secondary effects (changes in gut flora with the use of most antibiotics).

2. **Type B reactions:** These are unpredictable, dose independent, rare but associated with severe effects with a considerable mortality. They are further classified into allergic (immune mediated effects in the sensitized patient) and non-allergic (idiosyncratic or psychogenic) reactions.[19,22]

(a) **Allergic adverse drug reactions:** The term 'drug allergy', 'drug hypersensitivity', and 'drug reaction' are often used interchangeably. Immune mechanisms are involved in a number of adverse effects caused by drugs. The development of allergy implies previous exposure to the drug or to some closely related substances. Most drugs are of low molecular weight (< 1,000 daltons) and thus, are not antigenic. However, they can combine with substances of high molecular weight, usually proteins, to form an antigenic hapten conjugate. Drugs cause a variety of allergic responses, and sometimes a single drug can be responsible for more than one type of allergic response. Immune mediated reactions account for five to 10 percent of all drug reactions and constitute true drug hypersensitivity, with IgE-mediated drug allergies falling into this category.[20,21] Allergic ADRs are classified by Gell and Coombs[22] as:

Type I (anaphylaxis) reactions: These are due to the production of reaginic (IgE) antibodies. The antigen-antibody reaction on the surface of mast cells causes degranulation and release of pharmacologically active substances. They can manifest as urticaria, angioedema, inflammatory pruritus, vomiting, diarrhoea, and anaphylaxis.

Type II (cytotoxic) reactions: These are due to antibodies of class IgE and IgM which, on contact with antigens on the surface of cells, are able to fix complement, causing cell lysis (e.g. penicillin or cephalosporins).[19]

Type III (immune complex or Arthus) reactions: Circulating immune complexes produced by drug and antibody to drug deposit in organs, causing drug fever, rash, lymphadenopathy, and glomerulonephritis.

Type IV (delayed, cell mediated) reactions: They are due to drug forming an antigenic conjugate with dermal proteins and sensitized T-cells reacting to drug causing a rash (e.g. topical antibiotics).[19]

(b) **Non-allergic reactions.**[22]

Pseudo allergies: They result from direct mast cell activation and degranulation by drugs such as opiates, vancomycin, and radio-contrast media.

Idiosyncrasies: These reactions may be clinically indistinguishable from type I allergic reactions, but do not involve drug- specific IgE. They are qualitatively aberrant reactions that cannot be explained by the known pharmacologic action of the drug and occur only in a small percentage of the population. Typical example is drug induced haemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficiency patients.

Drug intolerance: This is a lower threshold to the normal pharmacological action of a drug, such as tinnitus after a single average dose of aspirin.

3. **Type C reactions:** These are continuous reactions due to long-term drug use (e.g. neuroleptic-related tardive dyskinesia or analgesic nephropathy).

4. **Type D reactions:** Delayed reactions of carcinogenesis or teratogenesis (e.g. alkylating agents, leading to carcinogenesis).

5. **Type E reactions:** End of use reactions such as adrenocortical insufficiency following withdrawal of corticosteroids, or withdrawal syndromes following discontinuation of treatment with diazepam, tricyclic antidepressants, or β-adrenoceptor antagonists.

Epidemiology

In the United States alone, approximately 26,500 children die every year from adverse drug reactions.[7] It is estimated that fatalities due to ADRs are the fourth to sixth leading cause of death in American hospitals. In Africa, information about incidence of ADRs is scanty. Reported cases were on specific drugs, such as ivermectin used in treating Onchocerciasis[23,24], thiacetazone used in treating tuberculosis in HIV infected children[25], and cotrimoxazole used in treating both HIV and non-HIV infected patients.[26]

ADRs have been reported to occur frequently in children but not as frequently as in adults[11]. Lack of information about incidence of ADRs in Africa may probably be as a result of under-reporting. The actual reported incidence of ARDs varies according to the population described and the case definition used,[7,27] the method used, the vigour with which ADRs are sought, as well as the number of concomitantly administered drugs to produce drug interactions.[7,28] Most reported incidences were from meta-analysis of prospective studies. A meta-analysis study in the United Kingdom reported ADRs incidence among hospitalised children from 4.37 percent to 16.78 percent with an estimated mean of 9.53 percent.[29] This study also reported incidence in paediatric hospital admissions related to ADRs from 0.54 percent to 4.1 percent, with a weighted mean of 2.09 percent. The incidence of ADRs in hospitalised patients ranges from 15 percent to 30 percent.[30-34] Between 11 percent and 30 percent of neonates in intensive care in a United Kingdom hospital were known to suffer at least an ADR.[34] Other prospective studies on ADRs in paediatric patients have reported incidence between 4.37 percent and 16.78 percent.[35,36] Also an incidence rate of 21.5 percent has been reported amongst children in Germany,[11] 15 percent to 27 percent, including 6 percent of life threatening ADRs in the United States and Canada,[37] 9.9 percent in Iran[38]; and 0.2 percent to 4 percent in Britain.[29] Between 3.75 percent to 16.6 percent paediatric hospitalisation resulted in ADRs, 27.9 percent of these reactions were severe.[39,40] Globally, incidence of ADRs is ≥ 10 percent meaning ADRs are common.[41] They contribute significantly to patients morbidity and mortality, and are a significant public health concern.[42,43]

Risk factors

1. **Age:** Infants and very young children are at high risk of developing adverse drug reactions than adults because their capacity to metabolise drugs is not fully developed.[44] For example, newborns cannot metabolise and eliminate the antibiotic chloramphenicol; newborns who are given the drug may develop gray baby syndrome; a serious and often fatal reaction. If tetracycline, another antibiotic, is given to infants and young children during the period when their teeth are being formed (up to about age 8 years), it may permanently discolour tooth enamel. Amongst children, it has been hypothesized and equally reported by Kramer *et al*[45] that patient 1 year of age or younger[46] are at greater risk of developing ADRs. However, Fattahi *et al*,[38] Impicciatore *et al*,[29] Martinez-Mir *et al*,[40,47] Cirko-Begovic *et al*[48] and Mjorndal *et al*[49] have shown that there was no particular age predisposition but contrarily, Kidon *et al*[20] reported increase in the risk of ADRs with age.

2. **Gender:** Like the age above, there is no particularly well established relationship between the risk of ADRs and sex of a child. Fattahi *et al*,[38] Mjorndal *et al*,[49] and Morales-Olivas *et al*[50] have reported no difference between genders in developing an ADR. Contrarily, other workers have shown female[40,47,51] and male[20,52,53] preponderances respectively.

7. **Multiple concomitant medication exposure:** 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.[38] It also has been noted that patients with an ADR were taking significantly more medications than were patients without an ADR.[38,73,74] Polypharmacy have been shown to be an important factor that predisposes patients to ADRs[38] and is similarly found in the adult patients.[51]

8. **Pre-existing diseases:** Presence of chronic disease,[20] malignancy,[20,75,76] immunodeficiency,[20,75,77-80] and severe viral infections[20,80] have been reported to independently increase the risk of developing ADRs in children. Any chronic illness is a major risk factor for ADRs, which is probably, but not solely, due to increased use of medication and polypharmacy.[20, 29] Atopic disease is not generally considered a risk factor for the development of ADRs. Atopic patients do not have a higher rate of sensitization to drugs; they are at increased risk for serious allergic reactions.[81] However, asthma, a chronic atopic disease, appears to be a risk factor for a severe ADRs[19,78] to any medication and a significant reactions to non-steroidal anti-inflammatory drugs.[20,82] Severe ADRs seen in asthmatics may reflect increased exposure to medication that have occurred in children with a chronic illness.

9. **Previous Adverse Drug Reactions:** History of previous adverse drug reactions[83] is a risk factor for developing ADRs.

10. **Others:** Duration of hospital stay,[11,83] increase in the dose of drugs by parents or prescribers,[46] use of drugs not licensed for use in children(unlicensed) or those drugs prescribed outside the terms of the product licensed(off-label)[36,84] are other factors that can influence the occurrence of ADRs in children. Prolonged hospital stay has been reported to increase the incidence of ADRs in children in Germany.[11] Twenty five to forty six percent of drug prescriptions in the U.K are either unlicensed or off-label,[85,86] safety data on these drugs are unavailable. Twenty five percent of drugs used as off-label and unlicensed medicines are the causes of spontaneously reported ADRs in children in the Trent region (U.K).[16]

Conclusion

Adverse drug reactions are global problems affecting children in both developing and developed countries. A higher level of clinical suspicion and vigilance, good knowledge of the predisposing factors, and proper monitoring of at-risk drugs in at-risk patients may help prevent ADRs, thus reducing its global incidence.

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