Adverse drug reactions in children requiring hospital admission

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Abstract

Objective To study the incidence of adverse drugs reactions (ADRs) in children admitted to Lady Ridgeway Hospital (LRH), Colombo.

Design A prospective hospital-based descriptive study.

Setting Medical units of LRH, Colombo.

Methods Information was collected by a hospital based investigator who visited the medical units at LRH from February to December 2002. The Naranjo algorithm was used to classify the information.

Remarks During the 11 month study period, 63 admissions were due to ADRs, the commonest being secondary to administration of antibiotics.

Conclusions ADRs accounted for only 0.16% of admissions as compared to about 2% in North America. The commonest ADRs were due to antibiotics.

Introduction

Drugs are essential components of health care systems worldwide. One important concern is that of drug safety. Most of the drugs will show some form of side-effect or adverse drug reaction. These can be mild, serious or life threatening. When a drug is initially marketed little is known about its safety in clinical use, and drug safety assessment should be considered an integral part of everyday clinical practice.

ADRs are a major clinical problem, accounting for 2 to 6% of all hospital admissions (1). Recent surveys in the USA have indicated that ADRs increase the length of hospital stay and costs (2). The WHO defines an ADR as "any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function" (3). This definition excludes therapeutic failures, intentional and accidental poisoning, drug abuse, errors in drug administration and non-compliance. ADRs are different from side-effects, which are expected and well known reactions to a drug resulting in little or no change in patient management.

ADRs could be type A (pharmacological) or type B (idiosyncratic). Type A reactions represent an augmentation of the pharmacological actions of a drug. These are dose-dependent and usually reversible on reducing the dose or withdrawing the drug. In contrast, type B adverse reactions are bizarre and cannot be predicted from the known drug pharmacokinetics.

Despite long standing concerns regarding hospital admissions prompted by ADRs, there is little information available concerning the extent of this problem in the paediatric population. In Sri Lanka there is under-reporting of ADRs, hence we undertook this study to estimate the hospital admissions precipitated by ADRs in children.

Methods

Children admitted to all the medical wards of the LRH from 1 February to 31 December 2002 with suspected ADRs were documented consecutively. An investigator stationed at the hospital systematically gathered information regarding the children, recording the demographic details, medications taken by the patient in the 3 months before admission, diagnosis, details of prescriptions and clinical events.

Reactions were classified by mechanism: unknown, pharmacologic, allergic, irritant, and miscellaneous. The severity was assessed by classifying them as non-serious, serious and fatal reactions. Non-serious reactions were not considered life-threatening but required treatment. Severe reactions were considered life-threatening. Fatal reactions were those which contributed directly or indirectly to death. The probability of an effect being due to a drug was classified as definite, probable, possible and doubtful according to the Naranjo algorithm (4) (Table 1). The duration of hospital stay, effect of reintroduction of the drug, outcome and long term disability were assessed. The data collected were analysed with the help of a computer program.

Results

During the period of study 63 out 39 625 of admissions were the result of ADRs. Thirty three patients (52.3%) were between the ages of 1 and 5 years and the mean age was 4.8 years. Twelve children (19%) were under the age of 1 year. There was one neonate who was admitted with raised intracranial pressure due to nalidixic acid. The male: female ratio was 1:1.4. The duration of hospital stay was less than 24 hours in 17 (27%), between 24 and 72 hours in 28 (46%), and greater than 72 hours in 17 (27%) patients. The nervous system was involved in 17 (27%), respiratory system in 6 (10%), gastrointestinal system in 8 (12%) and skin in 33 (52%). There were no renal or cardiovascular adverse reactions.

When the mechanism of action was examined 42 (67%) were pharmacological, 14 (22%) allergic manifestations, and 7 (11%) idiosyncratic. There were no fatalities. Seventeen percent (n=11) were serious adverse reactions and the rest were non-serious. According to the Naranjo algorithm 16 (25.3%) were definitive reactions, 42 (67%) were probable and 5 (7.7%) were possible.

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Table 1. The Naranjo algorithm

Question	*Yes*	*No*	*Do not know*
1. Are there previous conclusive reports on this reaction?	+1	0	0
2. Did the adverse event appear after the drug was administered?	+2	-1	0
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
4. Did the adverse reaction reappear when the drug was administered?	+2	-1	0
5. Are there alternate causes (other than the drug) that could have solely caused the reaction?	-1	+2	0
6. Was the drug detected in the blood in a concentration known to be toxic?	+1	0	0
7. Was the reaction more severe when the dose was increased or less when the dose was decreased?	+1	0	0
8. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
9. Was the adverse event confirmed by objective evidence?	+1	0	0

Table 2. Drugs most commonly implicated in hospital admission for ADRs

Drug	*Number*	*Representative reaction*
Ampicillin and amoxicillin	13	Erythema multiforme (13)
Cotrimoxazole	7	Rash (5), erythema multiforme (2)
Metoclopramide	7	Dystonic reactions (3) oculogyric crisis (3)
Amoxicillin/clavulanic acid	2	Stevens-Johnson syndrome
Aspirin	2	Reye syndrome
Penicillin	6	Rashes (4), Stevens-Johnson syndrome (2)
Flucloxacillin	1	Rash
Erythromycin	3	Rash (1), Stevens-Johnson syndrome (2)
Nalidixic acid	6	Rash (2), raised intracranial pressure (4)
Diclofenac sodium suppository	3	Rectal bleeding
Sodium valproate	2	Liver failure (1), ataxia (1)
Lamotrigine	1	Stevens-Johnson syndrome
Carbamazepine	1	Ataxia and cerebellar signs (1)
JE vaccine	6	Rash (4), encephalopathy (2)
DPT vaccine	3	Fits (2), head lag (1)

As a result of discontinuation of the drug, the reactions disappeared in 54 (85.7%), improved in 4 (6.3%) and persisted in 3 (4.7%). In 2 patients information was not available. In 3 patients the reaction recurred on reintroduction. One was for Japanese encephalitis vaccine and the others were for amoxicillin. In 3 patients, Stevens-Johnson syndrome due to amoxicillin/clavulanic acid (in 2) and amoxicillin (in 1) led to corneal damage.

Discussion

There were no fatalities recorded in this study probably due to the fact that in children multiple pathologies and long term multiple drug therapy are rare. The group of drugs principally involved in causing ADRs in children were antibiotics. In other studies the major contribution is by antineoplastic drugs (5). Our study was based at the LRH, and the majority of cancers are treated at the Cancer Institute, Maharagama.

Both children who developed Reye syndrome had received aspirin for thrombocytosis in Kawasaki disease. Diclofenac sodium is not registered in Sri Lanka as an antipyretic. The 3 children admitted with rectal bleeding had received diclofenac sodium suppositories for fever. Nalidixic acid is not recommended in infancy as it can cause raised intracranial pressure.

Single gene defects account for only a minority of ADRs. For most ADRs, particularly the idiosyncratic ones, predisposition seems to be multifactorial, involving not only defects at multiple gene loci but also environmental factors such as concomitant infection.

The ADRs should be detected early as they cause death in 0.1% of medical and 0.01% of surgical inpatients, adversely affect quality of life, cause patients to lose confidence in doctors, increase costs of patient care and may mimic disease, resulting in unnecessary investigations and delay in treatment. If ADRs are reported more regularly to a central authority, the medical profession could be kept better informed to minimise such events.

The number of ADRs will continue to increase unless health care professionals, as well as the general public, report ADRs in a timely manner. Sadly, only about 1% of ADRs are reported and this represents only the tip of an iceberg (6). In Sri Lanka the situation is worse, and reporting of ADRs is very rare. In Sri Lanka ADRs should be reported to the Department of Pharmacology, Faculty of Medicine, Kynsey Road, Colombo 8.

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