Adverse reactions to antibiotics in hospitalized Iranian children

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Received: October 4, 2006   Revised: November 11, 2007   Accepted: February 9, 2008

Background and Purpose: The aim of this study was to determine the frequency of adverse reactions to antibiotics by organ system in hospitalized children in the infectious ward of a pediatric diseases referral center in Iran.

Methods: All patients treated with antibiotics were evaluated daily for the presence of ADRs during a 5-month period. For each suspected ADR, a specialized questionnaire was completed in order to obtain the information necessary for analysis of ADRs.

Results: Among 300 patients, 65 ADRs were seen in 36 patients (12%) during their hospitalization. Pneumonia was the most common reason for administering antibiotics; ceftriaxone and rifampin were the most frequently implicated antibiotics in ADRs. There was a significant relationship between the number of drugs used and the rate of ADRs ($p=0.0001$). The most commonly affected organ systems were skin and appendages, and the gastrointestinal system. Maculopapular rashes were the most frequent skin ADRs.

Conclusions: As antibiotics are the most frequently used drugs in children, and also because of significant relationship between the number of drugs used and ADRs, limited use and careful selection of type and dose of antibiotics as well as close clinical observation are very important in minimizing ADRs.

Key words: Adverse effects; Anti-bacterial agents; Child, hospitalized; Incidence; Risk factors

Introduction

Treatment with antibiotics is a cornerstone of modern medicine [1]. Antibiotics are the drugs most frequently prescribed to pediatric outpatients and are responsible for most of adverse drug reactions (ADRs) in children [2-4].

The World Health Organization (WHO) defines an ADR as “a reaction to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of the diseases, or for modification of physiological function” [5]. This definition excludes adverse effects caused by errors (adverse drug events) in drug administration or non-compliance (taking more or less drug than the amount prescribed by the physician) [6].

Up to 7% of hospital admissions are for ADRs, and up to 16% of these reactions involve antibiotics [7]. Antibiotics as a drug class cause anaphylaxis in about 1 in 5000 exposures, although these reactions are not uniformly fatal. Anaphylaxis accounts for approximately 500 deaths annually [8]. Although most ADRs are mild and transient [2-4,9], some may be lethal or, rarely, life-threatening and necessitate hospitalization [10]. ADRs are more frequent in adults than in children [11]. Approximately 2-3% of hospitalized patients have been reported to have a skin reaction to antibiotic medications [12], and rashes occurred in 7.3% of children taking the most commonly used oral
antibiotics [13]. Some risk factors for ADRs in children are: differences in drug metabolism, the effects of developmental processes, multiple drug exposure, age younger than 12 months, and the presence of complex multisystem illnesses [14,15].

ADRs related to antibiotics are frequent in children [2], and this may lessen the compliance of antibiotic use in the pediatric age group and encourage physicians to prescribe more expensive antibiotics and consequently promote resistance of microbial strains [13]. We performed this study in order to determine the frequency of adverse antibiotic reactions on organ systems of hospitalized children in the infectious ward of a pediatric diseases referral center in Iran.

Methods

This study was conducted under the supervision of the Tehran University of Medical Sciences, and its ethics committee approved the protocol of the study. Informed consent was obtained from the patients and/or their parent or guardian.

During 5 months from February 14 to July 20, 2004, all patients admitted to the department of pediatric infectious diseases were evaluated. Patients with less than 24 h hospitalization or who had repeated admissions were excluded from the study. A specific questionnaire was recorded by an expert physician for every admitted child who was taking at least one antibiotic. All patients were visited daily and followed up until discharge. Daily nursing and physician notes and daily examinations of patients were evaluated, and ADRs were recorded according to WHO definitions. When a suspected ADR was encountered, data of the drug and reaction were documented in a suitably designed ADR documentation form that included the drug name, dosage, route and frequency of consumption. Reactions as a result of administration errors, non-compliance, drug overdose or abuse and therapeutic failure were excluded.

Reactions (usually more than one per report) were classified according to the Adverse Reaction Terminology (ART) of the WHO ADR Monitoring Register in Uppsala (WHO-ART) into system-organ classes [16]. According to the WHO terminology, an adverse reaction was serious if one of these states was met: results in death; life-threatening; requires inpatient hospitalization; prolonged hospitalization; results in persistent or significant disability/incapacity; a congenital anomaly/birth defect.

We assessed the seriousness of ADRs according to this definition. Potential drug causality of ADRs was assessed case by case using the WHO Probability Scale (Table 1) as described by Fattahi et al [17]. All data from questionnaires and medical records were coded and statistical analysis of the results was performed.

Statistical analysis of the results was performed using the Statistical Package for the Social Sciences for Windows (Version 11.5; SPSS, Chicago, IL, USA) software package. All measurements are expressed as mean ± standard error of the mean. Comparisons between proportions were performed using the chi-squared test. A significance level of \( p < 0.05 \) was used for all tests.

Results

During the 5-month period of the study, among 404 admitted patients, 300 cases that were treated with antibiotic were included in the study. Pneumonia was the most common reason for administering antibiotics and ceftriaxone was the most frequently administrated antibiotic. 157 patients (52.3%) were male and 143 (47.7%) were female. The mean age of admitted patients was 30 months and 15 days (30.5 months ± 4.46 months), with age ranging from 15 days to 14 years. The mean number of drugs administrated was 4 ± 0.36 per patient (range, 1 to 20 drugs). There was a significant relationship between the number of drugs used (including antibiotics and other medicines) and the incidence of ADRs (\( p=0.0001 \)).

Sixty five ADRs were seen in 36 out of 300 patients (12.0%), or approximately 1.8 ADRs for each patient. ADRs resulted in hospital admission in 4 patients and occurred during hospitalization in 32 patients. Twenty

<table>
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<tr>
<th>Table 1. Assignment of causality of adverse drug reactions</th>
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<tr>
<td><strong>Certain:</strong> consistent temporal association, including clinical course following withdrawal of drug, and where appropriate, rechallenge</td>
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<tr>
<td><strong>Probable:</strong> consistent temporal association but not confirmed by rechallenge</td>
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<tr>
<td><strong>Possible:</strong> likely association but could be explained by another disease or drug</td>
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<tr>
<td><strong>Unlikely:</strong> temporal association to drug administration not consistent with causality</td>
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<tr>
<td><strong>Conditional:</strong> lack of data necessary for proper assessment but more data being examined</td>
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<tr>
<td><strong>Unassessable:</strong> lack of data necessary for proper assessment</td>
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one patients (58%) with ADRs were male and 15 (42%) were female. The mean age of patients with ADRs was 11 months, 22 days ± 18 days.

Ceftriaxone and rifampin were the antibiotics most frequently associated with ADRs (16.7%), followed by amphotericin B and trimethoprim-sulfamethoxazole (11.0% each) and cephalothin and ampicillin (8.3% each) [Fig. 1].

The most frequent formulation was ampules/vials (69.4%), while tablets (16.7%), capsules and drops (5.6% each) and syrups (2.8%) were less often involved.

The organs most commonly affected by ADRs were the skin and appendages (32.3%), and gastrointestinal system (21.5%). Other organ systems were less commonly involved (Fig. 2). Maculopapular rashes were the most frequent skin reactions related to ADRs. The back, upper and lower extremities, chest and head and neck were the most common sites of rashes; eyes and mouth were rarely affected.

Injection site reactions such as pain, necrosis and nodules were seen in 3 patients (8.3%). Respiratory system involvement as well as tachypnea comprised 1.5% of ADRs. Elevated liver enzymes were detected in 3 patients. Musculoskeletal and endocrine involvement was not seen in patients with ADRs.

Urinary involvement and discoloration of urine comprised 7.7% of ADRs. Neurological/psychiatric disorders which presented with agitation, insomnia and psychotic disorders accounted for 3.1% of ADRs. Hypomagnesemia and hypokalemia was observed in 4.6% of patients, while 1.5% had hypomagnesemia alone. Other ADRs observed were fever (3.1% of ADRs), fever and chills (4.6% of ADRs) and fever, chills and headache (1.5% of ADRs). Hematological disorders comprised 3.1% of ADRs, and included monocytes, anemia and neutropenia. Cardiovascular diseases as well as hypertension and tachycardia accounted for 1.5% of ADRs. Among gastrointestinal disorders (21.5%), diarrhea (12.2%) and nausea and vomiting (4.5%) were the most common presentations.

Twelve suspected ADRs were serious (18.5%): 7 ADRs were life-threatening, 4 required inpatient hospitalization, and 1 resulted in prolonged hospitalization. In 53 cases (81.5%), ADRs were non-serious. All patients recovered without long-term sequelae.

Discussion

ADRs are a major concern of health care systems [6]. One study showed that in 1994, 10,600 cases of fatal ADRs were observed in hospitalized patients and ADRs were the fourth to sixth leading cause of death in the United States [6]. ADRs are less common in children [12,18] and the incidence of ADRs is nearly 1% in hospitalized children [12]. ADRs cause parental anxiety, and increased physician visits and medical costs [2]. Antibiotics are the most frequently used drugs in children and thus most pediatric ADRs are related to antibiotics [2-4].

In our study, among 300 admitted patients in the infectious ward of a pediatric referral center who were treated with antibiotics, 36 patients experienced ADRs (12%), a figure compatible with other studies [6,11]. Some studies have focused on adverse drug events, which include errors in administration.

Our study excluded medication errors and showed that there are a large number of ADRs even when the antibiotics are properly prescribed and administered. The higher rate of ADRs in this research compared with similar studies might be because of an increased susceptibility in Iranian populations. However, patients in Iran respond to lower doses of drugs than typically recommended in formularies or used in other countries. In addition, there are variations in potency...
among drug formulations available in Iran, leading to difficulties in establishing drug dosages.

In our study, the ADR rate had no relationship with gender, whereas Kidon and See showed male predilection in ADRs [19]. This was confirmed by Ibia et al, who found that 53% of children showing rashes were male and 93% of them were younger than 6 years old [13]. It has been noted that rashes are observed more often in boys less than 3, and in girls more than 9 years old [13]. The most commonly affected age groups in our study, as in other studies [15], were children less than 1 year old.

The antibiotics most frequently causing ADRs were ceftriaxone and rifampin, while cefaclor caused the most rashes (4.8%) [13]. This is probably because these types of antibiotics (third-generation cephalosporins) were the most commonly used antibiotics in hospitalized children in Iran. The most common adverse reactions were skin rashes (32.3%), as seen in other studies [13,11].

Cutaneous reactions to antibiotics cover the entire spectrum from benign to potentially life-threatening [7]. Some range from transient, mild erythema to toxic epidermal necrolysis, often resulting in disability and death [12]. Despite most ADRs being non-serious in our study, a few were serious and life-threatening, and the emergency physician must be able to readily recognize the manifestations of these reactions, accurately determine the cause, and assess associated morbidity and mortality.

The small number of patients studied and the difficulties in gathering the information about admitted children are some limitations of this research.

However, as antibiotics are the most frequent drugs used in pediatric patients and because of a significant relationship between the number of antibiotics used and the risk of ADRs, limited use and careful selection of antibiotics, together with close observation for ADRs are important requirements in order to diminish the harmful and potentially lethal consequences of ADRs.

References
Pediatric adverse antibiotic reactions