IJPT
1735-2657/14/131-26-29
IRANIAN JOURNAL OF PHARMACOLOGY & THERAPEUTICS

IJPT 13: 26-29, 2014

ORIGINAL ARTICLE

Adverse drug reactions causing admission to a Pediatric Hospital in Hamedan – Iran: a 2 years study

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Received May 27, 2013; Revised August 12, 2013; Accepted September 4, 2013

This paper is available online at *http://ijpt.tums.ac.ir*

ABSTRACT

Severe adverse drug reactions are an important cause of childhood morbidity and mortality. Despite this, few reports in the literature describe it. This study was designed to evaluate the admitted pediatric patients due to adverse drug reactions. This retrospective study was conducted at Pediatric ward of Besat Hospital. The records of hospitalized patients that admitted with diagnosis of adverse drug reactions enrolled in study over a 2 years period. The data collected on a data collection form using the records of the patients and included the patient demographic features (age, gender, allergy history, primary cause for drug administration) and drug information (name, duration of use, description of drug reaction, duration of drug reaction and concomitant use of drugs). Thirty-five patients were enrolled in study. Of them, 24 (68.6%) were male and 11 (31.4%) were female. Ages were under 1 years old in 5 (14%), between 1 to 5 years old in 22 (63%) and beyond 5 years old in 8 (23%) patients. Most patients (88.5%) had no known drug allergies. The primary cause for drug administration was upper respiratory tract infections (43%), diarrhea (26%), seizure (14%), gastroenteritis (8.5%) and vomiting (8.5%). Drugs most frequently cited included: Furazolidone (n = 9), Penicillin (n = 8), Amoxicillin (n = 7), Co-Trimoxazole (n = 4) and Phenobarbital (n = 4). Most frequent reactions were: skin rashes (83%), arthralgia (37%), fever (34%), pruritus (23%) and edema (11.5%). Understanding causality and preventability of adverse drug reactions will significantly aid in better therapeutic monitoring for children receiving the same therapy in future.

Keywords: *Adverse drug reactions, Hospitalization, Pediatric, Antibiotic*

The incidence of adverse drug reactions (ADRs) in the pediatric and general population is largely unknown. The ADRs affect 6.7% of hospitalized patients and 0.32% of hospitalized patients died from it. To date, the large number of drugs used to treat pediatric conditions for licensed uses lead to increased ADR in pediatric groups [1].

An ADR is defined by the World Health Organization as a noxious and unintended response to a drug that occurs at a dose normally used in man [2]. ADRs separate into two major subtypes: dose-dependent and predictable, and not dose-dependent and unpredictable. Predictable ADRs include drug intoxications, drug interactions and adverse effect of drugs. Predictable ADRs are related to pharmacological activity of drugs and the patients don't have any natural affection to this group [3]. Unpredictable ADRs usually occur in patients with genetic susceptibility and don't relate to pharmacological activity of drugs. Unpredictable ADRs include allergy, pseudo-allergy and idiosyncratic reactions which need to presence of hypersensitivity reaction before initiation of symptoms in patients. Immunologic or allergic reactions comprise approximately 6–10% of all ADRs and include hypersensitivity drug reactions [1].

Table 1. Adverse drug reactions in hospitalized pediatric patients

Medicine(s) used	Adverse drug reactions
Furazolidone	Fever, Rash, Urticaria, Edema, Arthralgia, Erythema multiforme, ,Erythema marginatom, Swelling and redness of limbs and joints
Metoclopramide	Extrapyramidal effects, Dystonia or tremors, Agitation, Perioral rhythmic movement, Upward gaze
Penicillin	Injection type: Prominent Fontanel, Maculopapular rash, Stevense -Johnson syndrome, Erythema multiforme, Joint swelling, Swelling of limb, Urticaria
Ampicillin	Maculopapuler rash, Morbilliform exanthema
Amoxicillin	Pruritus, Urticaria, Edema in lower limb, Maculopapuler rash
Hyocine	Fever, Pruritus, Abdominal pain, Erythema multiforme
Co-trimoxazole	Arthralgia, Urticaria, Pruritus, Acute generalized exanthematous pustulosis
Cephalexin	Pruritus, Papules and plaque in combination therapy with co-TMX
Cefixime	Pruritus, Claudication, Urticaria, Fever, erythema marginatom, Drug induced arthritis
Phenobarbital	Fever, Pancytopenia, Maculopapular rash
Clobazam	Fever, Urticaria
Na-valproate	Fever, Rash
Liskantina Primidona	Fever, Rash
Carbamazepine	Fever, Rash
Erythromycin	Fever, Rash

ADRs can lead to significant morbidity and death among children [4-11]. ADRs not only may result in hospital admission or prolonged hospitalization but also may lead to permanent disability or even death. Notably, in a meta-analysis by Lazarou *et al.* [4], fatal ADRs among both adults and children ranked as the fourth to sixth leading cause of death in the United States of America. Another study demonstrated that ADRs were associated with an average of 243 reported deaths among young children, from newborn to 2 years of age, each year [9].

The incidence of unwanted drug reactions is generally unknown. The treatment cycle could be interrupted by drug side effects; thus, in these cases changing the drugs sometimes may be necessary. Outcomes can extra costs for treatment and prolonged treatment period. Sometimes these side effects may cause new problems, therefore hospitalization and new treatment could be necessary [12]. Diagnosing the patient demographic features (age, gender, allergy history, primary cause for drug administration) and drug information (name, duration of use, and description of drug reaction, duration of drug reaction and concomitant use of drugs) can be helpful in determining the type, strategy and dosage of the prescribed drugs. According to the fact that epidemiologic studies are the basis of other studies, the incidence of unwanted drug reactions should be assessed. Due to lack of research findings about this problem in Hamedan, we evaluate the incidence of hospitalization due to ADRs in pediatric patients at Besat hospital in Hamedan city.

PATIENTS AND METHODS

The data collected on a data collection form by using the records of the patients and included the following information: patient demographic features (age, gender, allergy history, primary cause for drug administration) and drug information (name, duration of use, and description of drug reaction, duration of drug reaction and concomitant use of drugs). The records of hospitalized patients who were admitted with diagnosis of drug side effects, drug sensitivity, serum sickness, hives, rashes, Stevens-Johnson syndrome, and hypersensitivity syndrome were enrolled in study during 2 years. Their hospitalization folder had been checked and recorded. If the patient's folder was incomplete, the patient was removed from the study. All the data were put into questionnaire and compared using one-way ANOVA test in SPSS.16 software.

RESULTS

Thirty-five patients were enrolled in this study. Of them, 24 (68.6%) patients were male and 11(31.4%) patients were female. Ages were under 1 years old in 5 (14%) patients, between 1 to 5 years old in 22 (63%) patients and beyond 5 years old in 8 (23%) patients.

Most patients (88.5%) had no known drug allergies. More than one drug prescribed in 57% of patients. Duration of drug consumptions in 19 (54%) cases was less than 7 days. In 15 (43%) of cases, duration of drug consumption was between 7-14 days and in 1(3%) case, it was between 14-21 days. The adverse reaction began during the first week after drug exposure in 17 (48%) cases, during second week in 14 (40%) patients and during third week in 4 (11%) patients.

Most frequent reactions descriptors include: skin rashes (83%), arthralgia (37%), fever (34%), pruritus (23%), edema (11.5%), claudication (8.5%), protuberant fontanel (2.8%) and combination of extrapyramidal symptoms, agitation, upward gaze and perioral rhythmic movement (2.8%) (Table 1). The primary cause for drug

Table 2. Prescriptions of different classes of studied drugs and the most-frequently used individual drugs within each class in hospitalized pediatric patients with adverse drug reactions

Drugs (Class and Name)			Single drug used	Combination drugs	Summation
Penicillin	Narrow spectrum	Pen V	1	-	1
		Pen G	2	5	7
	Wide spectrum	Amoxicillin	2	5	7
		Ampicillin	1	-	1
Anti-convulsion	Phenobarbital		2	2	4
	Clobazam		-	1	1
	Carbamazepine		1	-	1
	Na-valproate		-	1	1
	Liskantina Primidona		1	-	1
Sulfonamide	Co-trimoxazole		1	3	4
Cephalosporin	First generation	cephalexin	-	2	2
	Third generation	cefixime	1	2	3
Anti-bacterial & antiprotozoal	Furazolidone		5	4	9
Dopamine antagonist	Metoclopramide		1	2	3
Anticholinergic	Hyocine		-	1	1
Macrolide	Erythromycin		1	2	3
Summation			19	30	49

administration was upper respiratory tract infections (43%), diarrhea (26%), seizure (14%), gastroenteritis (8.5%) and vomiting (8.5%). Drugs most frequently cited include: furazolidone (n = 9), penicillin (n = 8), amoxicillin (n = 7), co-trimoxazole (n = 4) and phenobarbital (n = 4) (Table 2).

DISCUSSION

The aim of this study was to determine the frequencies of drug reactions in pediatric patients who were hospitalized because of drug reactions at Besat Hospital in Hamedan city over a 2 year period. We have shown that the frequencies of drug reactions are more common in 1-5 year old boys. The majority of these patients had no history of allergy and drug reactions. The most common signs of drug reactions reported were: rash followed by artheralgia and fever. The most common used drugs resulted in drug reactions were antibiotics and anticonvulsive drugs.

In the retrospective study conducted by Carleton and his colleagues [13], 1193 patients were evaluated in Canada during 1998-2002; 59% of the patients were beyond 13 years old. The most frequently drug reactions were: psychological disorders, nervous system disorders and rashes. The most commonly-used drugs associated with these reactions were: isotretinoin (56 case), paroksetin (42 case), Methylphenidate (41 case), amoxicillin (40 case), valproic acid (32 case), bupropion (26 case) and carbamazepine (25 case). Drug reactions have been resulted in death in 42 patients and irreversible sequels in 14 cases. Death and disability were not reported in our study. The number of our cases was significantly less than the patients of this study, our cases were generally between 1-5 years old and the most common drug reactions announced were due to antibiotic consumption. Excessive use of antibiotic can be assumed as the reason of these differences.

The prospective study on 512 children who were 2 years old and under was conducted by Mrtinez and his colleagues [14] in Spain. Drug reactions were seen in 4.3% of pediatric patients. The drug reactions often reported in these children were: convulsion, vertigo, vomiting, tremor, fever and itching. The systems most commonly affected were: the central nervous system (40.5%), the gastrointestinal system (16.7%), and the skin (14.3%). The main drug groups concluded were: respiratory drugs (35%), antibiotics (25%), drugs affected the central nervous system (15%) and the used drugs in dermatology (10%). The differences between this study and ours are the affected organisms, drug groups and drug reactions. This study was also evaluated broad spectrum of pediatric patients who were 2 years old and under, therefore the unequal conclusions can be explained by paying attention to the differences in number and age groups.

The other study was conducted in Brazil by Santos and his colleagues [15]. The skin (49%) was the most commonly affected organism in the hospitalized pediatric patients. antibiotic consumption (53.2%) was the main cause of the problems occurred and damaged the organisms. Risk of drug reactions got increased to 3 times and more by using more drugs, being male, having prior history of hospitalization. Conclusions of this study are close to ours, as it has been demonstrated, rash was the most common sign due to using drugs and antibiotics were more responsible for drug reactions. Also the majority of the patients were male.

To best of our knowledge, the only study conducted in Iran was done by Mir Saeed Ghazi and his

Published online: January 28, 2014

Colleagues [16]. The unwanted drug reactions had been considered in this study. Also the primary signs of drug reactions were reported. This study has been conducted in Bahrami Pediatric Hospital and the known case of unwanted drug reactions in hospitalized pediatric patients has been evaluated since 1998 to 2005. The average ages of the patients were between 3 to 5 years old. Drug reactions had been seen 12-14 days of the first consumption. Skin maculopapular rashes were reported in all patients. Hives was more usual after rash. Arthralgia was reported in 40% of patients. The common laboratory finding was increased ESR in 40% of the patients. Phenothiazine and sulfasalazine which had been reported in 28% of the patients were the most common drugs which resulted in drug reactions. Penicillin (16%), furazolidone (16%), cephalosporins (4%) and sodium valproate (4%) were also reported. In 28% of the patients, simultaneous consumption of drugs was responsible for the reported side effects. They emphasize on the importance of decreasing the unwanted drug reactions especially in children by paying attentions to the side effects of the drugs, having knowledge about drug interactions and evaluating continuously the patients taken drugs. The results of our study in different areas is close to this study such as differences in kind of drugs, age, number of patients, delay in reaction and simultaneous consumption which can be because of the similarities of drug consumption strategy in different cities of our country.

In conclusion, excessive use of antibiotic in Iranians usually causes the need for more medication. It is necessary to have teaching programs for doctors and patients to reduce the request for unnecessary medications. Although using furazolidone can lead to adverse and resistant hives, it is prescribed easily in the diarrhea treatment. Therefore paying attention to the forazolidone consumption is necessary. Anti-convulsive medications in case of fever convulsion must only be used when there is absolute indication.

ACKNOWLEDGEMENT

This study was performed under observation of Hamedan University of Medical Sciences.

REFERENCES

1. Boguniewicz M,Leung D. Adverse Reactions to Drugs.In: Behrman RE, Kliegman RM, Jenson HB (editors). Nelson Textbook of Pediatrics. 19th ed. Philadelphia: Saunders. 2011, Pp: 824-825.
2. World Health Organization. International drug monitoring: the role of national canters. *World Health Organ Tech Rep Ser* 1972; 498:1–25.
3. Rawlins MD, Thompson JW. Pathogenesis of adverse drug reactions. In: Davies DM, editor. Textbook of adverse drug reactions. Oxford: Oxford University Press; 1977. p. 10.
4. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective Studies. *JAMA* 1998; 279:1200–5.
5. Impicciatore P, Choonara I, Clarkson A, Provasi D, Pandolfini C, Bonati M. Incidence of adverse drug reactions in paediatric In/out-Patients: a systematic review and meta-analysis of prospective studies. *Br J Clin Pharmacol* 2001; 52:77–83.
6. Temple ME, Robinson RF, Miller JC, Hayes JR, Nahata MC. Frequency and preventability of adverse drug reactions in paediatric patients. *Drug Saf* 2004; 27:819–29.
7. Mitchell AA, Goldman P, Shapiro S, Slone D. Drug utilization and reported adverse reactions in hospitalized children. *Am J Epidemiol* 1979; 110:196–204.
8. McKenzie MW, Stewart RB, Weiss CF, Cluff LE. A pharmacistbased study of the epidemiology of adverse drug reactions in pediatric medicine patients. *Am J Hosp Pharm* 1973; 30:898–903.
9. Moore TJ, Weiss SR, Kaplan S, Blaisdell CJ. Reported adverse drug events in infants and children under 2 years of age. *Pediatrics* 2002; 110 (5).
10. Mitchell AA, Lacouture PG, Sheehan JE, Kauffman RE, Shapiro S. Adverse drug reactions in children leading to hospital admission. *Pediatrics* 1988; 82:24–9.
11. McKenzie MW, Marchall GL, Netzloff ML, Cluff LE. Adverse drug reactions leading to hospitalization in children. *J Pediatr* 1976; 89:487–90.
12. Einarson TR. Drug-related hospital admissions. *Ann Pharmacother* 1993; 27: 832-40.
13. Carleton BC, Smith MA, Gelin MN, Heathcote SC. Paediatric adverse drug reactions reporting: understanding and future directions. *Can J Clin Pharmacol* 2007; 14:45-57.
14. Martinez I, Garcia M, Palop V, Ferrer JM, Estan L, Rubio E, Morales FJ. A prospective study of adverse drug reactions as a cause of admission to a paediatric hospital. *Br J Clin Pharmacol* 1996; 42:319-24.
15. Santos DB, Clavenna A, Bonati M, Coelho HL. Off label and unlicensed drug utilization in hospitalized children in Fortaleza, Brazil. *Eur J Clin Pharmacol* 2008; 64: 1111-8.
16. Mirsaeedghazi SB, Dibaei M, Rahbarimanesh AA, Akhlaghi H, et al. Adverse Drug Reaction, one causes in pediatric hospitalization. *Iran pediatrics disease* 2007; 17:11-4.

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