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Sarnai Sukhbaatar[1], Enkhtur Yadamsuren[2], Sarantuya Jav[3], Narantungalag Dorjsuren[1]
[1]Department of Pharmacology, School of Bio-Medicine, Mongolian National University of Medical Sciences, Ulaabaatar, Mongolia;
[2]Department of Dermatology, School of Medicine, Mongolian National University of Medical Sciences, Ulaabaatar, Mongolia;
[3]Department of Molecular Biology and Genetics, School of Bio-Medicine, Mongolian National University of Medical Sciences, Ulaabaatar, Mongolia

CUTANEOUS ADVERSE DRUG REACTIONS IN MONGOLIAN PEDIATRIC PATIENTS

Cutaneous adverse drug reactions (CADRs) are rare and tend to increase in recent years. The aim of the study is to reveal the medicines affecting the development of drug-related skin disorders. We analyzed pediatric data in the National Dermatology Center of Mongolia, which was built retrospectively in 2019 with CADRs cases treated in that hospital during 2013-2018. 204 pediatric patients CADRs cases were included. The common offending drug groups were antimicrobials (50.4%), anti-inflammatory drugs (28%) and antiepileptic drugs (1.47%). The incidence of cutaneous adverse reactions to drugs is higher in male than female.
Among the inpatients of National Dermatology Center of Mongolia, drugs that cause major skin disorders affect the antibacterial and nervous system. Usually toddlers more than adolescents affected by the drug related skin disorders.
Keywords: *adverse drug reaction, skin disorders, children*

Introduction: CADRs are problem of global health. The World Health Organization (WHO) [1] defines an adverse drug reaction (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 physiologic function".
Although the leading causes of population morbidity are stratified by location, diseases of the respiratory, digestive and cardiovascular systems are the three leading causes both in urban and rural areas[2]. Therefore, drug consumption are increasing every year. Drug induced skin disorders (DISD) such as allergic contact dermatitis (L23), dermatitis due to substances taken internally (L27), urticaria (L50), erythema multiform, Stevens-Johnson syndrome, toxic epidermal necrolysis (L51) and erythema nodosum (L52) are included in International Classification of Diseases – 10 revision (ICD-10) [3] are caused by irrational use of medicines are increasing in population. Irrational use of medicines is an extremely serious global problem that is wasteful and harmful. In developing and transitional countries, in primary care less than 40% of patients in the public sector and 30% of patients in the private sector are treated in accordance with standard treatment guidelines[4].
Cutaneous adverse drug reactions (CADRs) are most commonly associated with antimicrobial agents (AA), non steroidal anti-inflammatory drugs (NSAID) and anti-epileptic drugs (AED)[6] which are included "8th Essential drug list" of the Mongolia. In the Mongolia AA and AED are written by doctors on the prescription and NSAID can sold with or without prescription. Parliament of Mongolians decision №57 09th October, 2014 detailed and again declared that antibiotics should prescribed[5].
CADRs are one of the most common types of adverse drug reactions[6]. Incidence and severity of CADRs are increasing last years. Many factors particularly drugs consumption, age, sex are affecting CADRs.
The aim of the study is to reveal the medicines affecting the development of drug-related skin disorders.
Materials and Method: The NDCM is located in the capital city of Mongolia which specialized only tertairy teaching hospital can serve who is suffering from cutaneous adverse drug reactions. Medical histories were collected and archived between 2013 and 2018 in the archives of the NDCM. We conducted a study on the medical histories of 31,993 patients (adult and child), who were hospitalized at NDCM from 2013 to 2018.
In this retrospective study, we used medical histories with L23, L27, L50-52 diagnosis that are causes by any medication. Patients are included who used of prescription or non-prescription medication, CADRs are developed and those cases should require special medical care. The diagnosis of the CADRs was done by the dermatologists who are working in the NDCM. In patient with incomplete history were excluded in this study. All the patients were given adequate treatment (soothing lotions, local / oral antibiotics or steroids, antihistamines) depending upon the severity of CADRs.
Data about age, gender, diagnosis, treatment were retrospectively collected from patients' medical history.
Statistical analysis
Descriptive statistics was used for data analysis and results were expressed as percentages.
Ethical statements
Prior to beginning the study, the study design and ethics were approved by Ethical Review Committee of Mongolian National University of Medical Sciences (№2018/3-10, 08 June 2017).
Results: 1. Baseline characteristics
CADRs are possible for any age and included from 2 months to 18 years old. The mean age of diagnosis was 5.89 ± 5.28 years old. Of the total 204cases selected, 76 (37.3%) were females and 128 (62.7%) were males. The male to female ratio was 0.59:1.68.
Of the total 924 pediatric patients who is treated for those diagnosis in the last five years. Of them 204 (22.07%) CADRs were caused by drug consumption. The remaining over 78% was caused by food and chemical substances.
L27 was the most common diagnosis (n=115) 62.5%, followed by L50 (n=62) 24.5%, L51 (n=18) 8.38%, L23 (n=5) 2.5%, L52 (n=4) 1.9% (Table 1).

Table1 - CADRs amount between 2013 and 2018

	L50	L51	L52	L23	L27	Total
2013	4	2		1	19	26
2014	12	2	2	1	28	45
2015	5	3			25	33
2016	4	3	1		5	13
2017	13	3		2	20	38
2018	24	5	1	1	18	49
						204

2. Drugs responsible for CADRs.

Table2 show the drugs most commonly responsible for CADRs were antimicrobial (50.4%), followed by non steroidal anti-inflammatory drugs (NSAIDs) (28%) and antiepileptic drugs (1.47%).

Table2 - Etiology of pediatric CADRs

		Cutaneous findings	
Etiology	SJS	Rash	Blister
Antibiotics Penicillin Amoxicillin		42	17
Ampicillin		4	1
Cephalosporine		6	4
Macrolide		15	3
Sulfonamide		9	2
NSAIDS Acetaminophen		20	7
Ibuprofen		26	4
Antiepileptic Carbamazepine	3		
Other		39	2

The lag period between starting the drug and appearance of cutaneous reactions varied between 30 minutes and a day in maximum number of cases and a case severe CADRs are excluded.

Outcome of CADRs showed all patients cured and improved.

Discussion.

Hea Lin Oh et all study's[7] sex ratio was same. The study was performed in the Korean Severe CADRs (SCADRs) registry, which was built retrospectively in 2016 with SCADRs cases treated in 34 tertiary referral university hospitals during 2010-2015. They selected 47 SCADRs and 68.1% were male. Deng Q et all[8] also noticified twenty-five studies reported the proportion of men was 53.2%. But other studies' sex ratio was similar such as another study's[9] reported male were 48.7%.

In this study, CADRs prevalence rate was about 2/1000. Most epidemiological studies analyzed the occurrence of CADRs in inpatients and revealed a wide variation in the prevalence rate which ranged from 0.36% to 12.2%[10]. However, some study concluded a prevalence of 3.6/1000 among hospitalized patients was estimated[11]. On the other hand, incidence of CADRs was not a higher than other countries. These results showed us that we could manage, develop of prevention and provide information to physicians and pharmacists. The top CADRs were rash including non-specified rash, follicular rash, maculopapular rash and vesicular rash[12]. The most common reaction was immediate reactions, i.e. urticarial and angioedema contributing over half of cases. Cutaneous clinical manifestations are diverse ranging from mild or moderate reactions, such as urticarial and maculopapular rash. CADRs are known due to their high morbidity and mortality.

Most studies show that antibiotic, NSAIDS is caused CADRs[13-14]. Usually pediatric and general department use antibiotics widely because there are used for treatment and prophylaxis of various infectious conditions.

Use of multiple drugs is associated with higher incidence of drug reactions as observed with increased frequency in hospitalized patients. In globally, the major causative drug groups were antimicrobials, NSAIDs and anti-epileptic drugs. Therefore those group medicines should be prescribed and monitored specialized physicians. At the same time patients should be sensitized about hazards of self-medications.

Further moreover, we need to detect HLA-B*15:02; HLA-A*31:01 allele was identified as a strong genetic marker for carbamazepin-induced CADRs in Asian population.

Clinicians should carefully evaluate the signs and symptoms of all cutaneous adverse drug reactions thought to be due to drugs and immediately discontinue drugs that are not essential. Short cycles of systemic corticosteroids in combination with antihistamines may be necessary for widespread exanthematous rashes; while more aggressive corticosteroid regimens or intravenous immunoglobulin's associated with supportive treatment should be used for patients with Stevens-Johnson syndrome or toxic epidermal necrolysis[15].

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