약학박사 학위논문

지역약국 약사의 자발적 보고 자료를 대상으로 한 약물이상반응에 관한 연구

Spontaneous Reporting of Adverse Drug Reactions by Community Pharmacists in Korea

2015년 8월

서울대학교 대학원

약학과 예방·임상약학전공

유 윤 미

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이 논문을 약학박사 학위논문으로 제출함
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ABSTRACT

Spontaneous Reporting of Adverse Drug Reactions by Community Pharmacists in Korea

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Purpose: To evaluate the clinical manifestations and causative drugs associated with adverse drug reactions (ADRs) spontaneously reported by community pharmacists and to compare the ADRs by age.

Methods: ADRs reported to the Regional Pharmacovigilance Center of the Korean Pharmaceutical Association by community pharmacists from January 2013 to June 2014 were included. Causality was assessed using the WHO-Uppsala Monitoring Centre system. The patient population was classified into three age groups. We analyzed 31,398 (74.9%) ADRs from 9,705 patients, identified as having a causal relationship, from a total pool of 41,930 ADRs from 9,873 patients. Median patient age was 58.0 years; 66.9% were female.

Results: Gastrointestinal system (34.4%), nervous system (14.4%), and psychiatric (12.1%) disorders were the most frequent symptoms.

Prevalent causative drugs were those for acid-related disorders (11.4%), anti-inflammatory products (10.5%), analgesics (7.2%), and antibacterials (7.1%). Comparisons by age revealed diarrhea and antibacterials to be most commonly associated with ADRs in children ($p < 0.001$), whereas dizziness was prevalent in the elderly ($p < 0.001$). Anaphylactic reaction was the most frequent serious event (19.7%), mainly associated with cephalosporins and non-steroidal anti-inflammatory drugs. Among 612 ADRs caused by nonprescription drugs, the leading symptoms and causative drugs were skin disorders (29.6%) and non-steroidal anti-inflammatory drugs (16.2%), respectively.

Conclusions: According to the community pharmacist reports, the leading clinical manifestations and causative drugs associated with ADRs in outpatients differed among age groups.

Keywords: Adverse drug reaction, Spontaneous reporting, Community pharmacy, Outpatients, Age group, Pharmacovigilance

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INTRODUCTION

An adverse drug reaction (ADR), as defined by the World Health Organization (WHO), is “a noxious and unintended response of a drug, which occurs at a dose normally used in humans for prophylaxis, diagnosis, or therapy” [1]. Previous reports have suggested that 7–11.2% of ADRs result in hospitalization [2,3] and that the mean cost of ADRs leading to admission was 2721 Euros per patient [4]. Previous studies on ADRs have focused on inpatient care settings. While hospitalized patients are under close medical monitoring, outpatients are not. Because the contact is intermittent and consultation hours are constrained, it is difficult for physicians to secure sufficient communication time to ascertain the presence of ADRs in ambulatory care settings. Thus, the risk and expense of treatment of ADRs in outpatients may increase because remedial action is often delayed [5]. Considering the large proportion of prescriptions issued in ambulatory care, knowledge of ADRs in this population is important to prevent medication-related harm.

In outpatients, community pharmacists (CPs) may effectively monitor patient safety and provide adequate information through medication counseling [6,7]. It is easy for patients to visit community pharmacies because of their wide geographical distribution and accessibility without the need for an appointment. As CPs serve

patients with and without prescriptions, their active involvement in ADR monitoring and reporting is likely to improve the scope and quality of spontaneous ADR reporting [8].

In 2013, the Korea Institute of Drug Safety and Risk Management (KIDS) added the regional pharmacovigilance center of the Korean Pharmaceutical Association (RPVC-KPA), to existing RPVCs. While the existing RPVCs targeted each regional hub and their ADR reporting was mainly centered on inpatients in affiliated hospitals [9], the activity of RPVC-KPA was conducted on a national scale and focused on outpatients in community pharmacies nationwide. All CPs can report ADRs to RPVC-KPA through the spontaneous reporting system connected to their pharmacy's billing program or the KIDS website. Participating community pharmacies comprised 4.0% of the 20,971 registered nationwide community pharmacies in Korea as of March 2014 [10]. The reports by CPs comprised 3.4% of all ADR reports sent to KIDS by healthcare professionals [10]. This is a relatively low proportion in comparison to that in Netherlands, Spain, or Portugal, but it is comparable to the proportion in the UK, France, and Japan [11]. Considering the increase in the proportion of ADR reports by CPs from 0.8% (324 reports) in the first quarter of 2013 to 10.7% (5621 reports) in the second quarter of 2014, the participation of CPs in ADR

reporting is expected to expand [10]. Pharmacovigilance in outpatients can be improved by the active participation of CPs.

Although the data from spontaneous ADR reports by CPs may provide more pertinent information for ambulatory patients [12], few studies have been reported on this topic [8]. In addition, few studies have compared the ADR patterns by age group in ambulatory care patients [13]. A systematic review for the ADRs in ambulatory care showed that most studies investigated ADRs leading to hospitalization or emergency department visit [14]. Therefore, we aimed to evaluate the clinical manifestations and causative drugs associated with ADRs spontaneously reported by CPs and compare the ADRs by age.

METHODS

Data collection

ADRs spontaneously reported to RPC-KPA by CPs nationwide from January 2013 to June 2014 were collected. According to the WHO definition, this study only included ADRs associated with a dose normally used in humans and reports associated with a drug administered for ordinary prophylactic or therapeutic purposes. Reports related to drug abuse, suicide attempts, or medication errors were excluded. To reduce the possibility of duplication, each ADR was individually compared based on the patient's age, sex, and residence; location of the participating pharmacy; date of onset of the reaction; and related drugs.

The patient population was classified into three age groups: children (less than 18 years), adult (19–63 years), and elderly (more than 64 years) groups. Reports without age were excluded. Patient records were anonymized and de-identified prior to analysis. The Institutional Review Board of Seoul National University approved this study (IRB No. 1405/002-006) and waived the requirement of informed consent.

Causality assessment

The causality of a drug for ADR was assessed using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) criteria, which was composed of six categories: certain, probable, possible, unlikely, conditional, and unassessable [15]. Causality was independently assessed by two trained pharmacists. When the pharmacists disagreed on causality, they discussed the difference and achieved consensus in all cases. The inter-rater reliability in initial assessment was calculated and Cohen's κ score greater than 0.81 was considered "very good agreement" [16]. ADRs classified as "less than possible" in the causality assessment were excluded from subsequent analysis.

Analysis of clinical manifestations and causative drugs

Clinical manifestations were classified using the WHO-adverse reaction terminology (ART) system [17]. The system-organ classes

(SOC) and the preferred terms (PT) of the WHO-ART system were used as a main- and sub-category, respectively. Symptoms matched with the same PT were treated as the same event. Two or more PTs reported in one patient and two or more medications involved in one event were counted as different ADRs. The causative drugs were classified using the Anatomical Therapeutic Chemical (ATC) classification system [18].

The frequency of clinical manifestations and causative drugs was compared according to age group. Unlabeled ADRs were identified by assessing whether reported ADRs were included in the label of each causative drug. The relationship between serious ADRs and causative drugs was evaluated by comparing the count of specific ADRs according to specific drugs.

Analysis of serious events and nonprescription drugs

Serious ADRs were defined as cases that were fatal, caused hospitalization or persistent disability, or were life-threatening according to WHO criteria [19]. The patterns of ADRs caused by

nonprescription drugs were also analyzed by comparing the number of specific clinical manifestations according to specific drugs.

Statistics

Descriptive statistics were used to summarize the demographic and clinical characteristics of study participants. Means and standard deviations were used for continuous variables, whereas frequencies and percentages were used for categorical variables. The categorical characteristics of three age groups including children, adults, and elderly were compared. Chi-squared test or Fisher's exact test was applied to compare categorical variables between groups. The significance level was set at $p < 0.01$. For post hoc analysis, chi-squared test or Fisher's exact test with Bonferroni correction was employed and the significance level was set at $p < 0.003$. Data analysis was performed using SPSS version 21.0 (SPSS Inc., Chicago, IL).

RESULTS

From January 2013 to June 2014, 42,018 ADRs from 9,919 patients were reported. A total of 920 community pharmacies participated. The proportion of participating community pharmacies located in metropolitan versus rural areas was 59.4% versus 40.6%. Forty-six patients (88 ADRs) were excluded because of a lack of information about age. Causality assessment using WHO-UMC criteria for 41,930 ADRs in 9,873 patients classified 1.4% as certain, 5.4% as probable, 68.1% as possible, 24.7% as unlikely, 0.2% as conditional, and 0.2% as unassessable. The κ score was 0.83 showing "very good agreement" between the initial assessments of causality. After exclusion of the 10,532 ADRs (25.1%) having a less than possible degree of causality, 31,398 ADRs (74.9%) in 9,705 patients were analyzed. The mean number of events per patient was 1.4 and the mean number of causative drugs per event was 2.3.

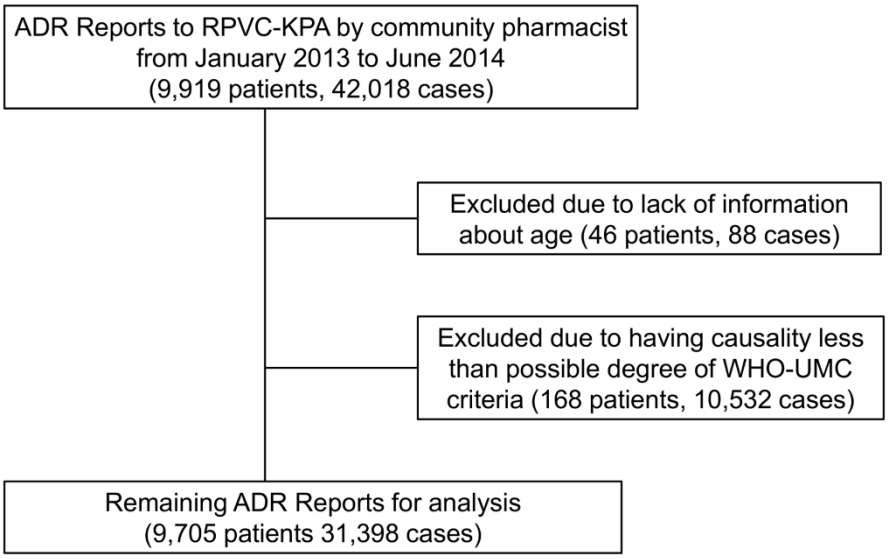


Fig. 1. The selection process for adverse drug reaction reports. ADR, adverse drug reaction; RPVC-KPA, Regional Pharmacovigilance Center-Korean Pharmaceutical Association; WHO-UMC, World Health Organization-Uppsala Monitoring Centre.

Demographic characteristics

The median age of the 9,705 patients was 58.0 years, ranging 3 months to 98 years (Table 1). The adult group comprised the largest portion of patients (64.0%), followed by the elderly group (32.5%) and children (3.5%). Females comprised 66.9% of all patients, with similar distributions in the adult and elderly subgroups. In contrast, female children comprised less than half of the pediatric group, which represented a significant difference from the other age groups ($p < 0.001$).

Table 1. Patient demographics

Characteristics	Value
Number of patients	9,705
Female (%)	66.9
Age, median (range, years)	58.0 (0.3–98.0)
Age, n (%)	
Children	**341 (3.5)**
<2 years	61 (0.6)
2–11 years	165 (1.7)
12–18 years	115 (1.2)
Adults (19–64 years)	**6,209 (64.0)**
Elderly	**3,155 (32.5)**
65–74 years	2,076 (21.4)
75–84 years	965 (9.9)
≥85 years	114 (1.2)
Reported events per patient (mean)	1.4
Reported drugs per event (mean)	2.3
Number of patients with serious events, n	52

Clinical manifestations of adverse drug reactions

The clinical manifestations most frequently associated with ADRs were gastro-intestinal (GI) system disorders (4,623 events, 34.4%) followed by nervous system disorders (1,932 events, 14.4%) and psychiatric disorders (1,620 events, 12.1%). The most common symptoms were dizziness (1,142 events, 8.5%), dyspepsia (1,139 events, 8.5%), and somnolence (847 events, 6.3%).

A comparison of clinical manifestations according to age revealed that GI system disorders and diarrhea were most common in children, but dry mouth was least frequent in this group ($p < 0.001$) (Table 2). The leading drugs causing diarrhea in children were antibacterial agents. The elderly group showed a significantly higher frequency of ADRs involved in nervous and urinary system disorders ($p < 0.001$). Dizziness was reported more frequently in the elderly than in any other age group ($p < 0.001$). The main drugs causing dizziness in elderly were analgesics and antiepileptics. Psychiatric disorders (including their subcategory somnolence) and skin disorders (including their subgroup rash and urticarial) were more frequent in children and adults ($p < 0.001$) (Table 2).

Table 2. Clinical manifestation of adverse drug reactions according to the system-organ classification and preferred terms[d]

Clinical manifestation	Total (%)	Children[a]	Adults[b]	Elderly[c]	p value[e]	Post hoc[f]
Gastro-intestinal system disorders	**4,623 (34.4)**	**200 (46.3)**	**2,875 (33.3)**	**1,548 (35.4)**	**<0.001**	**a>b,c**
Dyspepsia	1,139 (8.5)	4 (0.9)	747 (8.7)	388 (8.9)	<0.001	a<b,c
Nausea	802 (6.0)	20 (4.6)	550 (6.4)	232 (5.3)	0.025	
Diarrhea	575 (4.3)	115 (26.6)	311 (3.6)	149 (3.4)	<0.001	a>b,c
Dry mouth	570 (4.2)	2 (0.5)	315 (3.7)	253 (5.8)	<0.001	a<b<c
Vomiting	483 (3.6)	23 (5.3)	291 (3.4)	169 (3.9)	0.053	
Constipation	401 (3.0)	10 (2.3)	249 (2.9)	142 (3.2)	0.371	
Abdominal pain	324 (2.4)	16 (3.7)	196 (2.3)	112 (2.6)	0.123	
Nervous system disorders	**1,932 (14.4)**	**25 (5.8)**	**1,160 (13.4)**	**747 (17.1)**	**<0.001**	**c>b>a**

Dizziness	1,142 (8.5)	5 (1.2)	658 (7.6)	479 (10.9)	<0.001	c>b>a
Headache	366 (2.7)	3 (0.7)	243 (2.8)	120 (2.7)	0.03	
Psychiatric disorders	**1,620 (12.1)**	**71 (16.4)**	**1,111 (12.9)**	**438 (10.0)**	**<0.001**	**c<a,b**
Somnolence	847 (6.3)	37 (8.6)	635 (7.4)	175 (4.0)	<0.001	c<a,b
Insomnia	446 (3.3)	15 (3.5)	279 (3.2)	152 (3.5)	0.758	
General disorders	**1,551 (11.5)**	**38 (8.8)**	**994 (11.5)**	**519 (11.9)**	**0.163**	
Edema	380 (2.8)	3 (0.7)	254 (2.9)	123 (2.8)	0.023	
Asthenia	314 (2.3)	9 (2.1)	204 (2.4)	101 (2.3)	0.92	
Skin disorders	**1,543 (11.5)**	**68 (15.7)**	**1,095 (12.7)**	**380 (8.7)**	**<0.001**	**c<a,b**
Pruritus	457 (3.4)	15 (3.5)	289 (3.3)	153 (3.5)	0.906	
Rash	401 (3.0)	27 (6.3)	294 (3.4)	80 (1.8)	<0.001	c<a,b

Urticaria	191 (1.4)	11 (2.5)	150 (1.7)	30 (0.7)	<0.001	c<a,b
Urinary system disorders	**572 (4.3)**	**8 (1.9)**	**328 (3.8)**	**236 (5.4)**	**<0.001**	**c>a,b**
Face edema	340 (2.5)	6 (1.4)	214 (2.5)	120 (2.7)	0.205	
Cardiovascular disorders	**320 (2.4)**	**4 (0.9)**	**210 (2.4)**	**106 (2.4)**	**0.131**	
Palpitation	156 (1.2)	2 (0.5)	115 (1.3)	39 (0.9)	0.033	
Respiratory system disorders	**252 (1.9)**	**3 (0.7)**	**166 (1.9)**	**83 (1.9)**	**0.183**	
Metabolic disorders	**227 (1.7)**	**3 (0.7)**	**161 (1.9)**	**63 (1.4)**	**0.054**	
Musculo-skeletal system disorders	**211 (1.6)**	**1 (0.2)**	**129 (1.5)**	**81 (1.9)**	**0.023**	

[d]Number of events and percentage of individual events within each group.

[e]Chi-squared test of the three groups.

[f] Bonferroni correction ($p < 0.003$) with chi-squared or Fisher's exact test.

Causative drugs

The most prevalent causative drugs were alimentary tract and metabolism drugs (6,984 ADRs, 22.2%), followed by musculoskeletal system drugs (5,436 ADRs, 17.3%) and nervous system drugs (5,210 ADRs, 16.6%). According to the subclassification, drugs for acid-related disorders (3,588 ADRs, 11.4%), anti-inflammatory products (3,305 ADRs, 10.5%), analgesics (2,262 ADRs, 7.2%), and antibacterials (2,240 ADRs, 7.1%) were frequently associated with ADRs.

Drugs acting on the respiratory system and anti-infective drugs were more frequently involved in ADRs in the pediatric population than in other groups ($p < 0.001$). Drugs for the nervous system, cardiovascular system, genitourinary system and sex hormones, and blood and blood-forming organs were reported more frequently as causative drugs for ADRs in the elderly ($p < 0.001$) (Table 3). Unlabeled ADRs were not identified. A comparison of causative drugs according to sex revealed that urological agents were more prevalently involved in ADRs in males ($p < 0.001$) (Fig. 2).

Drugs for acid related disorders and anti-inflammatory products were

the most common causative drugs for nervous system adverse reactions. However, ADRs involving nervous system comprised highest proportions of ADRs which were reported to be related with antithrombotic agents and beta-blocking agents. Also, psychiatric disorders comprised largest proportion of ADRs associated with antiobesity and nasal preparations while antihistamines and drugs for acid related disorders were the most frequent suspect drugs of psychiatric disorders. Among the skin disorders, anti-inflammatory products and drugs for acid related disorders were the most common offending drugs. However the drugs with the highest proportion in skin disorders, were topical products for joint and muscle pain and antineoplastic agents (Figure 3).

Table 3. Causative drugs for adverse drug reactions according to the second level of anatomical therapeutic chemical classification system[d]

Causative drugs	Total (%)	Children[a]	Adults[b]	Elderly[c]	p value[e]	Post hoc[g]
Alimentary tract and metabolism[h]	**6,984 (22.2)**	**74 (7.3)**	**4,564 (22.8)**	**2,346 (22.6)**	**<0.001**	**a<b,c**
Drugs for acid related disorders	3,588 (11.4)	30 (3.0)	2,359 (11.8)	1,199 (11.6)	<0.001	a<b,c
Drugs for functional GI disorders	1,850 (5.9)	22 (2.2)	1,232 (6.2)	596 (5.8)	<0.001	a<b,c
Drugs used in diabetes	713 (2.3)	0 (0)	430 (2.1)	283 (2.7)	<0.001[f]	
Others	833 (2.7)	22 (2.2)	543 (2.7)	268 (2.6)		
Musculo-skeletal system[i]	**5,436 (17.3)**	**130 (12.9)**	**3,630 (18.1)**	**1,676 (16.2)**	**<0.001**	**b>a,c**
Anti-inflammatory products	3,305 (10.5)	100 (9.9)	2,233 (11.2)	972 (9.4)	<0.001	c<b
Muscle relaxants	1,057	2 (0.2)	721	334	<0.001	a<b,c

	(3.4)		(3.6)	(3.2)		
Others	1,074	28 (2.8)	676	370		
	(3.4)		(3.4)	(3.6)		
Nervous system[j]	**5,210**	**82 (8.1)**	**3,040**	**2,088**	**<0.001**	**a<b<c**
	(16.6)		**(15.2)**	**(20.1)**		
Analgesics	2,262	33 (3.3)	1,444	785	<0.001	a<b,c
	(7.2)		(7.2)	(7.6)		
Antiepileptics	1,131	26 (2.6)	649	456	<0.001	b<c
	(3.6)		(3.2)	(4.4)		
Psycholeptics	812	8 (0.8)	443	361	<0.001	c>a,b
	(2.6)		(2.2)	(3.5)		
Psychoanaleptics	774	13 (1.3)	383	378	<0.001	c>a,b
	(2.5)		(1.9)	(3.6)		
Others	231	2 (0.2)	121	108		
	(0.7)		(0.6)	(1.0)		
Respiratory	**4,280**	**389**	**2,784**	**1,107**	**<0.001**	**a>b>c**
system[k]	**(13.6)**	**(38.5)**	**(13.9)**	**(10.7)**		
Antihistamines	1,589	128	1,079	391	<0.001	a>b>c
	(5.1)	(12.7)	(5.4)	(3.8)		
Cough/cold	1,343	118 (11.7)	874	351	<0.001	a>b>c
preparations	(4.3)		(4.4)	(3.4)		
Drugs for OA	769	80 (7.9)	433	256	<0.001	a>b,c

diseases	(2.4)		(2.2)	(2.5)		
Nasal	491	51 (5.0)	347	93 (0.9)	<0.001	a>b>c
preparations	(1.6)		(1.7)			
others	79	12 (1.2)	51 (0.3)	16 (0.2)		
	(0.3)					
Cardiovascular	**3,207**	**4 (0.4)**	**1,794**	**1,409**	**<0.001**	**a<b<c**
system[l]	**(10.2)**		**(9.0)**	**(13.6)**		
Lipid modifying	875	1 (0.1)	536	338	<0.001	a<b,c
agents	(2.8)		(2.7)	(3.3)		
Agents acting on	783	1 (0.1)	442	340	<0.001	a<b<c
the RAS	(2.5)		(2.2)	(3.3)		
Calcium channel	375	0 (0)	214	161	<0.001[f]	
blockers	(1.2)		(1.1)	(1.6)		
Others	1,174	2 (0.2)	602	570		
	(3.7)		(3.0)	(5.5)		
Antiinfectives for	**2,658**	**262**	**1,880**	**516**	**<0.001**	**a>b>c**
systemic use[m]	**(8.5)**	**(25.9)**	**(9.4)**	**(5.0)**		
Antibacterials	2,240	252	1.584	404	<0.001	a>b>c
	(7.1)	(25.0)	(7.9)	(3.9)		
Others	418	10 (1.0)	296	112		
	(1.3)		(1.5)	(1.1)		
GU system and	**874**	**2 (0.2)**	**495**	**377**	**<0.001**	**a<b<c**

sex hormones[n]	**(2.8)**		**(2.5)**	**(3.6)**		
Urologicals	629 (2.0)	1 (0.1)	278 (1.4)	350 (3.4)	<0.001	a<b<c
Others	245 (0.8)	1 (0.1)	217 (1.1)	27 (0.3)		
Systemic hormonal preparations[o]	**848 (2.7)**	**34 (3.4)**	**611 (3.1)**	**203 (2.0)**	**<0.001**	**c<a,b**
Corticosteroids	733 (2.3)	33 (3.3)	536 (2.7)	164 (1.6)	<0.001	c<a,b
Others	115 (0.4)	1 (0.1)	75 (0.4)	39 (0.4)		
Blood and blood forming organs[p]	**768 (2.4)**	**3 (0.3)**	**412 (2.1)**	**353 (3.4)**	**<0.001**	**a<b<c**
Antithrombotic agents	597 (1.9)	1 (0.1)	292 (1.5)	304 (2.9)	<0.001	a<b<c
Others	171 (0.5)	2 (0.2)	120 (0.6)	49 (0.5)		
Antineoplastics[q]	**546 (1.7)**	**7 (0.7)**	**434 (2.2)**	**105 (1.0)**	**<0.001**	**b>a,c**
Dermatologicals[r]	**252 (0.8)**	**14 (1.4)**	**185 (0.9)**	**53 (0.5)**	**<0.001**	**c<a,b**

Sensory organs[s]	**250 (0.8)**	**6 (0.6)**	**133 (0.7)**	**111 (1.1)**	**0.001**	**c>b**
Others	**85 (0.3)**	**3 (0.3)**	**61 (0.3)**	**21 (0.2)**		

GI, gastro-intestinal; OA, obstructive airway; GU, genito-urinary.

[d]Number of adverse drug reactions (ADRs) and percentage of individual ADRs within each group.

[e]Chi-squared test among the three groups.

[f]Chi-squared test between the adult and elderly groups.

[g]Bonferroni correction ($p < 0.003$) with chi-squared test or Fisher's exact test.

[h]Ranitidine, pantoprazole, levosulpiride, trimbutine, metformin, and glimepiride, etc.

[i]Ibuprofen, loxoprofen, chlorphenesin, and orphenadrine, etc.

[j]Acetaminophen, combination of acetaminophen and tramadol, valproate, gabapentin, alprazolam, risperidone, donepezil, and duloxetine, etc.

[k]Olopatadine, levocetirizine, combination of chlorpheniramine and dihydrocodeine, combination of acetaminophen and ephedrine, montelukast, theophylline, combination of pseudoephedrine and triprolidine, and pseudoephedrine, etc.

[l]Atorvastatin, pravastatin, combination of valsartan and amlodipine, combination of telmisartan and amlodipine, amlodipine, and diltiazem, etc.

[m]Combination of amoxicillin and clavulanate, cefaclor, and ciprofloxacin, etc.

[n]Pentosan polysulfate, terazosin, and tolterodine, etc.

[o]Dexamethasone, triamcinolone, and methylprednisolone, etc.

[p]Aspirin, clopidogrel, and warfarin, etc.

[q]Cyclosporine, mycophenolate, and capecitabine, etc.

[r]Terbinafine, clobetasol propionate, and benzoyl Peroxide, etc.

[s]Hyaluronate, timolol, and fluorometholone, etc.

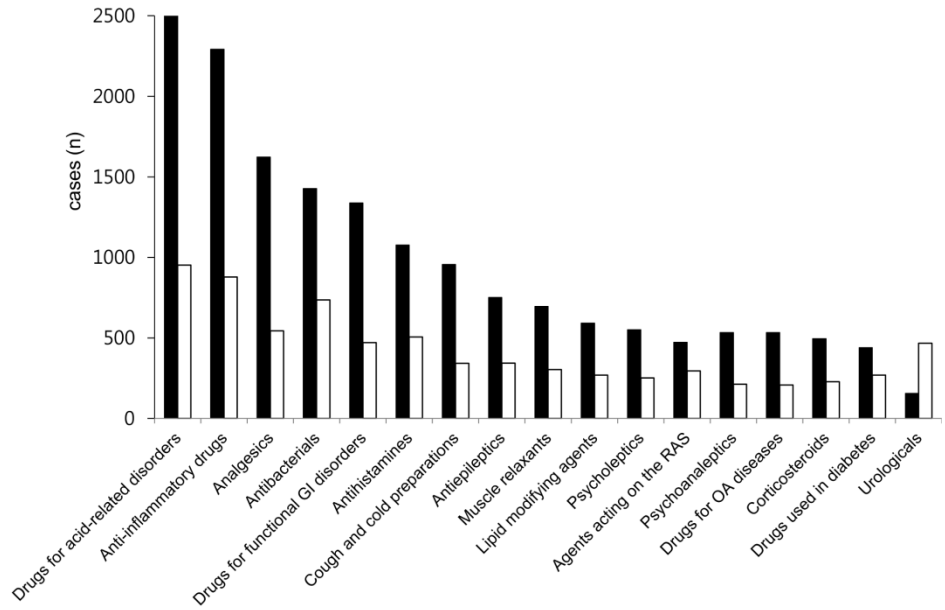
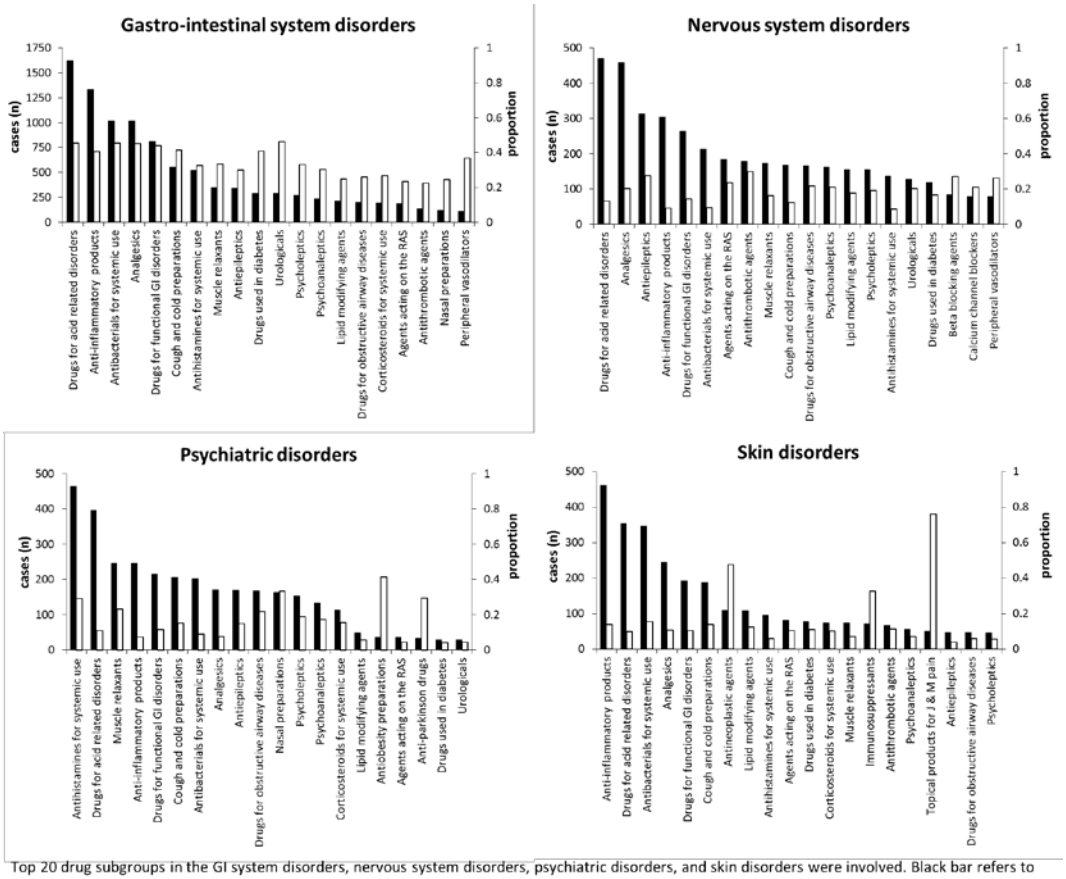


Fig. 2. Frequency of adverse drug reactions and causative drugs according to sex. GI, gastrointestinal; RAS, renin-angiotensin system; OA, obstructive airway. Black bars: female; white bars: male.



Top 20 drug subgroups in the GI system disorders, nervous system disorders, psychiatric disorders, and skin disorders were involved. Black bar refers to the number of adverse drug reaction cases and white bar means the proportion among all cases related with sepcific drug groups. GI, gastro-intestinal; RAS, renin-angiotensin system; J & M, joint and muscle

Figure 3. The number of specific adverse drug reaction case and the proportion of each case among all cases according to specific drug groups.

Serious events

In total, 66 serious events were identified in 52 patients who experienced a life-threatening event (15 patients), hospitalization (36 patients), or persistent disability (1 patient). The life-threatening events included symptoms associated with anaphylactic reactions, dyspnea, and circulatory failure. The persistent disability involved blindness and ocular hemorrhage associated with everolimus, an antineoplastic agent. The proportion of serious events in adults and elderly groups was 0.58% and 0.51%, respectively. There were no serious event reports for the pediatric population. Among serious events, the most common symptoms were anaphylactic reaction (13 events, 19.7%) (Table 4). Cephalosporins and non-steroidal anti-inflammatory drugs (NSAIDs) were most frequently associated with this symptom. Non-steroidal anti-inflammatory drugs (NSAIDs) (18 ADRs, 19.8%), analgesics (17 ADRs, 18.7%), and antibacterials (13 ADRs, 14.3%) were the main causative agents for serious adverse events (Table 5).

Table 4. Clinical manifestation in serious events

Classification	Number of events (%)	Clinical manifestation (n) [a]
General disorders	16 (24.2)	Anaphylactic reaction (13), edema (2), asthenia (1)
Gastro-intestinal system disorders	15 (22.7)	Vomiting (8), abdominal pain (3), gastro-intestinal hemorrhage (2), dyspepsia (1), tongue disorder (1)
Nervous system disorders	13 (19.7)	Dizziness (9), headache (1), vocal cord paralysis (1), dyskinesia (1), dystonia (1)
Cardiovascular disorders	6 (9.1)	Circulatory failure (2), ocular hemorrhage (1), palpitation (1), hypertension (1), hypotension postural (1)
Respiratory system disorders	3 (4.5)	Dyspnea (3)
Urinary system disorders	3 (4.5)	Dysuria (3)

Liver and biliary system disorders	3 (4.5)	Hepatic enzyme increased
Skin disorders	2 (3.0)	Bullous eruption (1), rash (1)
Vision disorders	2 (3.0)	Blindness (1), vision abnormal (1)
Reproductive disorders	2 (3.0)	Uterine hemorrhage (1), intermenstrual bleeding (1)
Metabolic disorders	1 (1.5)	Hypoglycemia (1)

[a]Numbers in parentheses indicate the number of serious events.

Table 5. Causative drugs and clinical manifestation in serious events

Causative drugs	Number of ADRs (%)	Clinical manifestation (n)[a]
Anti-inflammatory products[b]	18 (19.8)	AR (8), edema (2), vomiting (2), dizziness (2), CF, uterine hemorrhage, bullous eruption, vision abnormal
Analgesics[c]	17 (18.7)	AR (3), vomiting (5), AP, dizziness (5), headache, HE increased, dyspnea
Antibacterials[d]	13 (14.3)	AR (9), AP, GI hemorrhage (2), dyspepsia
Urologicals	5 (5.5)	asthenia, dizziness, hypotension postural, dysuria (2)
Psychoanaleptics	4 (4.4)	vomiting, AP, dysuria, palpitation
Drugs used in diabetes	4 (4.4)	CF, dyspnea, hypoglycemia (2)
Antithrombotic agents	4 (4.4)	GI hemorrhage (2), CF, dyspnea
Antiepileptics	2 (2.2)	vomiting, dizziness

Digestives	2 (2.2)	tongue disorder, dyskinesia
Drugs for acid related disorders	2 (2.2)	GI hemorrhage, hypertension
Drugs for functional GI disorders	2 (2.2)	vocal cord paralysis, dystonia
Sex hormones	2 (2.2)	dizziness, intermenstrual bleeding
Cough and cold preparations	2 (2.2)	AR, rash
Drugs for OA disease	2 (2.2)	AR, AP
Peripheral vasodilators	2 (2.2)	vomiting, dizziness
Antineoplastic agents	2 (2.2)	blindness, ocular hemorrhage
Antivirals	1 (1.1)	vomiting
Antimycotics	1 (1.1)	HE increased
Nasal preparations	1 (1.1)	dysuria
Cardiac therapy	1 (1.1)	CF
Lipid modifying agents	1 (1.1)	CF
Agents acting on the RAS	1 (1.1)	vomiting

Immunosuppressants	1 (1.1)	HE increased
Corticosteroids	1 (1.1)	HE increased

ADRs, adverse drug reactions; GI, gastrointestinal; OA, obstructive airway diseases; RAS, renin-angiotensin system; AR, anaphylactic reaction; AP, abdominal pain; HE, hepatic enzyme; CF, circulatory failure.

[a]Numbers in parentheses indicate the number of adverse drug reactions.

[b]Dexibuprofen, loxoprofen, and celecoxib, etc.

[c]Combination of acetaminophen and tramadol, buprenorphine, and sumatriptan, etc.

[d]Cefaclor, cefadroxil, and amoxicillin, etc.

Nonprescription drugs

Nonprescription drugs were implicated in 394 patients and 680 ADRs. The adult group comprised the largest portion of patients (76.4%), followed by the elderly group (18.8%) and children (4.8%). Skin disorders (181 events, 29.6%) including rash and pruritus were the most frequently reported manifestations, followed by GI system disorders (155 events, 25.3%) such as dyspepsia and nausea. Among a total of 186 causative drugs, NSAIDs (110 ADRs, 16.2%) and topical products for joint and muscular pain (56 ADRs, 8.2%) were most common. A combination drug containing acetaminophen and chlorzoxazone (40 ADRs, 5.8%) was the most prevalent individual drug, followed by naproxen (37 ADRs, 5.4%) and ibuprofen (29 ADRs, 4.2%) (Table 6). A comparison of ADRs by nonprescription drugs according to age in 394 patients revealed that NSAIDs and GI system disorders were more frequently involved in children than in other groups ($p < 0.001$). NSAIDs and GI system disorders respectively comprised 48.7% of the ADRs by nonprescription drugs in the pediatric group.

Table 6. Causative drugs and clinical manifestation among the nonprescription drugs[a]

Causative drugs	Number of ADRs (%)	Clinical manifestation (n)[b]
Musculo-skeletal system		
Acetaminophen/chlorzoxazone	40 (5.8)	dizziness (10), pruritus (3), urticaria (3), dyspepsia (3), vomiting (3), nausea (3), rash (2)
Naproxen	37 (5.4)	dyspepsia (6), edema (4), pruritus (4), rash (4), abdominal pain (2)
Ibuprofen	29 (4.2)	dyspepsia (4), vomiting (3), abdominal pain (3), urticaria (3), dizziness (2)
Ketoprofen patch	17 (2.5)	rash (6), pruritus (4), skin exfoliation (2)
Dexibuprofen	16 (2.3)	urticaria (6), edema periorbital (3), dizziness (2)
Ibuprofen arginine	15 (2.2)	edema periorbital (4), pruritus (3), nausea (2), sweating increase (2)

Flurbiprofen patch	13 (1.9)	rash (4), pruritus (2), skin exfoliation (2), dermatitis (2)
Clonixin	9 (1.3)	urticaria (3)
Alimentary tract		
Antacid combinations[c]	10 (1.4)	constipation (2)
Respiratory system		
Pseudoephedrine/triprolidine	18 (2.6)	insomnia (4), dizziness (2), sweating increase (2), somnolence (2)
Cetirizine	11 (1.6)	headache (2), somnolence (2)
Flurbiprofen 8.75 mg	9 (1.3)	dizziness (2), palpitation (2)
Nervous system		
Acetaminophen/methionine	25 (3.6)	edema (3), nausea (3), rash (3), urticaria (2), vomiting (2), dyspnea (2), drug dependence (2)
Gingko leaf ext.	10 (1.4)	pruritus (2), dyspepsia (2)
Nicotine patch	9 (1.3)	dermatitis (3), pruritus (2)
Diphenhydramine	7 (1.0)	abdominal pain (2)
GU system and sex hormones		

Agnus Castus fruit ext.	18 (2.6)	abdominal pain (4), rash (2), nausea (2), acne (2)
Desogestrel/ ethinyl Estradiol	14 (2.0)	menstrual disorder (4), nausea (2), weight increase (2)
Gestodene/ethinyl Estradiol	12 (1.7)	edema (2), acne (2)
Dermatologicals		
Benzoyl peroxide ointment	8 (1.2)	rash (3), pruritus (2)

ADRs, adverse drug reactions; GU, genito-urinary.

[a]680 adverse drug reactions from 394 patients.

[b]Clinical manifestations reported for more than one adverse drug reaction and the number of adverse drug reactions.

[c]Combinations of aluminum magnesium silicate/ranitidine/magnesium oxide/aluminum magnesium hydroxide.

DISCUSSION

To the best of our knowledge, this is the first large-scale study of CP-reported ADRs in outpatients in Korea. Reports of clinical manifestations affecting the GI system, nervous system, and psychiatric disorders were prevalent. The most frequent causative drugs were those used to treat acid-related disorders, anti-inflammatory products, analgesics, and antibacterials. ADR patterns differed by age group. Our findings suggest the need to establish pharmacovigilance strategies adapted to outpatient characteristics and age group.

In this study, females comprised around two-thirds (66.9%) of the study cohort who had experienced ADRs, which could be explained by the epidemiological population distribution (female, 58.3%) among the average daily number of outpatients [20]. A multinational study reported that the ADR reporting rate of antidepressants was not significantly different between men and women when considering drug consumption [21]. However, other studies have suggested a preponderance of ADRs in female patients [13,22,23]. The higher adverse event rate in females has been found to result from differences in pharmacokinetic factors [22], hormonal factors [24], drug prescription rate [23], medical care utilization [20,25], propensity of

symptom reporting [25], and a historical lack of drug research in this population [26]. In the present study, women also experienced more than twice the number of anaphylactic reactions compared to men. Ribeiro-Vaz et al. also showed that females are more likely to experience anaphylaxis [27].

Comparison of the ADR reports by CPs with the entire set of ADR reports to KIDS during the same period showed that the prevalent ADR symptoms were GI and nervous system disorders and the most frequent causative drugs were anti-inflammatory products, analgesics, and antibacterials in both reports [10]. However, the proportion of serious events (0.54%) in reports by CPs was much lower than that in the entire ADR dataset (11.2%) [10], which can be explained mainly by the relatively less severe medical state of outpatients and by the limited experience of CPs in ADR reporting. The non-seriousness that prevails in early periods of pharmacovigilance by a new expert group may be one of the reasons for the low proportion of serious events in this study [28].

The clinical manifestations and causative drugs showed specific trends according to age. In the pediatric group, GI system disorders, especially diarrhea, and antibacterial agents were most frequent. These results are consistent with previous reports. Two systematic reviews

and a prospective cohort study showed that antibacterial agents and GI disorders were the leading causes and symptoms, respectively, of ADRs in pediatric outpatients [14,29,30]. In this study, antibacterial agents comprised 46.1% of the drugs causing diarrhea in children. Infants aged less than 24 months and patients taking broad-spectrum penicillins or cephalosporins accounted for 37.0% and 81.9% of the children who experienced antibacterial-associated diarrhea. These results are consistent with the risk associated with reduced fecal flora in infants and broad-spectrum penicillins and cephalosporins in pediatric diarrhea [31,32].

Dizziness was the most common symptom in the elderly, consistent with reports of a 30% prevalence in older populations [33]. Maarsingh et al. showed that medications were the second leading cause of dizziness following comorbidities such as cardiovascular and peripheral vestibular disease in the elderly [34]. In this study, the main drugs associated with dizziness were those used to treat the nervous system (29.5%), such as combination drugs containing acetaminophen and tramadol (9.3%), gabapentin (3.9%), and pregabalin (3.8%). Considering the risk of secondary injury resulting from dizziness in the elderly, use of these drugs should be carefully monitored and evaluated.

Cephalosporin antibiotics and NSAIDs were mainly associated with

anaphylactic reactions, which was the major clinical manifestation in serious events. A review of a decade of spontaneous ADR reports showed similar results; antibiotics and the combination of NSAIDs and acetaminophen were primarily responsible for the incidence of anaphylaxis [27].

For nonprescription drugs, skin and GI system disorders were most prevalent, and were chiefly caused by NSAIDs such as naproxen and ibuprofen. A prospective multi-center study also reported that the most frequent nonprescription drugs causing ADR-related hospital admissions were NSAIDs including aspirin, diclofenac, and ibuprofen; the leading symptoms were GI disorders [35].

This study has several limitations. First, we relied on spontaneous reporting, which is subject to under-reporting and lack of information [36,37]. All data were retrospective and we were unable to confirm accuracy or replace missing data. However, spontaneous reporting by CPs has the advantages of providing the direct outpatient complaints [38]. Second, although these pharmacovigilance systems are intended to detect signals, unlabeled ADRs were not identified; therefore, we could not suggest any potential signals. Third, we could not account for the size of the at-risk population because of a lack of information on substantial drug usage (the number of prescriptions for each causative

drug at each participating pharmacy) in outpatients. Because commonly prescribed drugs are more likely to be the offenders in ADR events [39], considering the prevalence of drug usage might aid in the interpretation of ADR frequency.

CONCLUSION

In summary, among the outpatient ADRs spontaneously reported by CPs, those involving the GI system, nervous system, and psychiatric disorders were prevalent. Anti-inflammatory products, analgesics, and antibacterials were the leading causes of ADRs, including serious events. The patterns of outpatient ADRs reported by CPs also differed between age groups.

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APPENDIX

Appendix 1.

The Clinical Characteristics of Adverse Drug Reactions Reported from the Community Pharmacy

Objective: To evaluate the clinical manifestations and causative drugs of the outpatient adverse drug reactions (ADRs) reported by community pharmacy. **Methods:** From April 2013 to September 2013, all outpatient ADRs reported by community pharmacy to Regional Pharmacovigilance Center of Korean Pharmaceutical Association were included. The causality of ADRs was assessed by the criteria of WHO-Uppsala Monitoring Centre. The clinical features and the offending drugs were analyzed using the WHO-Adverse Reaction Terminology and the classification of American Hospital Formulary Service Drug Information, respectively. **Results:** 2,826 (97.0%) of the total 2,912 ADRs had causal relationship. The 1,923 patients with mean age of 55.1 years and female fraction of 66.5% were included in the ADRs. Gastrointestinal (33.6%), nervous system (14.9%), and skin (13.5%) symptoms were common in ADRs. Analgesic drugs (19.7%), gastrointestinal drugs (17.7%), and central nervous system drugs (11.0%) were prevalent offending drugs. The leading causative generic drug was the complex of acetaminophen and tramadol. Among 203 ADRs by the nonprescription drugs, the most common clinical features were skin (37.4%) and gastrointestinal

(23.6%) symptoms and the most prevalent offending drugs were analgesic drugs (40.0%) and mucocutaneous system drugs (16.3%). The combination of acetaminophen and chlorzoxazone was the leading causative generic in nonprescription drugs. **Conclusion:** In this study, gastrointestinal symptom was the most common manifestation and analgesic drug was the most common causative drug in outpatient ADRs reported by community pharmacy.

연구방법

연구대상 및 자료수집

2013년 4월부터 9월까지 6개월간, 전국 지역약국과 외래환자로부터 대한약사회 지역의약품안전관리센터에 보고된 ADR 사례를 대상으로 하였다. 각 ADR 보고로부터 환자의 이름, 성별, 생년월일, ADR 증상, 의심약물의 투여 시작일 및 종료일, 증상발현일, 증상에 대한 조치, 재 투여 시 증상발현 여부, 의심약물 및 병용약물, 처방의약품 여부 (처방조제, 약국일반의약품, 안전상비의약품, 기타 중 택일), 보고 약국명 및 지부소속에 관한 자료를 수집하였다.

한 보고사례에서 두 가지 이상의 증상이 발생한 경우에 서로 다른 보고 건수로 간주하였으며, 한 가지 증상이 두 가지 이상의

약물에 의해 발생한 경우에 해당 약물 모두를 원인약물로 간주하였다. 또한, 환자의 이름, 성별, 생년월일, 보고약국의 지부소속, 의심약물 및 ADR증상이 모두 일치하는 경우, 한 환자가 동일한 약물에 대해 같은 증상의 ADR을 2회 이상 보고한 것으로 판단하여 동일 보고사례로 간주하였다.

ADR 사례에서 환자의 성별이나 나이 정보가 없는 경우, 해당 사례를 성별이나 나이에 따른 분석에서는 제외하였고, 이외 기술통계학적 분석에는 포함하였다.

약물유해반응의 인과성 평가

약물과 ADR 간의 인과성평가는 World Health Organization-Uppsala Monitoring Centre (WHO-UMC) 기준을 근거로 하였으며, 확실함 (certain), 가능성 높음(probable), 가능성 있음(possible), 가능성 적음(unlikely), 평가곤란(conditional/unclassified), 평가불가(unassessable)의 6단계로 분류하였다.[15,16] WHO-UMC 기준에서 가능성 있음(possible) 이상으로 평가된 경우에 대해서만 유의한 ADR로 간주하고 분석에 포함하였다.

약물유해반응의 증상 분류

ADR 증상의 분류에는 32개의 기관분류(system organ classes)와 180개의 상급용어(high level terms) 및 2,085개의 우선용어(preferred terms), 3,445개의 포함용어(included terms)로 이루어져 있는 World Health Organization Adverse Reaction Terminology(WHOART) 코드 체계를 사용하였다.[17,18] 먼저 지역약국이나 외래환자가 보고한 ADR 증상과 일치하는 포함용어나 우선용어를 검색하였고, 이에 해당되는 기관분류를 선택하였다. 단, 본 연구에서는 Common Terminology Criteria for Adverse Events (CTCAE) v4.0 분류를 참고로,[19] WHOART의 기관분류 1코드가 동일한 경우 한 분류로 통합하고, 근골격계 이상과 콜라겐 이상을 근골격계 및 콜라겐 이상으로 통합하여, 32개로 이루어진 기관분류를 19개의 ADR 증상 분류로 표시하였다. 19개의 증상 분류는 피부, 근골격계, 신경계, 안과 및 이비인후과적, 정신과적, 위장관계, 간담도계, 대사 및 영양관련, 내분비계, 심혈관계, 호흡기계, 혈액계, 비뇨기계, 생식기계, 태아관련, 신생아 및 유아관련, 종양관련, 전신성, 기타 증상으로 나누었다(Index 1).

원인약물의 약효별 분류

원인약물의 약효별 분류에는 American Hospital Formulary Service

Drug Information 기준을 사용하였다.[20] 단, 본 연구에서는 Anatomical Therapeutic Chemical (ATC) Classification System 분류를 참고로 하여,[21] 평활근육 이완제와 기타약물 항목에서 비뇨생식기계 약물을 분리하였다. 또한, 기존 연구들에서 진통제를 별도로 분류하여 ADR 보고빈도를 나타낸 점을 고려하여,[7-12] 중추신경계 약물항목에서 진통제를 분리하여 표시하였다. 이에 따라 원인약물들은 진통제, 항히스타민제, 항감염제, 항암제, 자율신경계약 및 근이완제, 혈액생성 및 응고관련 약물, 심혈관계 약물, 중추신경계 약물, 진단관련 약물, 전해질 및 열량 조절제, 안과 및 이비인후과 약물, 위장관계 약물, 비뇨생식기계 약물, 호르몬제, 호흡기계 약물, 피부 및 점막 약물, 비타민 및 무기질, 기타 약물 등 18개 약효군으로 분류하였다(Index 2).

일반의약품 및 안전상비약품의 분석

처방전 없이 구입하여 복용한 일반의약품과 안전상비약품의 경우를 처방의약품과 구분하여 해당 약물들의 ADR 증상과 약효별 분류 특성을 분석하였다.

통계적 분석

기술통계분석을 사용하여 연속형 변수는 평균과 표준편차로 나타내었고, 범주형 변수는 빈도수와 백분율로 나타내었다.

연구결과

약물유해반응의 보고양상 분석

총 1,967명 환자에서 2,912건의 ADR 의심사례가 보고되었다. ADR 보고 사례수는 4월에 153예에서 5월 263예, 6월 265예, 7월 337예, 8월 404예, 9월에는 545예로 꾸준히 증가하였다. 지역별 사례수는 서울지역 492예, 부산지역 481예, 경기지역 330예, 인천지역에서 143예가 보고되었다. ADR 보고에 참여한 약국은 총 316개 약국이었으며, 지역별로는 경기지역 74개, 서울지역 54개, 부산지역 44개, 인천지역에서 31개 약국이 참여하였다.

약물유해반응의 인과성 평가

전체 2,912건의 보고건수에 대해 약물과 유해반응간의 인과성을 WHO-UMC 기준으로 평가하였을 때, 확실함 120건(4.1%), 가능성 높음 524건(18%), 가능성 있음 2,182건(74.9%), 가능성 적음 72건(2.5%), 평가곤란 14건(0.5%))으로 가능성 있음이 가장 많았다.

가능성 있음(possible) 이상으로 평가된 ADR만을 약물과 인과관계가 있다고 판단하고, 해당 환자 1,923명, 보고건수 2,826건(97.0%)에 대해 분석을 시행하였다.

환자 특징

유의한 인과관계를 보인 환자 1,923명중 연령이 보고된 환자는 1,828명이었고, 평균연령±표준편차는 55.1±17.0세였다. 12세 미만의 소아는 40명(2.2%), 12세이상 19세미만의 청소년층은 24명(1.3%), 19세이상 65세미만의 성인은 1,188명(65.0%), 65세 이상의 노인은 576명(31.5%)으로 성인이 가장 많았다. 성별이 보고된 환자는 1,812명이었으며, 이중 남성이 607명(33.5%), 여성이 1,205명(66.5%)이었다. 연령대별 여성의 비율은 소아에서 52.8%, 청소년층에서 50.0%, 성인에서 67.9%, 노인에서 64.2%로, 청소년층을 제외한 전체 연령대에서 여성의 비율이 남성보다 높았다. 환자 1인당 ADR 발생 건수는 평균 1.5건이었고, ADR 발생 건수당 관련 약물 수는 평균 2.2개로 나타났다.

약물유해반응 증상의 분석

ADR 증상의 분류별 발생빈도는 위장관계 증상이

950건(33.6%)으로 가장 많이 나타났으며, 다음으로 신경계 증상이 420건(14.9%), 피부 증상이 382건(13.5%), 전신성 증상이 380건(13.4%)으로 많았다(Table 1). 단일 증상으로 가장 빈도가 높았던 ADR 증상은 현기증으로 250건(8.8%)이었고, 복부불편감이 164건(5.8%), 오심이 154건(5.4%), 졸림이 151건(5.3%)으로 빈도가 높게 나타났다(Table 1).

원인약물의 분석

원인약물을 약효별로 분류하였을 때, 진통제가 1,204건(19.7%)으로 가장 많았으며, 다음으로 위장관계 약물이 1,103건(17.7%), 중추신경계 약물이 683건(11.0%), 심혈관계 약물이 594건(9.6%)으로 많았다(Table 2). 성분별 주요 약물로는 acetaminophen/tramadol 복합제 (383건), ranitidine (156건), aceclofenac (145건), mosapride (136건), streptokinase/streptodornase 복합제 (130건), eperison (114건), rebamipide (112건), loxoprofen (111건), acetaminophen (108건), Artemisia asiatica herb (88건), cefaclor (83건), amoxicillin/clavulanate 복합제 (82건), gabapentin (80건)이 높은 빈도를 보였다.

일반의약품 및 안전상비약품의 약물유해반응 분석

일반판매의약품 및 안전상비약품에서는 114명의 환자에서 203건의 ADR이 보고되었으며 해당 약품은 105개 품목이었다. ADR 증상은 피부 증상이 76건(37.4%)으로 가장 많이 나타났으며 다음으로 위장관계 증상이 48건(23.6%), 신경계 증상이 24건(11.8%), 전신성 증상이 22건(10.8%)으로 많았다. 가장 빈도가 높았던 증상은 가려움증과 발진으로 각각 20건(9.9%)이었고, 다음으로 두드러기가 15건(7.4%), 현기증과 구토가 각각 11건(5.4%)으로 빈도가 높게 나타났다(Table 3). 원인약물로는 진통제가 86건(40.0%)으로 가장 많았으며, 다음으로 피부점막계 약물이 35건(16.3%), 비타민 및 무기질계 약물이 20건(9.3%)으로 많았다. 약품으로는 acetaminophen/chlorzoxazone 복합제와 ketoprofen 플라스타제제가 높은 빈도를 보였다.

Table 1. Frequency of clinical manifestations in adverse drug reactions

Classification	No. of reports (%)	Main manifestations (n)
Gastro-intestinal system disorders	950 (33.6)	Abdominal discomfort (164), nausea (154), vomiting (129), diarrhea (101), mouth dry (91)
Nervous system disorders	420 (14.9)	Dizziness (250), headache (76), tremor (29), sensory disturbance (25), limpness body (9)
Skin and appendages disorders	382 (13.5)	Pruritus (114), Skin eruption (104), urticaria (50), diaphoresis (16), alopecia (13)
General disorders	380 (13.4)	Facial or generalized edema (122), asthenia (67), fatigue (35), fever (23), facial flush (21)
Psychiatric disorders	310 (11.0)	Somnolence (151), insomnia (95), anorexia (19), anxiety (7)
Vision/ Hearing/ vestibular disorders	76 (2.7)	Visual disturbance (28), taste alteration (18), red eye (9), eye pain (8)
Cardiovascular disorders	63 (2.2)	Palpitation (37), hypotension (10), hypertension (7)
Respiratory system disorders	58 (2.1)	Coughing (17), dyspnea (15), epistaxis (4), sore throat (4)
Urinary system disorders	50 (1.8)	Urine discoloration (18), dysuria (16), urinary retention (5)
Metabolic and nutritional disorders	43 (1.5)	Weight gain (22), hypoglycemia (11)

Musculo-skeletal/ collagen disorders	41	(1.5)	Myalgia (25), arthralgia (6)
Reproductive disorders	27	(1.0)	Lactation nonpuerperal (9), breast pain (6),
Blood cell/ clotting disorders	11	(0.4)	Bruise (10), bleeding time increased (1)
Liver and biliary system disorders	7	(0.2)	Hepatic enzymes increased (6)
Endocrine disorders	3	(0.1)	Gynecomastia (3)
Neoplasms	2	(0.1)	Breast cyst(1), breast fibrosis(1)
Miscellaneous	3	(0.1)	Application site burning (2), medication stuck in throat (1)

Table 2. Frequency of drugs to cause the adverse drug reactions

Classification	No. of reports (%)	Main drugs (n)
Analgesics	1204 (19.7)	Acetaminophen+tramadol (383), acetaminophen (108), tramadol (15), aceclofenac (145), loxoprofen (111), meloxicam (64), talniflumate (56), dexibuprofen(53), ibuprofen (51),
Gastrointestinal drugs	1103 (17.7)	Ranitidine (156), mosapride (136), rebamipide (112), Artemisia asiatica herb (88), itopride (68), levosulpiride (57), cimetidine (57)
Central nervous system agents	683 (11.0)	Gabapentin (80), pregabalin (77), alprazolam (47), hydroxyzine (44), diazepam (26), clonazepam (23)
Cardiovascular drugs	594 (9.6)	Atorvastatin (58), amlodipine+telmisartan (19), amlodipine (46), telmisartan(8), propranolol (30), hydrochlorthiazide + losartan (13), hydrochlorthiazide (23), losartan (14)
Anti-infective agents	571 (9.2)	Cefaclor (83), amoxicillin+clavulanate (82), clarithromycin (36), levofloxacin (28), ofloxacin (26)
Respiratory agents	361 (5.8)	Guaifenesin+chlorpheniramine+dihydrocodeine+methylephedrine (43), erdosteine (29), acetylcysteine (28), montelukast (26), pseudoephedrine (26)
Hormones and synthetic substitutes	356 (5.7)	Prednisolone (74), methylprednisolone (66), metformin +sitagliptine (8),

			metformin (47), sitagliptine (7), glimepiride (28)
Antihistamine drugs	276	(4.4)	Levocetrizine (51), azelastine (49), bepotastine (37), chlorpheniramine (25), fexofenadine (24)
Autonomic drugs & skeletal muscle relaxants	203	(3.3)	Eperisone (114), chlorphenesin (24), cyclobenzaprine (24), dantrolene (11), baclofen (9)
Blood formation/ coagulation agents	118	(1.9)	Aspirin 100mg (37), clopidogrel (25), ferrous sulfate (15), cilostazol (12), warfarin (10)
Genitourinary agents	118	(1.9)	Tamsulosin (23), terazosin (15), solifenacin (14), alfuzosin (12), propiverine (12)
Antineoplastic agents	95	(1.5)	Capecitabine (29), methotrexate (19), sunitinib (10), gefitinib (8), erlotinib (6)
Vitamins	95	(1.5)	Cholecalciferol+$CaCO_3$ (13), Cholecalciferol+Ca citrate (12), isotretinoin (15), folic acid (8)
Skin and mucous membrane agents	65	(1.0)	ketoprofen (14), Benzoyl peroxide (6), terbinafine (5),
Eye, ear, nose and throat preparations	61	(1.0)	Benzydamine (9), hyaluronate (9), timolol (3), timolol+dorzoamide(3), timolol+travoprost (2)
Miscellaneous	292	(4.7)	streptokinase+streptodornase (130), risedronate (18), tacrolimus (15), cyclosporine (12), mycophenolate (12),

Table 3. Frequency of clinical manifestations of adverse drug reactions on non-prescription drugs

Classification	No. of reports (%)	Main manifestations (n)
Skin and appendages disorders	76 (37.4)	Pruritus (20), Skin eruption (20), urticaria (15),
Gastro-intestinal system disorders	48 (23.6)	Vomiting (11), abdominal pain (11), nausea (9),
Nervous system disorders	24 (11.8)	Dizziness (11), headache (7), sensory disturbance (3)
General disorders	22 (10.8)	Facial or generalized edema (11), facial flush (4), allergic reaction(3),
Psychiatric disorders	8 (3.9)	Insomnia (4), drug addiction or dependence (3), anorexia (1)
Vision/ Hearing/ vestibular disorders	7 (3.4)	Red eye (3), visual disturbance (2), eye pain (1), visual field defect (1)
Cardiovascular disorders	7 (3.4)	Palpitation (7)
Respiratory system disorders	4 (2.0)	dyspnea (2), asthma aggravated (1), larynx pain (1)
Urinary system disorders	2 (1.0)	Urine discoloration (1), urinary retention (1)
Blood cell/ clotting disorders	2 (1.0)	Bruise (1), gingival bleeding (1)
Reproductive disorders	2 (1.0)	Burning feeling vagina (1), withdrawal bleeding missed (1)
Miscellaneous	1 (0.5)	Application site burning (1)

Appendix 2.

World Health Organization-Uppsala Monitoring Centre (WHO-UMC) Causality

Causality term	Assessment criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs

	• Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination • Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

Appendix 3.

Classification of clinical manifestations in adverse drug reactions according to the World Health Organization-adverse reaction terminology (WHO-ART) system

Classification	WHOART code
Skin and appendages disorders	0100
Musculo-skeletal system/Collagen disorders	0200-0300
Central and peripheral/Autonomic nervous system disorders	0410-0420
Vision/Hearing and vestibular/other sense disorders	0431-0433
Psychiatric disorders	0500
Gastro-intestinal system disorders	0600
Liver and biliary system disorders	0700
Metabolic and nutritional disorders	0800
Endocrine disorders	0900
Cardiovascular disorders	1010-1040
Respiratory system disorders	1100
Red blood cell/ White cell/Platelet, bleeding and clotting disorders	1210-1230
Urinary system disorders	1300
Reproductive disorders, male/female	1410-1420
Foetal disorders	1500
Neonatal and infancy disorders	1600
Neoplasms	1700

General disorders	1810
Miscellaneous(Application site disorders/ Resistance mechanism disorders Secondary terms/ Poison specific terms)	1820-2100

Appendix 4.

Classification of the causative drugs by the Anatomical Therapeutic Chemical classification system

Code	Contents
A	Alimentary tract and metabolism
B	Blood and blood forming organs
C	Cardiovascular system
D	Dermatologicals
G	Genito-urinary system and sex hormones
H	Systemic hormonal preparations, excluding sex hormones and insulins
J	Antiinfectives for systemic use
L	Antineoplastic and immunomodulating agents
M	Musculo-skeletal system
N	Nervous system
P	Antiparasitic products, insecticides and repellents
R	Respiratory system
S	Sensory organs
V	Various

국 문 초 록

약물이상반응은 환자의 입원과 치료기간의 연장을 유발하며, 치료비용을 상승시켜 환자와 보험제정의 경제적 부담을 가중시킨다. 의료진의 긴밀한 모니터링 하에 있는 입원환자에 비해 외래환자는 환자의 자발적인 의사표현이 없으면 ADR을 알아내기 어렵고, 그로 인해 약물이상반응에 대한 대처도 늦어져 위험과 비용이 더욱 증가할 수 있다.

지역약국은 전국에 널리 분포되어 있어 환자의 접근이 편리하며, 약에 관한 상담이 비교적 용이하여, 외래환자의 약물이상반응을 효과적으로 모니터링하고 상담 및 정보를 제공할 수 있는 요양기관이다. 대한약사회 지역의약품안전센터는, 2013년 식품의약품안정처에 의해 전국 지역약국과 외래환자를 대상으로 약물감시활동을 수행하도록 지역의약품안전센터로 지정되었다.

그 이전까지 지역의약품안전센터를 통한 자발적인 ADR 보고는 대부분 입원환자 사례를 중심으로 이루어져왔다. 약물이상반응사례 분석연구들도 입원환자 사례를 중심으로 이루어져왔으며, 아직까지 외래환자에서의 자발적 유해사례보고에 대한 연구가 미비한 실정이다. 지역약국 약사에 의해 보고된 약물이상반응사례에 대한 분석자료는 외래환자에서의 약물이상반응을 예방하는데 중요한 정보를 제공할 수 있을 것이다. 또한 개별 연령군을 대상으로 한

약물이상반응에 대한 연구들은 있어왔으나, 외래환자에서 보고된 약물이상반응을 연령군별로 비교 및 분석한 연구는 제한적이다. 이에 본 연구는 전국 지역약국에서 대한약사회 지역의약품안전센터에 보고된 약물이상반응사례를 연령군별로 분석하여, 외래환자에서의 약물이상반응의 양상 및 원인약물들을 알아보고자 하였다.

2013년 1월부터 2014년 6월까지 18개월간 지역약국 약사에 의해 대한약사회 지역의약품안전센터에 보고된 약물이상반응사례를 대상으로 하였다. 환자의 나이에 따라 소아군(18세 미만), 성인군, 노인군(65세 이상)으로 분류하여 군별 약물이상반응의 증상과 원인약물의 보고빈도 및 보고 분율을 비교하였다.

인과성평가는 World Health Organization-Uppsala Monitoring Centre 기준을 근거로 하였다. 약물이상반응 증상과 원인약물의 분류에는 각각 World Health Organization Adverse Reaction Terminology 코드와 Anatomical Therapeutic Chemical Classification System 분류 체계를 사용하였다.

보고된 약물이상반응 42,018건 중 31,398건(74.9%)이 인과관계를 가졌다. 분석대상 9,705명의 환자의 나이 중앙값은 58.0세였으며 여성이 66.9%를 차지하였다. 연령군은 성인군 64.0%, 노인군 32.5%,

소아군 3.5%로 구성되었다.

다빈도 약물이상반응 증상은 위장관계(34.4%), 신경계(14.4%), 정신과계(12.1)로 어지러움(8.5%), 소화불량(8.5%), 졸림(6.3%)의 보고빈도가 높았다. 약물이상반응 원인약물로는 위산장애관련 약물(11.4%), 항염증제(10.5%), 진통제(7.2%), 항균제(7.1%)가 높은 빈도를 보였다. 약물이상반응 증상과 원인약물을 연령군별로 비교하였을 때, 소아군에서는 설사와 항균제가 다른 군에 비해 높은 보고분율을 보였다($p<0.001$). 노인군에서는 어지럼증을 포함한 신경계 증상과 비뇨기계 증상이 높게 나타났다($p<0.001$).

중대한 유해사례는 52명의 환자에서 보고되었다. 아나필락시스 반응(19.7%)이 중대한 유해사례의 주된 증상이었고 비스테로이드성 항염증제와 세파로스포린계 항균제가 주요 원인약물이었다. 비처방의약품으로 인한 약물이상반응 612건에서는 피부증상(29.6%)의 보고빈도가 높았으며, 원인약물로 비스테로이드성 항염증제의 보고빈도가 높았다.

지역약국약사에 의해 보고된 외래환자에서의 약물이상반응 사례에서 위장관계, 신경계, 정신신경계 증상이 보고빈도가 높았으며, 항염증제, 진통제, 항생제는 다빈도 원인약물이자 중대한 유해사례의 주요 원인약물이었다. 외래환자에서의 약물이상반응의

증상 및 원인약물의 양상은 연령군별로 차이가 있음을 확인하였다. 따라서, 외래환자의 각 연령군별 특징에 따른 맞춤형 약물감시활동(pharmacovigilance) 정책의 수립이 필요함을 알 수 있었다.

주요어 : 약물이상반응, 자발적 보고, 지역약국, 외래환자, 연령군, 약물감시활동

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