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Signal detection of amoxicillin adverse drug reaction using Korea Adverse Event Reporting System Database

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Seoul National University

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의학석사 학위논문

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지도교수 박병주

이 논문을 의학석사 학위논문으로 제출함

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Signal detection of amoxicillin adverse drug reaction using Korea Adverse Event Reporting System Database

By

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(Directed by Byung Joo Park, MD, MPH, PhD)

A Thesis Submitted to the Department of Medicine in Partial Fulfillment of the Requirements for the Degree of Master of Philosophy in Preventive Medicine at Seoul National University College of Medicine

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Approved by Thesis Committee:

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논문 제목	Korea Adverse Event Reporting System Database 를 이용한 아목시실린의 약물유해반응 실마리정보 검색
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제 출 일 : 2016 년 1 월 6 일

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Abstract

Signal detection of amoxicillin adverse drug reaction using Korea Adverse Event Reporting System Database

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Objective: To detect adverse drug reaction (ADR) signals of amoxicillin compared to other antibiotics using Korea Adverse Event Reporting System (KAERS) Database and compare the information with drug labels of nine countries.

Methodology: We conducted pharmacovigilance data mining using KAERS database to analyze the AE reports of amoxicillin, the most frequently reported drug during the study period, against a background of all reports suspected by other antibiotics in the database. Frequentist and Bayesian methods were used to calculate disproportionality distribution of drug-AE pairs. The AE which was detected by all the three indices including PRR,

ROR, and IC was defined as a signal. In addition, we identified whether the detected signals were listed on the drug labels among nine countries or not.

Result: From December 1988 until June 2014 KAERS database contains 807,582 AE reports, among which 1,722 reports were attributed to amoxicillin. Among the 192,510 drug-AE pairs, 2,913 drug-AE pairs were for amoxicillin and 189,597 were for other antibiotics. 241 adverse events were suggested as amoxicillin associated, among which 52 adverse events were detected as amoxicillin's signals. After compared to drug labels of nine countries, 12 adverse events including ineffective medicine, bronchitis, rhinitis, sinusitis, dry mouth, gastroesophageal reflux, gastric carcinoma, abnormal crying, hypercholesterolemia, induration, pulmonary carcinoma, and influenza-like symptoms were not listed on any drug labels of nine countries.

Conclusion: We found pharmacovigilance data mining was good tool for detecting new signals which were not listed on drug approval labels of nine countries, however it should be followed by signal evaluation including causality, clinical significance, and preventability through well designed pharmacoepidemiologic research.

Keyword: KAERS database**,** amoxicillin, adverse event, data mining, signals, pharmacovigilance.

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List of Abbreviations

OECD = Organization for Economic Co-operation and Development

Lao PDR = Lao People's Democratic Republic

ADR = Adverse Drug Reaction

KAERS = Korea Adverse Event Reporting System

KIDS = Korea Institute of Drug Safety and Risk Management

AE = Adverse Event

KFDA = Korea Food and Drug Administration

ICSRs = Individual Case Safety Reports

ATC = Anatomical Therapeutic Chemical Classification

WHO-ART = World Health Organization - Adverse Reaction Terminology

PT = Preferred Term

PRR = Proportional Reporting Ratio

ROR = Reporting Odds Ratio

BCPNN = Bayesian Confidence Propagation Neural Network

IC = Information Component

95% CI = 95% Confidence Interval

U.S.A. = United States of America

U.K. = United Kingdom

SOCs = System Organ Classes

Contents

I. Introduction

Amoxicillin was introduced to the United States in 1974 as an oral preparation (1). Amoxicillin is classified as a class of antibiotics called penicillin's. Further members of this class include ampicillin, piperacillin, ticarcillin, and various others. These antibiotics have a similar mechanism of action. Amoxicillin is used for bacterial infections, such as some respiratory tract infections, infections of the urinary tract, ear infections, and dental abscesses. It works by killing the bacteria causing the infection. The most common adverse reactions observed in clinical trials on amoxicillin were diarrhea, rash, vomiting, and nausea (2).

Apart from the personal risk of adverse drug reaction, there are much bigger consequences impinge on society because of the extensive use of antibiotics. The increase in drug-resistant organisms has corresponded with an increased use of antibiotics, as large amount of antibiotics were freely dispensed by pharmacists without doctors' prescription (3).

In addition, the recent emergence of multidrug-resistant pathogens and pharmacokinetics-pharmacodynamics considerations may result in off-label use of a certain class of antibiotics, including amoxicillin. From evidence of true drug sensitization confirmed that sensitization to amoxicillin may develop within infectious mononucleosis (4). Prevalence of *Helicobacter pylori* resistance to amoxicillin reported a 31% resistance rate for patients from southern Italy (5). In Korea from 2003 through 2012 for amoxicillin the primary resistance rate of *H. pylori* was increasing from 6.3% to 14.9% (6). In Japan, amoxicillin resistance rate for *H. pylori* was 13.6% (7). Study in Brazil also found an unexpectedly elevated

proportion, that is, 29% of patients harboring strains showed resistance to this antibiotic (8) .

Furthermore, a higher rate of antibiotic resistance was significantly correlated with higher consumption of antibiotics (9-11). South Korea is the country of the highest antibiotic resistance rate in the world and has been one among the top seven antibiotics consuming countries among 25 OECD countries (12, 13). Even though in 2000 Korea started the legislative separation of drug prescription and dispensing to reduce misuse or overuse of antibiotics (14), in real clinical setting antibiotics are still commonly prescribed.

In Lao PDR, one of the developing countries, widespread unregulated provision of antibiotics, dispensing insufficient doses, reduced adherence to complete dose regimens, and the poor quality of the drug supply are thought to contribute to the wide spread antibiotic resistance (15). In comparison with wealthier countries in Asia, there is little information on the clinical epidemiology of infectious diseases for Lao PDR. Available information suggests that antibiotic resistance level seems to be relatively low compared to other surrounding countries. On the other hand, lower respiratory tract infection is the first cause of Disability-adjusted Life Year(DALY) loss and the second cause of deaths in Laos in 2010 (16). In addition, data from Lao PDR showed a high rate of *Staphylococcus aureus* bacteremia in young infants and concerning level of antimicrobial resistance in gram-negative organisms. This study also found that *E.coli* isolates were susceptible to ampicillin (17). Even though in Lao PDR there is no private hospitals but the private sector for health service is growing very rapidly, particularly in civic areas, which

consists of 1,993 private pharmacies(18). Furthermore, antibiotics are widely available without prescription at private pharmacies and drug stores in Laos (15). So the antibiotics might have used very widely in Laos, especially as the data from a central hospital in Vientiane, amoxicillin is the most commonly used antibiotic in Lao PDR(Table 1) (19) .

Table 1. Number of Drugs Used in a Central Hospital in Vientiane, Lao PDR from 2012 to 2014.

Drug name	Number of cases	(%)
Amoxicillin	508,684	33.7
Cephalexine	213,133	14.1
Ceftriaxone	153,457	10.2
Metronidazol	84,144	5.6
Roxithromycin	80,962	5.3
Others	468,993	31.1
Total	1,509,373	100.0

Besides that, this study was the first attempt to detect signals of amoxicillin using Korea Adverse Events Reporting Database. In addition, amoxicillin is widely used in Laos, this study result could be used as very helpful information for the safe use of amoxicillin in Laos as well as in South Korea.

Adverse drug reactions represent negative consequences of pharmacotherapy. Even though there exists knowledge on newly approved drug of how to provide the

best patient care, any drug can cause an adverse effect. The importance of post-marketing surveillance has been emphasized because adverse drug reaction (ADR) cannot be fully detected during the premarketing developing process. This study used pharmacovigilance data mining for signal detection. Where a drug-associated adverse event means a signal, which can have a potential for being an adverse drug reaction.

Therefore, this study aimed to reveal the safety profile of amoxicillin in a user-derived manner and to compare with the information provided by the manufacturer and compare the information on drug labels of nine countries.

II. Materials and Methods

2.1 Source of Data

We mined reported cases related amoxicillin from Korea Adverse Event Reporting System (KAERS) Database**.** KAERS is a system developed by Korea Institute of Drug Safety and Risk Management (KIDS) to facilitate reporting and managing adverse event (AE) reports. All reports of AEs have been accumulated in KAERS DB. The Korean AE Reporting System was first launched in 1988 by the Korea Food and Drug Administration (KFDA), and spontaneous AE reports have been collected since then. KAERS database includes the data collected through spontaneous reports, reports from studies including re-examination reports, post-marketing studies, individual case safety reports, and literature information. Suspected drugs and AE information are reported to the KIDS in a form named 'Individual Case Safety Reports (ICSRs)'. Computerized adverse event reporting system including voluntary reporting by health care workers and the public. However, manufacturers should report mandatorily for serious and unexpected adverse events. Name of drugs in KAERS DB are coded according to ATC coding system and adverse events are coded according to the WHO-ART (World Health Organization Adverse Reaction Terminology) coding system for the Preferred Term (PT). From December 1988 until June 2014 the total number of reports were 807,582.

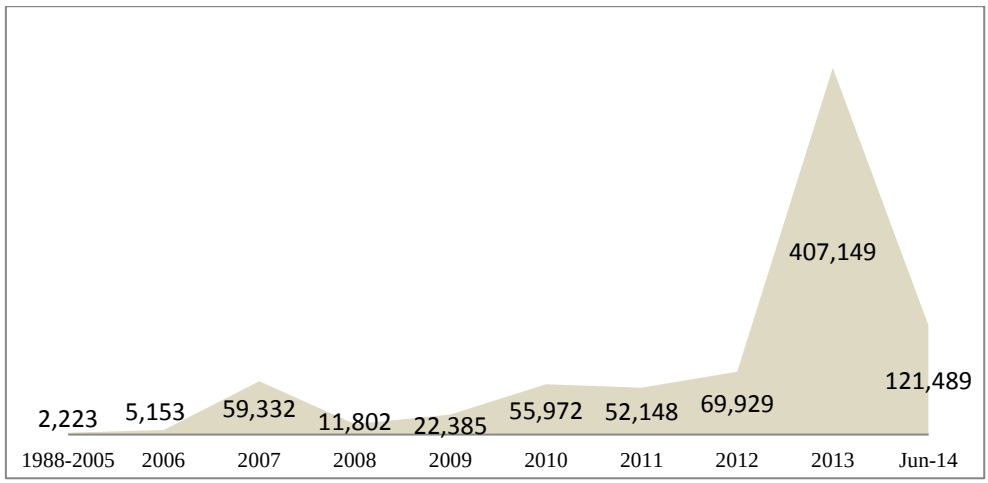

Figure 1. Number of Reported Adverse Events through KAERS from December 1988 until June 2014

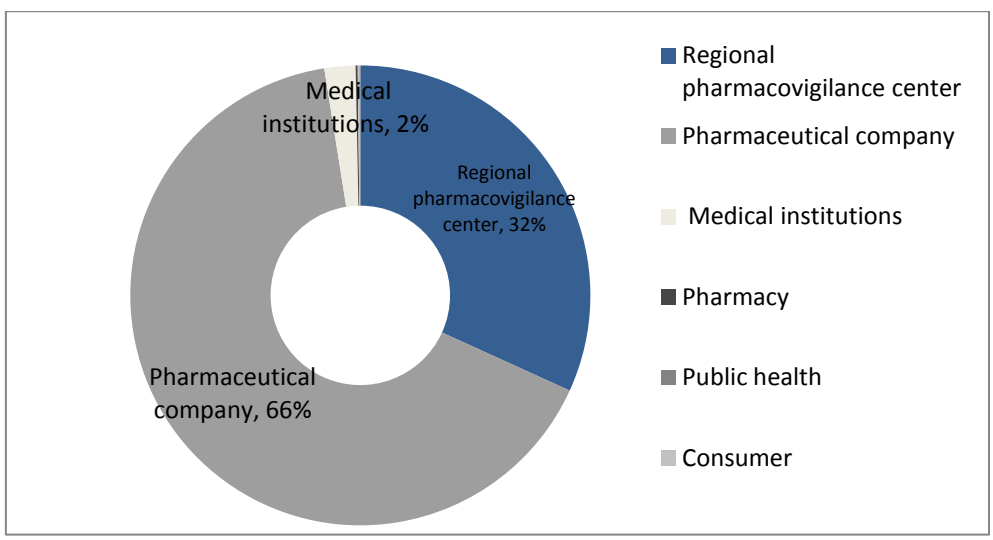

Figure 2. Number of Reported Adverse Events by Source of Information through KAERS from December 1988 until June 2014

2.2 Query Terms

In our study, we chose study drug as amoxicillin and drugs for comparison as all other antibiotics shown in Table 2.

Table 2. Antibiotics by Therapeutic Class except Amoxicillin

Antibiotics Class	Drugs in the Therapeutic Class
TETRACYCLINES	Tetracyclines
AMPHENICOLS	Amphenicols
BETA-LACTAM ANTIBACTERIALS, PENICILLINS	Penicillins with extended spectrum Beta-lactamase sensitive penicillins Beta-lactamase resistant penicillins Beta-lactamase inhibitors Combinations of penicillins, incl. beta-lactamase inhibitors
OTHER BETA-LACTAM ANTIBACTERIALS	First-generation cephalosporins Second-generation cephalosporins Third-generation cephalosporins Fourth-generation cephalosporins Monobactams Carbapenems Other cephalosporins and penems
SULFONAMIDES AND TRIMETHOPRIM	Trimethoprim and derivatives Short-acting sulfonamides Intermediate-acting sulfonamides Long-acting sulfonamides Combinations of sulfonamides and trimethoprim, incl. derivatives
MACROLIDES, LINCOSAMIDES AND STREPTOGRAMINS	Macrolides Lincosamides Streptogramins
AMINOGLYCOSIDE ANTIBACTERIALS	Streptomycins Other aminoglycosides
QUINOLONE ANTIBACTERIALS	Fluoroquinolones Other quinolones
COMBINATIONS OF ANTIBACTERIALS	Combinations of antibacterials
OTHER ANTIBACTERIALS	Glycopeptide antibacterials Polymyxins Steroid antibacterials Imidazole derivatives Nitrofuran derivatives Other antibacterials

2.3 Analysis of Disproportionality

Frequentist and Bayesian methods were used to calculate disproportionality. Proportional reporting ratio (PRR) was first used by Evans et al. (20). PRR is the ratio of reporting rate for one specific event among all events for a given drug to the comparator being the reporting rate for all adverse events by all other drugs present in the database. A disproportion is considered on the basis of three pieces of information: PRR≥2, $\chi 2 \geq 4$ and at least 3 reported cases. The reporting odds ratio (ROR) is the ratio of the odds of reporting of one specific event versus all other events for a given drug compared to this reporting odds for all other drugs present in the database (21). A signal is considered when the lower limit of the 95% confidence interval (CI) of the ROR is greater than one (22). The signal metric or signal score in Bayesian Confidence Propagation Neural Network (BCPNN) is the information component (IC) which can be the additional information obtained on the probability of the event by specifying a drug. A signal usually requires that the lower 95% CI of the IC exceeds zero (23) as shown in Table 3. In this study, adverse events were detected as signals when all the three indices met the criteria illustrated above. Finally, signals we found from KAERS DB were compared among drug label information of South Korea, U.S.A, U.K, Japan, Germany, Swiss, Italy, France, and Laos. We Used WHO-ART System Organ Classes (SOCs) for grouping adverse events in Table 7 and Table 8. All statistical analyses were performed using the SAS software (Release 9.4, SAS Institute Inc, Cary, NC) and Microsoft EXCEL2010.

Table 3. Definition and Signal Detection Criteria of Implemented Data Mining Indices

No. of reports	Specific AE	ALL other AEs
Drug of interest	A	B
All other drugs	C	D

Indices	Definition	Criteria of signal detection
PRR	{A/(A+B)}/{C/(C+D)}	PRR≥2, chi-squared≥4 and A≥3
ROR	(A/B)/(C/D)	lower limit of the 95% CI > 1
IC	$\log_2$P(AE, drug)/P(AE)P(drug)	lower 95% CI of the IC > 0

PRR: proportional reporting ratio, ROR: reporting odds ratio,IC: information component, AE: adverse event (24).

III. Results

Among the total antibiotic 192,510 drug-AE pairs, 2,913 drug-AE pairs were for amoxicillin and 189,597 were for other antibiotics (Table 4). It is clear that total number of reports by antibiotics has increased year by year.

Table 4. Number of Adverse Events Reported by Amoxicillin and Other Antibiotics from December 1988 to June 2014

Year	Amoxicillin	Other antibiotics
1988-2005	50	1,025
2006	120	1,283
2007	48	8,587
2008	60	5,482
2009	102	8,046
2010	247	21,672
2011	281	23,310
2012	304	27,242
2013	1,255	64,391
06/2014	446	28,559
Total	2,913	189,597

The characteristics of reports were presented at Table 5. The number of reports attributed to amoxicillin was 1,722. Among them male patients were 660(38.4%), female patients were 853(49.5%) and gender unknown patients were 209(12.1%). The patient age groups were widely distributed; adults were 53.0 % followed by elderly patients (11.6%), pediatric patients (9.4 %), adolescent patients (2.0%) and age unknown patients (24.0%).

1,722 reports came from different reporting sources. The most frequent reporting source of adverse events for amoxicillin was regional pharmacovigilance center (1,009, 58.6%), followed by pharmaceutical companies (599, 34.8%) and medical institutions (92, 5.3%).

Furthermore, the most frequent type of reports was spontaneous reports (647 case, 37.6%), followed by research (including review) (290 case, 16.8%) and literature (179 case, 10.4%).

Table 5. Characteristics of Reports Associate with Amoxicillin from December 1988 to June 2014

Characteristics		Number of reports	(%)
Gender	Male	660	38.4
	Female	853	49.5
	Unknown	209	12.1
Report type	Spontaneous report	647	37.6
	Research (including review)	290	16.8
	Literature	179	10.4
	Others	606	35.2
Information sources	Doctor	505	29.3
	Pharmacist	256	14.9
	Nurse	148	8.6
	Consumer	23	1.3
	Others	309	18.0
	Unknown	481	27.9
Report source	Regional pharmacovigilance center	1,009	58.6
	Pharmaceutical company	599	34.8
	Medical institutions	92	5.3
	Pharmacy	9	0.5
	Consumer	7	0.4
	Others	6	0.4
Age group	Pediatric	161	9.4
	Adolescent	34	2.0
	Adults	913	53.0
	Elderly	200	11.6
	Unknown	414	24.0
Total		1,722	100.0

Table 6. Frequently Reported Adverse Events Associated with Amoxicillin in KAERS Database

Adverse events	Number of AEs	(%)
Rash	331	11.4
Urticaria	193	6.6
Medicine Ineffective	174	6.0
Diarrhea	170	5.8
Pruritus	143	4.9
Pharyngitis	105	3.6
Bronchitis	90	3.1
Rhinitis	84	2.9
Nausea	67	2.3
Fever	67	2.3
Vomiting	66	2.3
Taste Perversion	66	2.3
Angioedema	58	2.0
Dyspepsia	53	1.8
Dyspnoea	46	1.6
Dizziness	44	1.5
Abdominal Pain	44	1.5
Otitis Media	43	1.5
Allergy	41	1.4
Pneumonia	34	1.2
Others	994	34.0
Total	2,913	100.0

The total number of drug- adverse event pairs with amoxicillin was 2,913. Among them 241 adverse events were suspected as amoxicillin associated. The relatively

high frequency adverse events are listed in Table 6, including rash (331, 11.4%), urticaria (193, 6.6%), medicine ineffective (174, 6.0%), diarrhea (170, 5.8%), pruritus (143, 4.91%), pharyngitis (105, 4.0%), bronchitis (90, 3.1%), rhinitis (84, 2.9%), nausea (67, 2.3%), and fever (67, 2.3%).

Among 241 adverse events, 52 adverse events were detected as amoxicillin's signals (Table 7). Comparing to drug labels of nine countries, 12 adverse events including ineffective medicine, bronchitis, rhinitis, sinusitis, dry mouth, gastroesophageal reflux, gastric carcinoma, abnormal crying, hypercholesterolemia, induration, pulmonary carcinoma, and influenza-like symptoms were not listed on any drug labels of nine countries (Table 8).

Table 7. Detected Signals for Amoxicillin by Data Mining Using KAERS Database

System-organ classes	Adverse event	Number of reports	PRR (Chi Square)	ROR(95%LCI)	IC 95% LCI
Skin and appendages disorder	Urticaria	193	1.293 (13.2)	1.313(1.1)	0.16*
	Angioedema	58	3.483(98.0)*	3.533 (2.7)*	1.38*
	Dermatitis	28	17.193(338.0)*	17.350 (11.4)*	3.23*
	Stevens Johnson Syndrome	16	4.844(45.5)*	4.865 (2.9)*	1.55*
	Bullous Eruption	12	3.282(18.2)*	3.291 (1.8)*	0.95*
	Fixed Eruption	8	8.678(48.0)*	8.699 (4.2)*	2.08*
	Epidermal Necrolysis	5	6.140(19.7)*	6.149 (2.5)*	1.51*
	Pruritus Genital	4	18.596(51.8)*	18.620 (6.1)*	2.67*
	Rash Pustular	4	2.993(5.1)*	2.995 (1.1)*	0.52*
	Induration	3	5.007(8.9)	5.011 (1.5)*	1.11*
Vision disorders	Conjunctivitis	9	2.178(5.6)*	2.181 (1.1)*	0.31*
Special senses disorders	Taste Perversion	66	19.092(876.2)*	19.512 (14.8)*	3.53*
Psychiatric disorders	Somnolence	12	1.779(4.0)	1.782 (1.0)	0.11*
	Nervousness	9	3.149(12.6)*	3.156 (1.6)*	0.82*
Gastrointestinal disorders	Dyspepsia	53	1.595(11.6)	1.606 (1.2)	0.29*
	Dry Mouth	22	4.757(60.9)*	4.786 (3.1)*	1.61*
	Gastroenteritis	15	6.299(61.0)*	6.326 (3.7)*	1.87*
	Gastritis	6	2.959(7.5)*	2.963 (1.3)*	0.62*
	Gastroesophageal Reflux	6	6.974(27.7)*	6.986 (3.0)*	1.73*
	Periodontal Destruction	6	20.554(84.8)*	20.594 (8.2)*	2.92*
	Gi Haemorrhage	4	2.893(4.8)*	2.895 (1.1)*	0.47*
	Tooth Disorder	3	9.763(20.5)	9.772 (2.9)*	1.90*
	Gastro-Intestinal Disorder NOS	3	10.848(23.0)	10.858 (3.2)*	2.02*
	Flatulence	3	2.789(3.3)	2.791 (0.9)	0.35*
	Gastric Ulcer	3	2.325(2.2)	2.326 (0.7)	0.11*
Metabolic and nutritional disorders	Hypercholesterolaemia	4	2.284(2.8)	2.286 (0.8)	0.16*

Respiratory disorders	Pharyngitis	105	6.247(424.9)*	6.443 (5.3)*	2.25*
	Bronchitis	90	11.441(3.0)*	11.774 (9.4)*	2.99*
	Rhinitis	84	5.713(301.9)*	5.853 (4.7)*	2.10*
	Upper Respiratory Tract Infection	33	2.616(31.8)*	2.635 (1.9)*	0.89*
	Sinusitis	30	10.848(230.1)*	10.950 (7.4)*	2.72*
	Epistaxis	9	4.068(19.6)*	4.077 (2.1)*	1.16*
	Respiratory Disorder	9	5.007(26.8)*	5.019 (2.6)*	1.43*
	Sputum Disorder	5	2.229(3.3)	2.231 (0.9)	0.18*
	Asthma	3	3.099(4.1)	3.102 (1.0)	0.49*
Urinary tract disorders	Face Oedema	24	3.433(39.4)*	3.453 (2.3)*	1.19*
Neoplasms	Gastric Carcinoma	4	9.298(25.9)*	9.309 (3.3)*	1.94*
	Pulmonary Carcinoma	3	3.004(3.8)	3.006 (0.9)	0.45*
Body as a whole-general disorders	Medicine Ineffective	174	24.513 (2860.2)*	26.007 (21.8)*	3.93*
	Allergy	41	2.320(29.9)*	2.339 (1.7)*	0.76*
	Anaphylactic Reaction	31	3.577(54.7)*	3.605 (2.5)*	1.30*
	Oedema	22	1.822(8.0)	1.828 (1.2)	0.30*
	Oedema Periorbital	15	3.770(28.9)*	3.784 (2.3)*	1.20*
	Oedema Generalised	14	3.254(20.9)*	3.265 (1.9)*	0.98*
	Allergic Reaction	13	2.411(10.4)*	2.417 (1.4)*	0.55*
	Malaise	12	1.644(3.0)	1.647 (0.9)	0.00*
	Anaphylactic Shock	9	3.149(12.6)*	3.156 (1.6)*	0.82*
	Abnormal Crying	4	7.036(18.7)*	7.045 (2.5)*	1.61*
	Halitosis	3	13.017(27.7)	13.030 (3.8)*	2.21*
	Influenza-Like Symptoms	3	10.277(21.7)	10.286 (3.0)*	1.96*
Application site disorders	Injection Site Inflammation	8	3.027(10.4)*	3.033 (1.5)*	0.73*
Immune disorders and infections	Otitis Media	43	10.404(315.7)*	10.545 (7.6)*	2.75*

PRR: proportional reporting ratio, ROR: reporting odds ratio, IC 95% LCI: information component lower limit of 95% confidence interval. *Detected signal by each index, PRR, ROR or IC .

Table 8. Signals for Amoxicillin and Existence of the Information on Drug Labels of nine Countries

System-organ classes	Adverse event	Number of reports	South Korea	U.S.A	U.K	France	Italy	Japan	Switzerland	Germany	Laos
Skin and appendages disorder	Urticaria	193	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Angioedema	58	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Dermatitis	28	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Stevens Johnson Syndrome	16	Y	Y	Y	Y	Y	Y	Y	Y	*
	Bullous Eruption	12	Y	Y	Y	Y	Y	Y	Y	Y	*
	Fixed Eruption	8	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Epidermal Necrolysis	5	Y	Y	Y	Y	Y	Y	Y	Y	*
	Pruritus Genital	4	Y	*	Y	Y	Y	*	Y	Y	*
	Pruritus Genital	4	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Induration	3	*	*	*	*	*	*	*	*	*
Vision disorders	Conjunctivitis	9	*	*	Y	Y	Y	Y	Y	Y	*
Special senses disorders	Taste Perversion	66	*	Y	*	*	*	Y	*	Y	*
Psychiatric disorders	Somnolence	12	Y	Y	*	*	Y	*	Y	Y	*
	Nervousness	9	Y	Y	*	*	*	Y	*	Y	*
Gastrointestinal disorders	Dyspepsia	53	Y	*	*	*	Y	*	Y	Y	*
	Dry Mouth	22	*	*	*	*	*	*	*	*	*
	Gastroenteritis	15	Y	Y	Y	*	Y	*	Y	Y	*
	Gastritis	6	Y	*	*	*	Y	*	*	*	*
	Gastroesophageal Reflux	6	*	*	*	*	*	*	*	*	*
	Periodontal Destruction	6	Y	Y	Y	Y	Y	*	Y	Y	*
	Gi Haemorrhage	4	Y	Y	Y	*	Y	*	Y	Y	*
	Flatulence	3	Y	*	*	*	Y	*	Y	Y	*
	Gastric Ulcer	3	Y	*	*	*	Y	*	*	*	*
	Tooth Disorder	3	*	Y	Y	*	Y	*	Y	Y	*
	Gastro-Intestinal Disorder NOS	3	Y	Y	Y	Y	Y	Y	Y	Y	*
Metabolic and nutritional disorders	Hypercholesterola-emia	4	*	*	*	*	*	*	*	*	*

Respiratory disorders	Pharyngitis	105	*	*	*	Y	Y	*	Y	Y	*
	Bronchitis	90	*	*	*	*	*	*	*	*	*
	Rhinitis	84	*	*	*	*	*	*	*	*	*
	Upper Respiratory Tract Infection	33	Y	*	*	*	*	*	*	*	*
	Sinusitis	30	*	*	*	*	*	*	*	*	*
	Epistaxis	9	Y	Y	Y	Y	Y	*	Y	Y	*
	Respiratory Disorder	9	Y	*	Y	Y	Y	Y	Y	Y	*
	Sputum Disorder	5	Y	*	*	*	*	*	*	*	*
	Asthma	3	*	Y	Y	Y	Y	*	Y	Y	*
Urinary tract disorders	Face Oedema	24	*	Y	Y	Y	Y	Y	Y	Y	*
Neoplasms	Gastric Carcinoma	4	*	*	*	*	*	*	*	*	*
	Pulmonary Carcinoma	3	*	*	*	*	*	*	*	*	*
Body as a whole-general disorders	Medicine Ineffective	174	*	*	*	*	*	*	*	*	*
	Allergy	41	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Anaphylactic Reaction	31	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Oedema	22	*	Y	Y	Y	Y	Y	Y	Y	*
	Oedema Periorbital	15	*	Y	Y	Y	Y	Y	Y	Y	*
	Oedema Generalised	14	*	Y	Y	Y	Y	Y	Y	Y	*
	Allergic Reaction	13	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Malaise	12	Y	*	Y	*	*	*	*	Y	*
	Anaphylactic Shock	9	Y	Y	*	*	Y	*	Y	Y	Y
	Abnormal Crying	4	*	*	*	*	*	*	*	*	*
	Halitosis	3	Y	*	Y	*	Y	*	Y	Y	*
	Influenza-Like Symptoms	3	*	*	*	*	*	*	*	*	*
Application site disorders	Injection Site Inflammation	8	Y	Y	Y	*	*	*	*	Y	*
Immune disorders and infections	Otitis Media	43	*	*	Y	Y	Y	*	Y	Y	*

Y: The AE which was listed on drug label, *: The AE which was not listed on drug label.

United States of America(U.S.A), United Kingdom(U.K)

IV. Discussion

From the analyses conducted, we identified 12 AE cases associated with amoxicillin which were not listed on drug labels of nine countries studied. Among them, it was noted that Ineffective Medicine was the most frequently reported adverse event, one of the possible explanations for this might be due to low adherence for medication used. Some patients may not follow the advice of medical professionals for duration of taking the drug. In the United States poor adherence to medication prescribed or course of medical treatment accounts for substantial worsening of morbidity and mortality and financial costs (25-27). Poor medication adherence is a major cause of medication-related hospital admission from 33 to 69 percent (25-29). It is clear if the patients adhere and follow the prescription of the doctor correctly, the result will be most effective in medication treatment (29). Therefore, patient should be educated to keep high adherence to physician's prescription.

Previous study suggests amoxicillin provides little symptomatic benefit for patients presenting in primary care for acute lower-respiratory-tract infection (30). Moreover, *H. pylori* infection is a common chronic gastric infection in worldwide, so *H. pylori* resistance for amoxicillin could cause fatal problems, increasing eradication failures, which can be one of the reason for treatment failures of amoxicillin (5). In line with the literature (31-34), it was found that chronic atrophic gastritis associated with *H. pylori* infection increases risk of gastric carcinoma. In case of hypercholesterolemia some case reports found that *H. pylori* associated protein-losing hypertrophic gastropathy with hypercholesterolemia

(35) .

For the adverse events such as bronchitis, sinusitis and rhinitis are one of the indications of prescribing antibiotics (36). However, those adverse events were detected in our study as signals of amoxicillin. The reason may be explained by unaware indication of using medication for the patients. Sometimes patients use antibiotics in incorrect time, either too early or too lately using them. Even though those adverse events such as gastric carcinoma, abnormal crying, gastroesophageal reflux and pulmonary carcinoma are not listed on the drug label, the symptoms of those diseases can appear on the drug label. In case of gastric carcinoma, its symptoms such as abdominal pain, vomiting, bloody stool can be indicated in adverse effects of amoxicillin. Besides that, for the symptoms of pulmonary carcinoma such as difficult breathing, coughing, and chest pain also included in adverse effects of amoxicillin. It points out that asthma is not listed in drug labels of Asian countries but is on all drug labels of western countries. In this phenomenon, ethnic group may be one of the factors that can affect the occurrence of adverse events.

Differently from amoxicillin's drug labels of other countries in our study, Laos has a few adverse effects that listed on the drug label. The reason might be due to not established adverse drug reaction (ADR) reporting system in Laos. Even though drug monitoring and evaluation became one of the thirteen elements of Lao national drug policy since 1992 (37), spontaneous ADR reports have not been collected until now. Safety actions were done passively in response to other developed countries' safety alert and communications. The drug monitoring,

adverse drug reaction reporting and product surveillance seems to be an essential component of drug safety system in Laos and sufficient budget should be provided to constructing ADR reporting system database reflecting the structure of KAERS database.

KAERS database is including all the cases reported and no one can intentionally exclude any AE report from their database. In fact, adverse events are underreported in spontaneous reporting system. The rate of reporting can vary with the particular adverse event, but the average is approximated about 6% (38). For as much the knowledge and opinion of health professionals are significant determinants of spontaneous AE reporting (39), the reporting rate for unknown drug-ADR associations such as the one examined here are less likely to be reported.

The most important limitation of our study derives from spontaneous reporting database. The KAERS database has several limitations (40). They do not include an unexposed control group, and lack of information on denominator of a suspected drug exposure that does not allow the quantification of risk. Therefore a definite causality evaluation cannot be provided, but requires complementary post-marketing safety assessment method such as cohort study, case-control study, or case-crossover study. Under-reporting of the adverse events could reduce sensitivity because it underestimates the frequency and thereby the impact of a given ADR.

Nevertheless, this study was the first attempt to detect amoxicillin signals using KAERS DB. KAERS database is an outstanding source of signal detection for

hypothesis generation. Nonetheless, the causality evaluation of the association between any suspected drug and adverse events cannot be confirmed with KAERS database alone, but finding meaningful information early is very important in pharmacovigilance for ensuring drug safety. In addition, further study should be needed for assessing causality through well designed pharmacoepidemiologic studies.

In conclusion, we detected new signals of amoxicillin, which were not listed on the labels of nine countries. Through data mining the purpose of pharmacovigilance as signal detection was easily satisfied, however early signals may be too equivocal. Therefore to confirm causality and for regulatory decision making, it should be followed by signal evaluation including the causality, clinical significance and preventability through pharmacoepidemiologic studies.

V. References

1. Klein JO. Amoxicillin/clavulanate for infections in infants and children: past, present and future. Pediatr Infect Dis J 2003;22(8 Suppl):S139-48.

2. Gillies M, Ranakusuma A, Hoffmann T, Thorning S, McGuire T, Glasziou P, et al. Common harms from amoxicillin: a systematic review and meta-analysis of randomized placebo-controlled trials for any indication. Can Med Assoc J 2015;187(1):E21-E31.

3. Pechere JC. Patients' interviews and misuse of antibiotics. Clin Infect Dis 2001;33 Suppl 3:S170-3.

4. Onodi-Nagy K, Kinyo A, Meszes A, Garaczi E, Kemeny L, Bata-Csorgo Z. Amoxicillin rash in patients with infectious mononucleosis: evidence of true drug sensitization. Allergy Asthma Clin Immunol 2015;11(1):1.

5. Dore MP, Piana A, Carta M, Atzei A, Are BM, Mura I, et al. Amoxycillin resistance is one reason for failure of amoxycillin-omeprazole treatment of *Helicobacter pylori* infection. Aliment Pharm Therap 1998;12(7):635-9.

6. Lee JW, Kim N, Kim JM, Nam RH, Chang H, Kim JY, et al. Prevalence of primary and secondary antimicrobial resistance of *Helicobacter pylori* in Korea from 2003 through 2012. Helicobacter 2013;18(3):206-14.

7. Nishizawa T, Suzuki H, Tsugawa H, Muraoka H, Matsuzaki J, Hirata K, et al. Enhancement of Amoxicillin Resistance after Unsuccessful *Helicobacter pylori* Eradication. Antimicrob Agents Chemother 2011;55(6):3012-4.

8. Mendonca S, Ecclissato C, Sartori MS, Godoy APO, Guerzoni RA, Degger M, et al. Prevalence of *Helicobacter pylori* resistance to metronidazole, clarithromycin, amoxicillin, tetracycline, and furazolidone in Brazil. Helicobacter 2000;5(2):79-83.

9. Goossens H, Ferech M, Stichele RV, Elseviers M, Grp EP. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet 2005;365(9459):579-87.

10. Jensen US, Muller A, Brandt CT, Frimodt-Moller N, Hammerum AM, Monnet DL, et al. Effect of generics on price and consumption of ciprofloxacin in primary healthcare: the relationship to increasing resistance. J Antimicrob Chemoth 2010;65(6):1286-91.

11. Song YA SIJ, M.O. Chang, H.J. Ban, N.C. Jin, H.K. Kim,, K.H. Park JHS, and S.Y. Bae. Relationship between antibiotic use and antibiotic resistance in major nosocomial pathogens at a University Hospital. Chonnam Med J 2008;44(3):137.

12. Lee YS, Kwon JW, Oh OH, Sohn HS. Temporal decrease in overall antibiotic consumption accompanying antibiotic prescribing rate disclosure policy: evidence from analysis of national health insurance claims data in South Korea. Arch Pharm Res 2014;37(10):1295-300.

13. Song JH, Jung SI, Ko KS, Kim NY, Son JS, Chang HH, et al. High prevalence of antimicrobial resistance among clinical Streptococcus pneumoniae isolates in Asia (an ANSORP study). Antimicrob Agents Chemother 2004;48(6):2101-7.

14. Kim HJ, Ruger JP. Pharmaceutical reform in South Korea and the lessons it provides. Health Affair 2008;27(4):W260-W9.

15. Khennavong M, Davone V, Vongsouvath M, Phetsouvanh R, Silisouk J, Rattana O, et al. Urine antibiotic activity in patients presenting to hospitals in Laos: implications for worsening antibiotic resistance. Am J Trop Med Hyg 2011;85(2):295-302.

16. http://vizhub.healthdata.org/irank/arrow.php, Institute for Health Metrics and Evaluation, University of Washington 2015.

17. Anderson M, Luangxay K, Sisouk K, Vorlasan L, Soumphonphakdy B, Sengmouang V, et al. Epidemiology of bacteremia in young hospitalized infants in Vientiane, Laos, 2000-2011. J Trop Pediatr 2014;60(1):10-6.

18. WHO and Ministry of Health LP. Health Service Delivery Profile Lao PDR 2012.

19. Ministry of Health VLP. Report of drugs used from 2012 to 2014. 2014.

20. Evans SJW, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf 2001;10(6):483-6.

21. Poluzzi E, Raschi E, Piccinni C, De Ponti F. Data mining techniques in pharmacovigilance: analysis of the publicly accessible FDA adverse event reporting system (AERS). Data mining applications in engineering and medicine Croatia. InTech 2012:267-301.

22. Van Puijenbroek EP, Bate A, Leufkens HG, Lindquist M, Orre R, Egberts AC. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. Pharmacoepidemiol Drug Saf 2002;11(1):3-10.

23. Hauben M. A brief primer on automated signal detection. Ann Pharmacother 2003;37(7-8):1117-23.

24. JM Seong, NK Choi, SY Jung, YJ Kim, JY Lee, BJ Park. Signal Detection of Sildenafil in Korean Spontaneous Adverse Event Reports. J Pharmacoepi Risk Manag 2009;2:38-44.

25. McDonnell PJ, Jacobs MR. Hospital admissions resulting from preventable adverse drug reactions. Ann Pharmacother 2002;36(9):1331-6.

26. Rodgers PT, Ruffin DM. Medication nonadherence: Part II--A pilot study in patients with congestive heart failure. Managed Care Interface 1998;11(9):67-9, 75.

27. Senst BL, Achusim LE, Genest RP, Cosentino LA, Ford CC, Little JA, et al. Practical approach to determining costs and frequency of adverse drug events in a health care network. Am J Health-system Pharm 2001;58(12):1126-32.

28. Levy G, Zamacona MK, Jusko WJ. Developing compliance instructions for drug labeling. Clin Pharma Ther 2000;68(6):586-91.

29. Osterberg L, Blaschke T. Adherence to medication. New Engl J Med 2005;353(5):487-97.

30. Little P, Stuart B, Moore M, Coenen S, Butler CC, Godycki-Cwirko M, et al. Amoxicillin for acute lower-respiratory-tract infection in primary care when pneumonia is not suspected: a 12-country, randomised, placebo-controlled trial. Lancet Infect Dis 2013;13(2):123-9.

31. Ohata H, Kitauchi S, Yoshimura N, Mugitani K, Iwane M, Nakamura H, et al. Progression of chronic atrophic gastritis associated with *Helicobacter pylori* infection increases risk of gastric cancer. Int J Cancer 2004;109(1):138-43.

32. Haruma K, Komoto K, Kamada T, Ito M, Kitadai Y, Yoshihara M, et al. *Helicobacter pylori* infection is a major risk factor for gastric carcinoma in young patients. Scand J Gastroenterol 2000;35(3):255-9.

33. Parsonnet J, Friedman GD, Vandersteen DP, Chang Y, Vogelman JH, Orentreich N, et al. *Helicobacter pylori* infection and the risk of gastric carcinoma. New Engl J Med 1991;325(16):1127-31.

34. Sierra Lopez R, Bertoli F, Penafiel EF. *Helicobacter pylori* infection and the risk of gastric carcinoma. Report of a case. Rev Med Panama 1994;19(1):48-54.

35. Kapsoritakis AN, Potamianos S, Matrella E, Koukouraki S, Oeconomaki E, Tzardi M, et al. *Helicobacter pylori*-associated protein-losing hypertrophic gastropathy with hypercholesterolemia. Dig Dis Sci 1999;44(9):1843-7.

36. Gonzales R, Malone DC, Maselli JH, Sande MA. Excessive antibiotic use for acute respiratory infections in the United States. Clin Infect Dis 2001;33(6):757-62.

37. Paphassarang C, Tomson G, Choprapawon C, Weerasuriya K. The Lao national drug policy: lessons along the journey. Lancet 1995;345(8947):433-5.

38. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: A systematic review. Drug Safety 2006;29(5):385-96.

39. Lopez-Gonzalez E, Herdeiro MT, Figueiras A. Determinants of under-reporting of adverse drug reactions: A systematic review. Drug Safety 2009;32(1):19-31.

40. Bate A, Evans SJW. Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiol Drug Saf 2009;18(6):427-36.

요약 (국문초록)

목적: 한국의약품안전관리원의 의약품부작용원시자료(KIDS-KD)를 이용하여 다른 항생제와 비교를 통한 아목시실린의 실마리정보를 찾고 9 개 나라의 약물허가정보를 비교한다.

방법: 가장 최신의 KAERS database 를 이용하여 아목시실린과 다른 항생제의 부작용정보들을 데이터마이닝기법으로 분석하였다. 불균형분석의 세 가지 방법인 PRR(Proportional Reporting Ratio), ROR (Proportional Odds Ratio), IC(Information Component)를 사용하였고, 세 가지 지표의 기준을 모두 만족시킨 유해사례를 실마리 정보로 정의하였다. 찾아낸 실마리정보들을 9 개 나라의 약물허가정보와 비교하였다.

결과: 1988 년부터 2014 년 6 월까지 KAERS database 에는 87,167 명 에게 발생한 807,582 건의 부작용이 보고되었는데, 그 중 192,510 건의 항생제 관련 부작용 보고가 있었고, 1,722 명에게 발생한 2,913 건이 아목시실린 복용후 발생한 부작용으로 인한 보고였다. 아목시실린에 의한 부작용 종류는 241 종이었으며, 그중 52 종의 부작용이 실마리정보로 파악되었다. 9 개 국가의 약물허가정보와 비교하였을 때 약효없음, 기관지염, 비염, 부비동염, 구강건조, 역류성 식도염, 위암, 비정상적인 울음, 고콜레스테롤혈증, 국소경화, 폐암, 인플루엔자를

포함한 12 개의 실마리정보들이 9 개국 약물허가정보에 포함되어 있지 않았다.

결론: 약물감시체계에서 수집된 부작용보고자료에 데이터마이닝기법을 적용하여 실마리정보를 파악하는 것은 신약허가시 작성된 약물허가정보에 수록되지 않은 부작용정보를 파악하는 유용한 도구임을 확인하였다. 실마리정보의 인과성, 임상적 의의, 예방가능성을 포함한 내용들을 평가하기 위해 잘 설계된 약물역학연구를 수행할 필요가 있다.

주요어: KAERS database, 아목시실린, 부작용, 데이터마이닝, 실마리정보, 약물감시체계, 약물역학연구

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