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Adverse Events and Signal Generation Induced by the Use of Quinolone Vs. Cephalosporin: A Nationwide Spontaneous Adverse Event Reporting Database, 2005-2017

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Abstract

Objective: Quinolones are one of the most commonly prescribed classes of antibacterial in the world. We comparatively analysed the status of adverse events (AE) due to quinolones with respect to the use of cephalosporins and detected signals for quinolones.

Methods: We used data from the Korea Institute of Drug Safety & Risk Management-Korea Adverse Event Reporting System Database (KIDS-KD), collected between 2005 and 2017. Differences in patient demographics, report type, reporter, causality, and serious-AEs between quinolones and cephalosporins was compared, the annual frequency ratio of quinolone AEs versus cephalosporin AEs were compared. Metrics including proportional reporting ratio (PRR), reporting odds ratio (ROR), and information component (IC), used to detect signals for quinolones, and they were compared with the information on the drug labels in the USA, EU, and Korea.

Results: The total number of AE reported for quinolones and cephalosporins was 22,352 and 76,325, respectively. Both drugs were most used in patients over 60 years of age, and this tendency was more pronounced for quinolones [proportion of patients over 60 years of age: quinolones 45.62% (10,196) vs. cephalosporins 32.85% (25,074)]. The frequency ratio of quinolone AEs to cephalosporin AEs (quinolone AEs/cephalosporin AEs) increased gradually over the years from 2008 (0.11) to 2016 (0.32). The frequency of quinolone AEs was higher than that of cephalosporins in disorders of the skin and appendages only. Thirty-seven cases (10.0%) for quinolones were confirmed as signal information from a total of 369 drug-AE pairs. The number of signals satisfied all three methods (PRR, ROR, and IC) were 23 of 37. Total 9 cases (abscess, leg pain, vein pain, cachexia, skin discoloration, hyperventilation, stomatitis ulcerative, photopsia, and cardiac enzymes increased) out of 37 signals were identified as new signals that were not present on either the Korea, USA, or EU labels.

Conclusion: Newly detected signals for quinolones should be continuously monitored to assess causality.

Keywords: Quinolones; Cephalosporin; Adverse Event (Ae); Signal Detection; Drug-Ae; Data Mining; Drug Label

Introduction

Quinolones are one of the most commonly prescribed classes of antibacterial in the world and are used to treat a variety of bacterial infections owing to their broad spectrum of activity in humans [1,2]. Despite these advantages, adverse events (AEs) due to quinolone use have been reported. The use of quinolones has been associated with adverse events in the gastro-intestinal tract (GIT), musculoskeletal system, central nervous system (CNS), and the dermatological and the hepatic systems in clinical trials and post-marketing surveillance [3-5]. The rate of the average incidence of AEs due to the use of quinolone antibiotics was 2.0 % among all AEs, and the most common adverse reaction in South Korea between 2003 and 2017 was pruritus [6]. To minimize the AEs induced by quinolone antibiotics, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) recommended restricting the use of fluoroquinolone and quinolone antibiotics (used orally or by injection or inhalation) in June 2018 [7]. The FDA has also updated warnings for fluoroquinolone antibiotics regarding the risks of mental health and low blood sugar adverse reactions in July 2018 [8]. However, post-marketing safety data on quinolones may vary between countries owing to variations in disease and drug utilization patterns and differences in regulatory policies [9]. To the best of our knowledge, globally, there are a limited number of studies conducted on adverse reactions related to quinolones [10]. Recently, in 2016, 256 cases of fluoroquinolone-related AEs were noted in the spontaneous reporting database over 12 years in Nigeria [11]. However, the main limitation of this study was that demographic characteristics, such as age, gender, and indications for fluoroquinolone, were not found because the reporters did not report them to the pharmacovigilance center. However, there have been no pharmacovigilance studies using data mining of an Adverse Event Reporting Database by matching specific AEs with the use of quinolones in South Korea. Therefore, this study aimed to comparatively analyse the AEs induced by quinolones and other antibiotics using a spontaneous reporting system and determine the signals of quinolones by a comparison of the obtained information with that on the drug labels in the USA, Europe, and South Korea.

Methods

Database and study drug

We used spontaneous AE reports from January 1, 2005, to December 31, 2017, in the Korea Adverse Events Reporting System (KAERS) database, which was developed by the Korean Institute of Drug Safety & Risk Management (KIDS) in 2012 to effectively manage AE reports [12]. AEs for the drugs were extracted from the above database and only the AEs that were classified as "certain", "probable", or "possible" by the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) causality assessment system were contained in analysis. We excluded data without anatomical therapeutic chemical (ATC) or AE codes, age, or sex. In addition, the initial reports of suspected drugs as AEs were only included for this analysis. The AEs were collected as the preferred terms (PTs) recommended by the World Health Organization-Adverse Reactions Terminology (WHO-ART) version 092. We collected AE reports for quinolone antibiotics as the study drug. The comparator drug selected was a cephalosporin antibiotic, a broad-spectrum antibiotic used for a variety of indications and the most commonly prescribed antibiotic. We included all AEs that were induced by the study drugs and comparator drugs in the analysis. Drug-AE pairs were matched by using one-to-one correspondence between the drugs and AEs.

Comparison of the AE status of quinolones and cephalosporins

We comparatively analysed AEs reports for quinolones and cephalosporins between January 2005 and December 2017. Demographic characteristics, type, and report source by professionals and the affiliation of reports, degree of causality, and types of serious AEs (SAEs) were compared to each other using their frequency and percentage (%). The annual frequency and proportion of AEs and SAEs were computed for quinolones and cephalosporins. The annual frequency ratio of quinolone AEs and SAEs versus cephalosporin AEs and SAEs were compared. The frequency and proportion of AEs based on system organ class (SOC) were also compared for quinolones and cephalosporins.

Measures

Sex and age were analysed. Sex was classified into two sub-groups: male and female. Patient age was classified into seven sub-groups: younger than 10 years of age, 10s (11-20 years of age), 20s (21-30 years of age), 30s (31-40 years of age), 40s (41-50 years of age), 50s (51-60 years of age), and older than 60 years of age. The data were analysed by report type (spontaneous, research, article, and other), report source by profession (doctor, pharmacist, nurse, consumer, and other), and by affiliation (regional drug safety centre, hospitals and clinics, pharmacies, manufacturers, consumers, and other). The causality of AE-pairs related to quinolones and cephalosporins was evaluated based on the WHO-Uppsala Monitoring Center (WHO-UMC) causality assessment system, which is one of the most widely used methods [13]. The evidence level was classified into three groups (certain, probable, or possible). A 'certain' event was defined as an 'event definitive pharmacologically or phenomenologically', i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon (e.g. 'Grey Baby Syndrome' and chloramphenicol or anaphylaxis immediately after the administration of a drug that had been given previously); this means that any other event is automatically excluded and can never qualify for 'certain', even in the case of a positive rechallenge observation. For a 'probable' event, the event was 'unlikely' to be attributable to another cause. In addition, the dechallenge situations (i.e. what happened after drug withdrawal) were different. A 'possible' event could be explained by the disease or other drug and there was no information on any events that may have occurred after drug withdrawal [14]. For serious AEs, both drugs (quinolones and cephalosporins) were compared by the six types of serious AEs: disability, birth defect/congenital anomaly, threat, death, hospital, and other.

Signal indices of quinolones by data mining

We analysed the signal detection information based on SOC codes from quinolone-AE pairs extracted by using a data mining method. The data mining method uses computer algorithms to search large-scale databases for unexpected or hidden patterns [15]; it has been applied for drug monitoring since the late 1990s [16]. The signal is obtained by data mining spontaneous reporting data, which specifically refers to information that is unlikely to exclude the possibility of a causal association with drugs [17]. The proportional reporting ratio (PRR), reporting odds ratio (ROR), and Bayesian confidence propagation neural networks of information components (IC) were used for signal index calculations in data mining methods [18-20]. PRR was achieved from the division of a specific AE fraction of a specific drug reporting by a specific AE fraction of another drug reporting. The signal judgment criteria were PRR ≥ 2, chi-square ≥ 4, and number of occurrences ≥ 3. The ROR was defined as the odds of a specific AE occurring in patients who were exposed to a specific drug divided by the odds of the specific AE for other drugs; ROR ≥ 2, chi-square ≥ 4, and number of occurrences of AEs ≥ 3 were the determination criteria. The IC value is the log of the probability of using a certain drug multiplied by the probability of the occurrence of a specific AE, in the case that the use of that drug and the occurrence of the specific AE were independent of each other. The criteria for determining the IC value was when the lower limit of the 95% confidence interval was higher than 0. ADRs satisfying one or more of the three criteria were defined as signals.

Comparison of quinolone label information in Korea, the USA, and the EU

The signals detected in the KAERS database were compared with drug labelling information from Korea, the USA, and the EU. The Korean drug label was found through the online systems that are operated by the Korea Ministry of Food and Drug Administration [21]. The USA and EU label information was obtained from the Daily Med website [22] and the European Medicines Agency's homepage [23], respectively. New signal information was defined as an AE that was not present on the Korean, USA, or EU labels.

Statistical analysis

To analyse the differences in the frequency and tendency of AE reports over time for each of the quinolones and cephalosporins, a comparative analysis was conducted for each year based on reported information. We computed the frequency and percentage (%) for each categorical variable. Statistical analysis was performed according to the characteristics of each variable by using the chi-squared test. P-values less than 0.05 were considered statistically significant. All statistical analyses were computed by using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and Excel 2016 (Microsoft Corp., Redmond, WA, USA),

and the detected signals were compared with the Korean, USA, and EU drug labels.

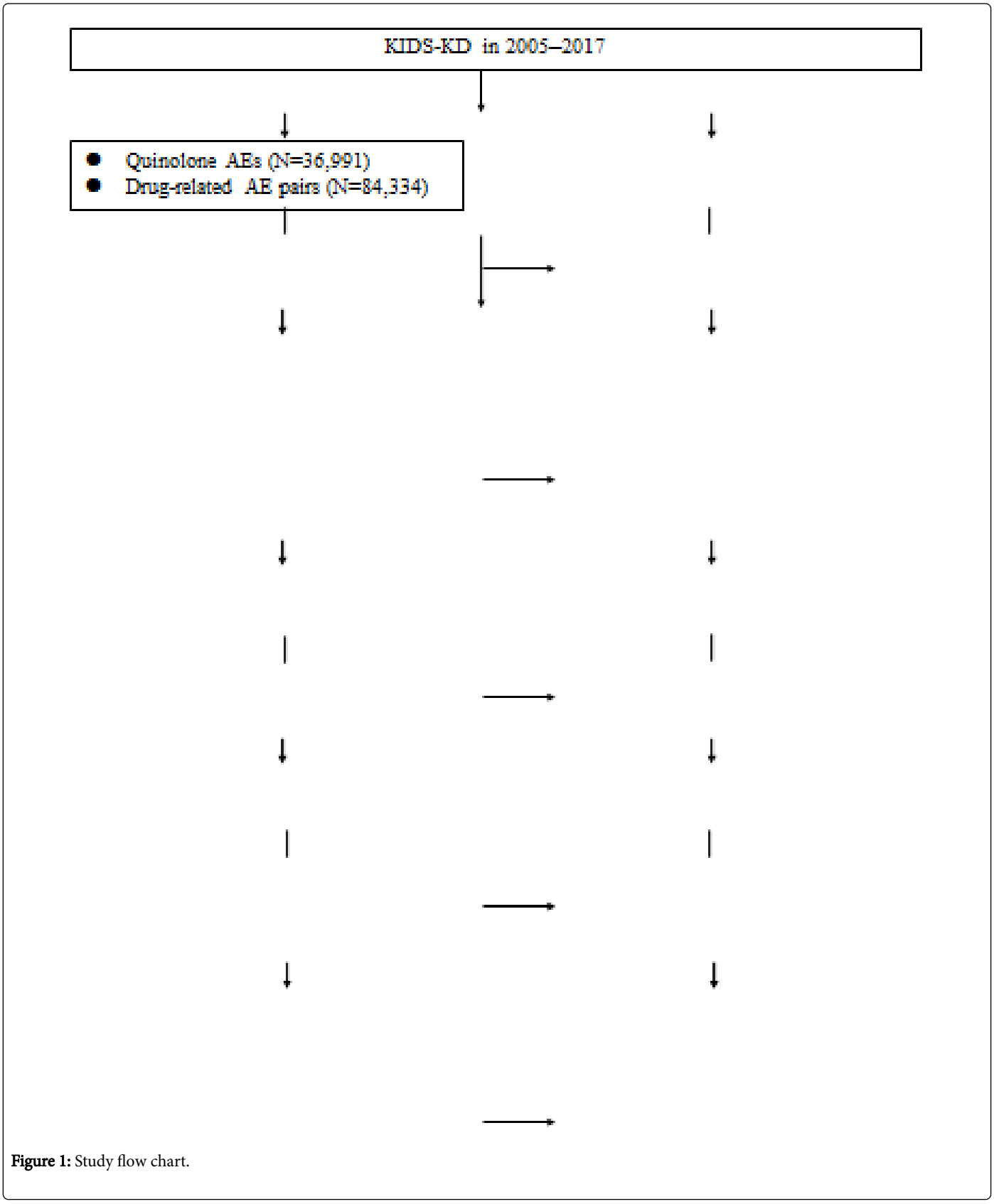


Figure 1: Study flow chart.

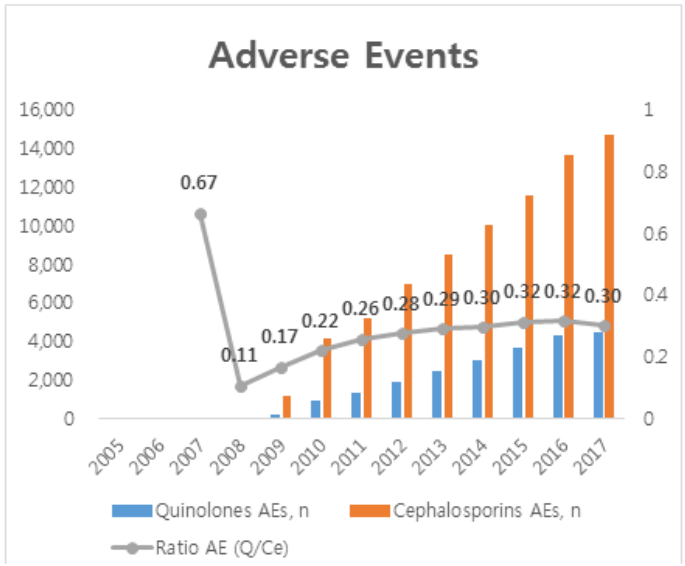
Ethical consideration

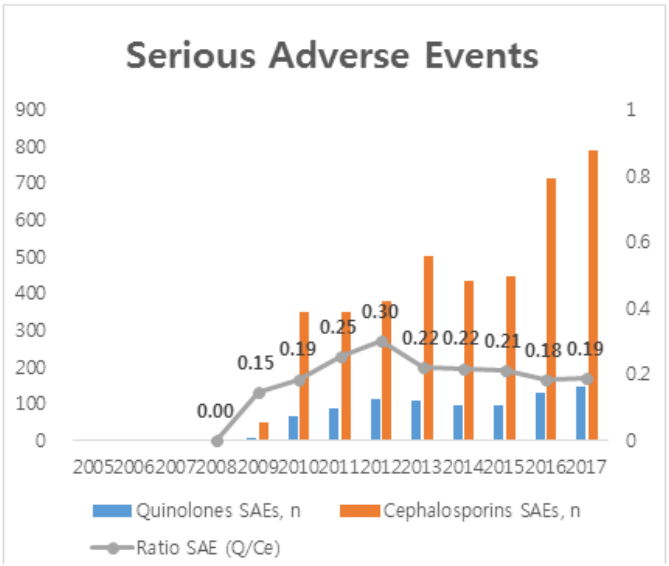
This study was approved by the institutional review board of the Sungkyunkwan University in Korea (SKKU-IRB-2018-06-012).

Results

Between 2005 and 2017, the number of AE reports for quinolones and cephalosporins was 36,991 and 118,181, respectively. The number of quinolone-related AE pairs was 84,334 and that of cephalosporin-related AE pairs was 1,636,282. After the removal of data with duplicate cases, excluding cases without ATC/AE codes, WHO-ART code, sex, and age, and including only cases of suspected drugs and initial reports, the final number of quinolone-related AE reports and drug-AE pairs was 22,352 and 30,993, respectively, and that of cephalosporin (comparator)-related AE reports and drug-AE pairs was 76,325 and 145,772, respectively (Figure 1).

Between July 1, 2005, and December 31, 2017, the total numbers of AE reports for quinolones and cephalosporins were 22,352 and 76,325, respectively. The proportion of AE reports for quinolones and cephalosporins had a similar male-to-female ratio, which was higher for both drugs in females [quinolones 58.31% (13,033) vs. cephalosporins 55.50% (42,362)] than in males [quinolones 41.69% (9,319) vs. cephalosporins 44.50% (33,963)]. Both drugs were most used in patients over 60 years of age, and this tendency was more pronounced for quinolones [proportion of patients over 60 years of age: quinolones 45.62% (10,196) vs. cephalosporins 32.85% (25,074)]. The proportion of AE report type, report source by profession, and reporter source by affiliation were similar for quinolones and cephalosporins. The most common report type, the highest profession, and the affiliation of reporter of AE reports for quinolones and cephalosporins were spontaneous report, nurses, and regional drug safety centers, respectively. The causality evaluation showed that quinolones had significantly probable (36.67%, 8,196) and possible (60.63%, 13,551) events; cephalosporins had significantly probable (33.16%, 25,310) and possible (63.67%, 48,599) events. The total number of SAEs was 856 (3.83%) for quinolones and 4,022 (5.27%) for cephalosporins (Figure 2).





	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Quinolones AEs, n	0	0	8	9	203	927	1,355	1,940	2,480	3,003	3,645	4,325	4,457
Quinolones SAEs, n	0	0	0	0	7	65	89	114	111	95	95	131	149
Cephalosporins AEs, n	0	0	12	84	1,200	4,167	5,213	7,023	8,523	10,089	11,569	13,689	14,756
Cephalosporins SAEs, n	0	0	0	1	48	349	351	378	504	436	449	714	792
Ratio AE (Q/Ce)			0.67	0.11	0.17	0.22	0.26	0.28	0.29	0.30	0.32	0.32	0.30
Ratio SAE (Q/Ce)				0.00	0.15	0.19	0.25	0.30	0.22	0.22	0.21	0.18	0.19

Quinolones AEs, n Quinolones SAEs, n Cephalosporins AEs, n Cephalosporins SAEs, n Ratio AE (Q/Ce) Ratio SAE (Q/Ce)

Figure 2: Comparison of the annual proportion of frequency of adverse events reported for quinolones and cephalosporines (2005-2017).

Of the types of SAEs in the quinolones and cephalosporins, the highest proportions were reported in the hospital [406 (47.43%) vs. 1,591 (39.56%)], followed by other [377 (44.04%) vs. 2,003 (49.80%)] (Table 1).

The frequency and proportion of AE reports for quinolones and cephalosporins increased annually, and the frequency of AE reports for both drugs has risen sharply since 2009. The frequency ratio of quinolone AEs to cephalosporin AEs (quinolone AEs/cephalosporin AEs) increased gradually from 2008 (0.11) to 2016 (0.32). In contrast, the annual frequency ratio of cephalosporin SAEs vs. quinolone SAEs increased from 2008 (0) to 2012 (0.30) and then decreased until 2017 (0.19) (Figure 2).

Category	Subcategory	Quinolones N=22,352 (100%)	Cephalosporins N=76,325 (100%)
Gender	Male	9,319 (41.69%)	33,963 (44.50%)
	Female	13,033 (58.31%)	42,362 (55.50%)
Age	Under 10 years	117 (0.52%)	4,649 (6.09%)
	11-20 years	432 (1.93%)	4,264 (5.59%)
	21-30 years	1,766 (7.90%)	7,113 (9.32%)
	31-40 years	2,259 (10.11%)	9,421 (12.34%)
	41-50 years	2,966 (13.27%)	11,140 (14.60%)
	51-60 years	4,616 (20.65%)	14,664 (19.21%)
	Over 60 years	10,196 (45.62%)	25,074 (32.85%)
Report type	Spontaneous	18,751 (90.54%)	61,342 (88.57%)
	Research	49 (0.24%)	642 (0.93%)
	Article	29 (0.14%)	59 (0.09%)
	Other	1,881 (9.08%)	7,214 (10.42%)
Report source by professions	Doctors	3,925 (18.95%)	12,372 (17.86%)
	Pharmacists	2,938 (14.19%)	11,612 (16.77%)
	Nurses	12,491 (60.31%)	40,508 (58.49%)
	Consumers	142 (0.69%)	372 (0.54%)
	Others	1,214 (5.86%)	4,393 (6.34%)
Reporter source by affiliation	Regional drug safety center	20,073 (96.92%)	66,910 (96.61%)
	Hospitals and Clinics	519 (2.51%)	1,537 (2.22%)
	Pharmacies	25 (0.12%)	59 (0.09%)
	Manufacturers	84 (0.41%)	729 (1.05%)
	Consumers	2 (0.01%)	2 (0.00%)
	Other	7 (0.03%)	20 (0.03%)
Degree of causality	Certain	605 (2.71%)	2,416 (3.17%)
	Probable	8,196 (36.67%)	25,310 (33.16%)
	Possible	13,551 (60.63%)	48,599 (63.67%)
Types of Serious Adverse Event	Disability	14 (1.64%)	56 (1.39%)
	Birth defect/Congenital anomaly	1 (0.12%)	0 (0.00%)
	Threat	44 (5.14%)	291 (7.24%)
	Death	14 (1.64%)	81 (2.01%)
	Hospital	406 (47.43%)	1,591 (39.56%)
	Other	377 (44.04%)	2,003 (49.80%)

Table 1: Characterization of adverse events, causality, reporting between quinolones and cephalosporins between July 2005 and December 2017 in South Korea.

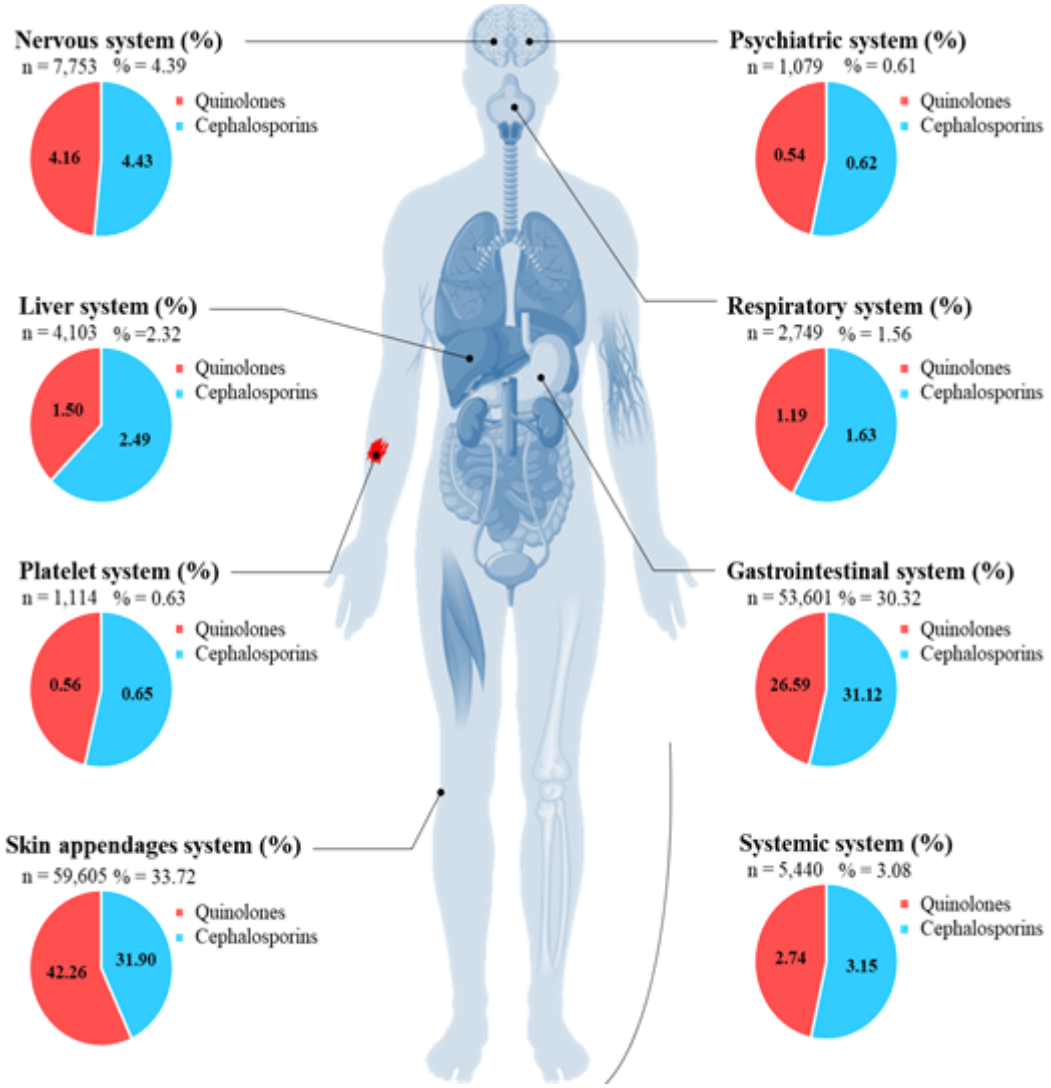


Figure 3: Comparison of adverse event status for quinolones and cephalosporins by the World Health Organization-Preferred Terms from the Korea Adverse Events Reporting System Database (2005-2017) in South Korea.

In total, 30,993 and 154,772 quinolone- and cephalosporin-related AE pairs were reported (Appendix 1). Skin and appendages system disorders were the most frequently reported AEs (n=59,605), followed by gastrointestinal system (n=53,601) and nervous system (n=7,753) (Figure 3).

The frequency of cephalosporin AEs was higher than that of quinolone AEs in all systems except skin and appendages disorders. In contrast, the frequency of quinolone AEs was only higher than that of cephalosporins in skin and appendages disorders (Figure 3). In particular, pruritus [quinolones (5,540, 17.88%) vs cephalosporins (19,201, 13.05%)] was the most frequent AE, followed by rash [quinolones (4,826, 15.57%) vs cephalosporins (15,007, 10.34%)] and urticaria [quinolones (2,437, 7.86%) vs cephalosporins (11,221, 7.70%)] in both quinolone- and cephalosporin-related AE pairs (Table 3).

SOC classification (WHO-ART SOC code)	Adverse Events	Quinolones N=30,993 (100%)	Cephalosporins N=145,772 (100%)	P-value
Skin and appendages disorders	Pruritus	5,540 (17.88%)	19,021 (13.05%)	<.0001
	Rash	4,826 (15.57%)	15,077 (10.34%)	
	Urticaria	2,437 (7.86%)	11,221 (7.70%)	

	Angioedema	296 (0.96%)	1,187 (0.81%)	
Central and peripheral nervous system disorders	Dizziness	899 (2.90%)	5,025 (3.45%)	
	Headache	390 (1.26%)	1,439 (0.99%)	
Psychiatric disorders	Insomnia	168 (0.54%)	911 (0.62%)	
Gastro-intestinal system disorders	Nausea	3,237 (10.44%)	14,764 (10.13%)	
	Vomiting	1,774 (5.72%)	10,466 (7.18%)	
	Diarrhoea	1,405 (4.53%)	8,842 (6.07%)	
	Diarrhoea, *Clostridium difficile*	861 (2.78%)	4,990 (3.42%)	
	Dyspepsia	625 (2.02%)	4,384 (3.01%)	
	Abdominal pain	338 (1.09%)	1,915 (1.31%)	
Liver and biliary system disorders	Hepatic enzymes Increased	338 (1.09%)	2,815 (1.93%)	
	Hepatic function abnormal	128 (0.41%)	822 (0.56%)	
Respiratory system disorders	Dyspnea	369 (1.19%)	2,380 (1.63%)	
Platelet, bleeding, and clotting disorders	Thrombocytopenia	173 (0.56%)	941 (0.65%)	
Body as a whole - general disorders	Fever	401 (1.29%)	2,578 (1.77%)	
	Chest pain	273 (0.88%)	1,179 (0.81%)	
	Malaise	175 (0.56%)	834 (0.57%)	

Table 3: Comparison of adverse event status for quinolones and cephalosporins by World Health Organization-Preferred Terms from the Korea Adverse Events Reporting System Database (2005-2017) in South Korea.

Thirty-seven cases (10.0%) for quinolones were confirmed as signal information from a total of 369 drug-AE pairs. The number of signals that satisfied all three methods (PRR, ROR, and IC) was 23 of 37. The number of signals all listed on the Korea, USA, and EU labels was 24. In total, nine cases (skin discoloration in skin and appendages disorders, photopsia in vision disorders, stomatitis ulcerative in gastro-intestinal system disorders, cachexia in metabolic and nutritional disorders, cardiac enzymes increased in myo-, endo-, pericardial and valve disorders, vein pain in vascular (extra cardiac) disorders, hyperventilation in respiratory system disorders, leg pain in body as a whole-general disorders, and abscess in resistance mechanism disorders) were identified as new signals that were not present on the Korean, USA, or EU labels (Table 2).

SOC classification (WHO-ART SOC code)	Adverse Event	PRR	ROR	IC	Label		
					KR	USA	EU
Skin and appendages disorders	Photosensitivity reaction	3.14*	3.14*	0.01*	Y	Y	Y
	Skin discoloration	2.29*	2.29*	0.53*	N	N	N
	Pruritus	1.76	1.93	0.59*	Y	Y	Y
	Rash	1.19	1.23	0.16*	Y	Y	Y
	Angioedema	1.17	1.17	0.01*	Y	Y	Y
Musculo-skeletal system disorders	Arthralgia	3.34*	3.35*	0.92*	Y	Y	Y
	Muscle weakness	2.09*	2.09*	0.07*	Y	Y	Y
	Myalgia	1.27	1.27	0.00*	Y	Y	Y
Central and peripheral nervous system disorders	Hyperkinesia	4.70*	4.70*	0.27*	N	Y	Y
	Neuropathy peripheral	2.87*	2.88*	0.20*	Y	Y	Y

	Headache	1.27	1.28	0.12*	Y	Y	Y
	Vision abnormal	1.58	1.58	0.0[4]*	Y	Y	Y
Vision disorders	Photopsia			0.16*	N	N	N
	Application site pain	14.11*	14.11*	0.70*	Y	Y	Y
	Deafness	9.41*	9.41*	0.34*	Y	N	N
Hearing and vestibular disorders	Hearing decreased	2.24*	2.24*	-0.04	Y	Y	Y
	Sleep disorder	2.48*	2.48*	0.05*	Y	Y	Y
Psychiatric disorders	Anorexia	1.42	1.42	0.13*	Y	Y	Y
	Pancreatitis	37.63*	37.64*	1.03*	Y	Y	Y
	Peptic ulcer	6.27*	6.27*	0.19*	Y	N	N
Gastro-intestinal system disorders	Stomatitis ulcerative	2.82*	2.82*	-0.06	N	N	N
	Hyperglycaemia	2.44*	2.44*	0.16*	Y	Y	Y
Metabolic and nutritional disorders	Cachexia	2.31*	2.32*	0.35*	N	N	N
Cardiovascular disorders, general	ECG abnormal	-	-	0.47*	N	N	Y
Myo-, endo-, pericardial & valve disorders	Cardiac enzymes increased	-	-	0.16*	N	N	N
	QT prolonged	29.40*	29.44*	1.75*	Y	Y	Y
	Tachycardia ventricular	14.11*	14.11*	0.25*	Y	Y	Y
Heart rate and rhythm disorders	Arrhythmia	2.40*	2.41*	0.30*	Y	Y	Y
	Phlebitis	16.20*	16.23*	1.66*	Y	Y	Y
	Vasculitis	3.62*	3.62*	0.59*	Y	Y	Y
Vascular (extracardiac) disorders	Vein pain	2.51*	2.51*	0.63*	N	N	N
Respiratory system disorders	Hyperventilation	3.36*	3.36*	-0.03	N	N	N
Platelet, bleeding and clotting disorders	Prothrombin decrease	2.23*	2.23*	-0.08	Y	Y	Y
Body as a whole - general disorders	Leg pain	3.53*	3.53*	0.47*	N	N	N
	Infusion site reaction	15.56*	15.58*	1.56*	Y	Y	Y
Application site disorders	Injection site reaction	4.86*	5.05*	1.44*	Y	Y	Y
Resistance mechanism disorders	Abscess	4.70*	4.70*	0.05*	N	N	N

Abbreviations: WHO-PT: World health organization-preferred terms; PRR: Proportional reporting ratio; ROR: Reporting odds ratio; IC: Information component; ECG: Electrocardiogram

Table 2: Detected signals for quinolone antibiotics by World Health Organization-Preferred Terms from the Korea Adverse Events Reporting System Database (2005-2017) in South Korea.

Discussion

As the antibiotic market has grown, AEs associated with the use of antibiotics have also emerged as a great concern. Our study analysed AE signals for quinolones by a data mining method using the latest spontaneous AE reporting database and compared the drug labelling information from Korean, USA, and EU for quinolones; this is of note because studies on AEs related to quinolone usage have mostly been conducted based on cohort studies or meta-analyses but not as an analysis of AE reporting databases worldwide.

Both AEs for quinolones and cephalosporins occurred most frequently in patients over 60 years of age in all age groups and 1.39 times more frequently in the quinolone group (45.62%) than in the cephalosporin group (6.09%). In contrast, AEs occurred 11.7 times more frequently in the cephalosporin group (32.85%) than in the quinolone group (0.52%) in paediatric patients under 10 years of age. This difference could be attributed to the greater restrictions on the use of quinolone antibiotics in children in Korea than in Japan, the UK, the USA, or Canada [24]. All quinolone antibiotics were labelled as age contraindicated drugs for children in South Korea, whereas nine of ten

quinones in Japan [25] and four of five quinones in the UK [26], except for ciprofloxacin, which had a suggested child dosage, were restricted for use in children. The USA had no age contraindications on any quinolone antibiotics, except for a relative contraindication on ciprofloxacin and only had a suggested child dosage for ciprofloxacin and levofloxacin [27]. Canada had no age contraindications on all five quinolone antibiotics, but there was no suggestion of an age-specific dosage [28]. In contrast, cephalosporins were not specifically contraindicated in children, so the difference in reporting frequency of quinolone and cephalosporins in the age group under 10 years may be due to differences in drug use.

The annual increase pattern of frequency and proportion of AE reports for quinolones and cephalosporins was similar, and the number of AE reports has increased sharply in both all drugs since 2009. This was due to the fact that the policy for activating AE reporting, such as the establishment of regional pharmacovigilance agency, was implemented from 2009, and was not due to an increase in drug usage [29].

The most frequent AEs for quinolones were pruritus (17.88%), rash (15.57%), nausea (10.44%), urticaria (7.86%), and vomiting (5.72%). This finding was similar to the results of a systematic review that quantified the occurrence of common AEs on fluoroquinolones and other antimicrobials. The most commonly reported AEs were nausea, vomiting, diarrhoea; headache, dizziness, and rash, regardless of antibiotic type, and fluoroquinolones were associated with more central nervous system and gastrointestinal-related AEs compared with other types of antimicrobials [30].

Pancreatitis, which had the highest PRR and ROR, of approximately 37.6, among all signal information for quinolones, was detected as signal information for quinolones, because the frequency for quinolone (eight cases) was relatively higher than that for cephalosporins (one case). More than eight cases for quinolone were AEs due to all ciprofloxacin use. However, there was no significant association between ciprofloxacin and pancreatitis in patients with infectious colitis, although the incidence of ciprofloxacin-induced pancreatitis was approximately 3% in a Korean study [31]. Rashidi et al. (2016) [32] also investigated the aetiology of acute pancreatitis due to drugs, but the association with quinolone was not analysed. Therefore, further studies related to the causality evaluation between pancreatitis and quinolone use will be needed in the future.

Arrhythmia was also found on the drug labels in Korea, USA, and EU as signal information satisfying all of the PRR, ROR, and IC. However, whether arrhythmia was an AE caused by quinolone use was different in Korean and North European studies. In a population-based cohort study using Korean drug reimbursement claims data, the risk of ventricular arrhythmia was statistically significantly increased by the use of moxifloxacin [33]. The study cohort was derived from a source population of all Danish and Swedish adults; however, fluoroquinolone oral therapy was not associated with an increased risk of severe arrhythmia [34].

Hyperkinesia, which has the major symptoms of hypertrophic syndrome, vertigo, restless legs, and psychomotor retardation, was included on the US and European drug labels, but not on the Korean label. Both quinolone and cephalosporin have been reported in the same six cases (hyperkinesia). The high PRR value of 4.7 appears to be due to the difference in the number of drug-related AE pairs between the two drugs. In contrast, electrocardiogram (ECG) abnormalities, photopsia, and cardiac enzymes increased without PRR and ROR values were found as signal information by only IC value (more than 0). It is estimated that PRR and ROR were not calculated because there were no AEs reported in the cephalosporins group. In addition, of the above three AEs, ECG abnormalities were only described as very rarely possible AEs (probability of occurrence of less than 1 in 10,000) on the European drug label and were not on either the Korean or USA labels. However, the other two AEs (photopsia and cardiac enzymes increased), were not present on either the Korean, USA, or EU labels.

This study has notable strengths. We analysed representative and comprehensive AEs induced by quinolone use based on all reports from all groups, including reporting data by pharmaceutical companies, by using a nationwide AE spontaneous reporting database accumulated over many years. Nevertheless, our findings have several limitations. First, the actual occurrence rate of AEs induced by quinolones and cephalosporins may be somewhat underestimated owing to underreporting by using spontaneous AEs reporting data. Nevertheless, this signal information can be used as evidence for causality. Finally, we could not consider the interaction effects of quinolones and concomitant medications. As concomitant medications with quinolones were not included in the analysis data, it was difficult to determine how the interactions with concomitant medications affected the reporting of quinolone AEs. Thus, the results of this study should be carefully interpreted as AEs induced by only quinolones alone.

Conclusion

Thirty seven cases were confirmed to provide signal information related to quinolones use and nine cases (abscess, leg pain, vein pain, cachexia, skin discoloration, hyperventilation, stomatitis ulcerative, photopsia, and cardiac enzymes increased) were identified as new signals that were not present on the Korean, USA, or EU labels. Therefore, newly detected signals for quinolones should be continuously monitored to assess causality.

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