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Korean Pharmacovigilance System Based on EHR-CDM

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Abstract

An electronic health record (EHR) contains various clinical information for pharmacovigilance studies, but they remain difficult to use.. From 2016 to 2018, the ministry of food and drug safety and Korea institute of drug safety & risk management (KIDS) converted the EHRs of more than 9 million patients to a MOA common data model (CDM). KIDS developed the Medical record observation and assessment for drug safety network (MOA-Net), a web portal site to build a network between CDM data partners. Through MOA-Net, hospitals participated in pharmacovigilance studies and confirmed the usability and adequacy of the CDM.

Keywords:

Electronic health record, pharmacoepidemiology, pharmacovigilance

Introduction

Recent advances in health informatics has led to an increased interest in a new type of distributed database system known as a common data model (CDM). CDM is a database model with a standardized schema and vocabulary system. By using CDM, it became possible to perform simultaneous multi-center analysis using a reusable, parametrized query tool without exposing any kind of private information out of the medical institutes. In the Republic of Korea, the Ministry of Food and Drug Safety (MFDS) and the Korea Institute of Drug Safety & Risk Management (KIDS) developed an active pharmacovigilance system using CDM based on electronic health records (EHRs) since 2016. KIDS named this customized Korean model MOA (Medical record observation and assessment for drug safety)-CDM. During 2016-2017, MFDS constructed MOA-CDM at 9 hospitals in Korea. In 2018, KIDS selected five major hospitals including local representative drug safety centers as an attempt to expand the CDM. Also, KIDS developed MOA-Net, a web-based, multi-directional portal service to network government and data partners. Through MOA-Net, hospitals participated in pharmaco-vigilance studies and confirmed the usability and adequacy of the CDM.

Methods

Building MOA-CDM requires several steps such as extracting raw data from EHR, transforming the database schema and vocabularies into a common format, and loading. The standard schema of MOA-CDM includes essential parts of Sentinel CDM from the United States Food and Drug Administration (U.S. FDA)[1; 2] and the observational medical outcomes partnership (OMOP) CDM from observational health data science and informatics (OHDSI)[3; 4]. Since Korean hospitals mostly use Korean electronic data interchange (EDI) code and Korean standard classification of diseases (KCD) code in the National health insurance system, we mapped the local vocabularies into standard vocabularies. Local vocabularies are saved as source_value in OMOP CDM tables [4]. The standard vocabularies that we selected are as shown below [5; 6; 7; 8]:

Table 1. Vocabulary Mapping

Category	Local vocabulary (before mapping)	Standard vocabulary (after mapping)
Drug	EDI code	RxNorm
Condition	KCD-7	SNOMED-CT
Procedure	EDI code	EDI code
Measurement	Vary by hospital	LOINC

* SNOMED-CT: Systematized nomenclature of medicine-clinical terms, EDI: Korean electronic data interchange, LOINC: Logical observation identifiers names and codes

We designed the workflow of the Korean active pharmacovigilance system based on the CDM as follows: first, MFDS requests the analysis of domestic status to KIDS when a drug safety issue occurs. KIDS designs the analysisby referring to the literature review and experts advice. Next, KIDS distributes the analysis module through the MOA-Net and invites data partners to research. Participated data partners run the module using their own data and provide results to KIDS through the portal. Finally, KIDS integrates the results from the data partners and suggests answers for MFDS' safety concern.

We checked the adequacy and efficiency of the pharmaco-vigilance system based on CDM as follows. First, we performed abnormality detection and logical error test to enhance the quality of CDM data. We applied the Achilles heel rules from OMOP CDM [3; 4] as a standard of logical error test. We also checked the rate of concepts that are mapped into standardized vocabularies successfully. Second, we designed three nested, case-control studies about current pharmaco-vigilance issues in Korea - (1) Diclofenac beta di-methyl-aminoethanol & angioedema, (2) Clazpine & pleurisy, and (3) Allopurinol & thyroid stimulating hormone (TSH) increase. For every case, we randomly selected four controls by incidence density sampling method. We matched them for age, sex, and cohort-in-date. We aimed to calculate descriptive statistics of subjects, and unadjusted odds ratio (crude OR) as a signal statistics of adverse drug reaction. We developed analysis tools using structured query language (SQL) and R. Then, we distributed the tools and collected analysis of results from data partners through MOA-Net.

Results

In Korea, more than 9 million patient information records from 14 national representative hospitals were acquired to construct

a CDM database. The database converting EHR to CDM includes more than 127 kinds of clinical laboratory tests, and more than 5,000 drugs available in Korea. Every database entered the logical error test by the Achilles heel rule successfully. In the mapping rate test, we found some unusual concepts were not mapped into standard vocabularies. Most of the unmapped concepts turned out to be old drugs that are not currently used, or very new drugs in clinical trials. Continuous review and examination in mapping are still in progress to improve the quality of vocabularies by experts.

A total of 6 hospitals participated in three phamacovigilance studies. Among the three studies, we found two significant adverse drug reaction signals – clozpine & pleurisy, and allopurinol & TSH increase. For clozapine and pleurisy, we identified 81 cases of pleurisy and 308 matched controls. When all non-users were compared with users of clozapine, the risk of pleurisy (unadjusted OR) was increased by 8.46 fold (95% CI: 1.4-51.28). For allopurinol and TSH increase, we identified 10,663 cases of TSH increase and 42,631 matched controls. When all non-users were compared with users of allopurinol, the risk of TSH increase (unadjusted OR) was increased 3.52 fold (95% CI: 2.96-4.20). Although these statistics are not enough to conclude the relationship between drug use and adverse effect in the way that it is an unadjusted result, it still implies considerable association as a signal statistics. For diclofenac dimethylaminoethanol and angioedema, we couldn't assess the relationship because diclofenac use was considerably rare in our subjects. However, we identified significant differences in Non Steriod Anti Infammatory Drugs (NSAIDs), antibiotics use and history of urticaria which are all well-known risk factors in angioedema. The analysis result is as follow:

Table 2. Pharmacovigilance Results

Subject	Case (N)	Control (N)	OR	95% C.I.
Diclofenac-angioedema	1,719	6,876	1.33	0.14-12.85
Clozapine-pleurisy	81	308	8.46	1.4-51.28
Allopurinol-TSH increase	10,663	42,631	3.52	2.96-4.20

Conclusions

The Korean pharmacovigilance system based on MOA-CDM promises for active drug safety surveillance. As a result of performing several projects via MOA-CDM pharmacovigilance system, we found that the CDM system is faster and more efficient than analyzing health claims data to answer drug safety concerns. Also, it was possible to elaborate on research designs for adverse drug reaction using clinical information such as laboratory test results.

However, we need to overcome some difficulties in using CDM. First, we should consistently improve quality of data and vocabulary mapping. Also, hospitals should update their data periodically to assess the safety of new drugs. Therefore, automatic, real-time ETL (extraction-transformation-loading) and mapping engines should be developed by hospitals. Second, there is a risk of serious underestimation in pharmacovigilance studies using CDM because interhospital data sharing is impossible. For example, if a patient was prescribed medication elsewhere first and visited the hospital after they noticed an adverse drug reaction, an algorithm would classify him as a non-exposed case. On the other hand, if a patient was prescribed medication in a hospital and visited the hospital again when they noticed adverse drug reaction, an algorithm would classify him as an exposed control. Thus, researchers should be aware of the risk of bias and carefully interpret analysis result from CDM. Also, more medical institutional participation is requisite to enhance the effectiveness of this network.

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