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Application of a drug-interaction detection method to the Korean National Health Insurance claims database

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ABSTRACT

Drug interactions (DIs) constitute a serious problem and are considered to contribute to 6–30% of all adverse events (AEs). The use of existing data, including claims data, is expected to be helpful in detecting unknown DIs by complementing conventional spontaneous reporting systems. In the present study, an 'Ω shrinkage measure' was applied to the Korean National Health claims database to test the potential of the claims database as a DI surveillance resource. A well-known DI between non-steroidal anti-inflammatory drugs (NSAIDs) and diuretics was analyzed using the model. International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes related to DIs were assigned to the AEs of the DIs: I50, I50.0, I50.1, I50.9, R60, R60.1, R60.9, and J81. An elevated occurrence of AEs versus the expected level was observed using a two-sided 95% lower credibility interval limit above zero, $\Omega_{025} = 0.245$, which was the screening limit. The result was consistent with the actual DI between the two drugs. The finding indicates that the claims data have the potential to be used as a DI surveillance resource and that the Ω shrinkage measure may be a promising tool for detecting DIs in claims data.

1. Introduction

Adverse events (AEs) constitute a serious problem and are a leading cause of drug-related death (Lazarou et al., 1998). In particular, because it is common for the chronically ill to be treated with polypharmacy, the unpredictability of drug use is ever increasing. One of the problems that can arise with multiple drug use is drug interactions (DIs) in which one drug influences the effects of another, primarily by increasing or decreasing its effects. Patients can suffer harm, both from excessive effects of a drug and from the neutralization of a medicine that is necessary for the patient. It is believed that 6–30% of AEs are due to DIs (Pirmohamed and Orme, 1998). However, detection of DIs remains challenging due to a lack of understanding of pharmacological mechanism(s) and practitioners' occasional misjudgments of DIs as simple AEs.

The use of post-marketing surveillance data has been emphasized in the early detection of AEs due to DIs. Among such post-marketing surveillance data, a major source of DI detection is AE case reports. AE case reports are mostly submitted spontaneously by healthcare professionals or patients. The submitted reports are generally collected and processed to be analyzed for detection of AEs. The most extensive post-marketing AE database is 'Vigibase', which is maintained by a collaboration of the Uppsala Monitoring Centre (the UMC) and World Health Organization (WHO) (Hugman et al., 2004). Vigibase is a computerized database containing AE case reports from member countries worldwide.

Several attempts have been made to use AE case reports from Vigibase and other AE case-report databases for DI research. van Puijenbroek and colleagues investigated DIs between oral contraceptives and itraconazole by calculating the AE reporting odds ratios (van Puijenbroek et al., 1999) and examined the effects of pairs of NSAIDs with diuretics using a logistic regression model with AE case reports (van Puijenbroek et al., 2000). Another study was done to compare a multiplicative model and an additive model using known interactions of drugs (Thakrar et al., 2007). A group at UMC proposed a model with additive risk, namely, the 'Ω shrinkage measure', which calculates an observed-to-expected ratio as a measure of disproportionality. This approach was adopted for AE case reports after its evaluation using known DIs (Norén et al., 2008; Qian et al., 2010).

Most efforts to detect AEs, including DIs, have focused on AE case reports. However, a movement has emerged to use other databases as sources for AE detection. In 2007, the U.S. Food and Drug Administration (FDA) initiated the New Sentinel Network, which uses multiple existing data sources, including health insurance claims data and electronic medical records (EMR) to complement the system that uses AE case reports (Platt et al., 2009). If the system is fully developed, both the early detection of signals and con-

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firmation of signals from other sources are expected by virtue of the massive scale of the available data.

Korea has implemented an obligatory health insurance system managed by the Health Insurance Review and Assessment Service (HIRA), which covers the Korean population. In the database of this system, enormous amounts of data on up to 50 million patients are collected nationally on a regular basis. Some researchers have tried to take advantage of this massive data set to detect AE signals (Choi et al., 2011, 2010; Kim et al., 2011). However, no attempt has been made to assess DIs using the database.

In this study, we examined the potential of using the HIRA as a DI surveillance source by applying an analysis method to data on a known DI case, which was processed from the HIRA. The method was developed by Norén et al. and was originally proposed for analyzing DIs in AE case reports. As a known interaction example case, DIs between NSAIDs and diuretics were analyzed. Administration of non-steroidal anti-inflammatory agents (NSAIDs) can inhibit the synthesis of prostaglandins in the kidney, which can cause sodium and water retention and hence diminish the effectiveness of diuretics (Brater et al., 1980; Clive and Stoff, 1984; Heerdink et al., 1998; Herchuelz et al., 1989; Schlondorff, 1993).

2. Material and methods

2.1. Data source

In Korea, all healthcare service claims are submitted to the HIRA by healthcare providers. Then, the HIRA determines the amount of reimbursement by reviewing the submitted healthcare service records. The assessed information is computerized and stored in the database, enabling analysis at a massive scale. Submitted research designs are reviewed by a committee, and only researchers of approved studies are allowed to access HIRA data within a restricted range. The data include information on national health insurance coverage: general information on services, medical treatments, diagnoses, and outpatient prescriptions. We used patient information, drug codes, diagnosis codes, and dates of prescribing in this study. Patient information covered age, gender, and an identification number, which was assigned arbitrarily. Drugs and diagnoses were encoded according to the Anatomical Therapeutic Chemical (ATC) classification system and the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), respectively. We extracted 1 year of outpatient data (from 1 Jan 2008 to 31 Dec 2008) with additional diagnosis data for 7 months (from 1 Jun 2007 to 31 Dec 2008) from the HIRA database. Subjects were those aged over 17 years who visited a medical care institution during a 3-week period, between 1 and 21 June 2007, and who therefore had a record of receiving medical service. Codes in the claims data that were not in the list of codes or an age of over 130 years were regarded as errors. All the data of insurants containing errors were excluded.

2.2. Drug-interaction example case

We chose a well-known DI to evaluate the model to be applied to the HIRA data. In the interaction, ICD-10 codes that matched AEs derived from DIs were chosen. A physician checked and revised the list of ICD-10 codes, which were chosen by a pharmacist. The decreased effect of diuretics can be expressed as the occurrence of edema or heart failure, reflected by the following ICD-10 codes: I50, I50.0, I50.1, I50.9, R60, R60.1, R60.9, and J81 (Table 1). For the drugs, ATC codes starting with C03 and M01A were regarded as NSAIDs and diuretics, respectively.

Table 1
Chosen ICD-10 codes and their titles that match the ADRs for DIs between NSAIDs and diuretics.

ICD-10 code	Title
I50	Heart failure
I50.0	Right ventricular failure (secondary to left heart failure)
I50.1	Left ventricular failure
I50.9	Heart failure, unspecified
J81	Pulmonary edema
R60	Edema (not elsewhere classified)
R60.0	Localized edema
R60.1	Generalized edema
R60.9	Fluid retention (not otherwise specified)

ADR, adverse drug reaction; DI, drug interaction; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th Revision; NSAID, non-steroidal anti-inflammatory drug.

2.3. Data preprocessing

When patients visited clinics regularly to follow up on chronic diseases or to get a prescription, diagnoses recorded periodically could be mistaken for newly occurring diagnoses. To prevent this, it was important to eliminate records of repeated diagnoses. In our prior study using HIRA data, over 99% of the prescribed days of drugs were for no longer than 180 days. Considering the gap between actual visits and the expected day of visits as being up to 20 days, only diagnoses having no prior occurrence within 200 days were considered newly occurring diagnoses. Likewise, when a drug was prescribed again within 20 days after the administration period of the same drug ended, it was considered that the drug was used continuously, and the prescribing records were merged.

2.4. Model for DI detection

2.4.1. Generation of drug-diagnosis pairs that correspond to AEs

Unlike AE case reports, HIRA data consist of records of drugs and diagnoses. Drug-diagnosis pairs were used to calculate DI. The generation of drug-diagnosis pairs from HIRA data is shown in (Fig. 1). First, X and Y denote two drugs between which an interaction is known, and Z denotes all kinds of newly occurring diagnoses that are coded in ICD-10 codes. All of the events on the horizontal line were arranged in order of incident date. Z_1 represents a newly occurring diagnosis when the periods of drugs X and Y overlap, Z_2 represents a newly occurring diagnosis when either X or Y is prescribed, and Z_3 represents a newly occurring diagnosis when neither of the two drugs is prescribed. Each drug-diagnosis pair processed from HIRA data corresponded to

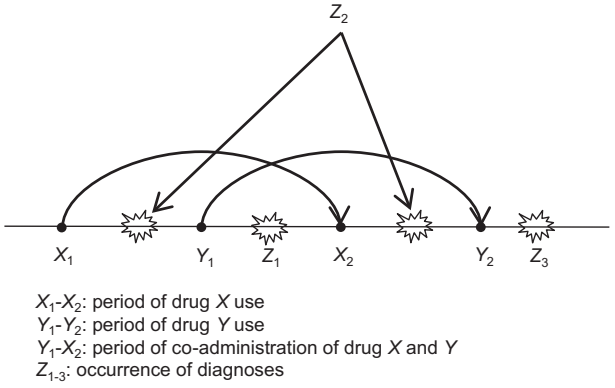

Fig. 1. Description of the process used to generate drug-diagnosis pairs from HIRA data. HIRA, Health Insurance Review and Assessment Service.