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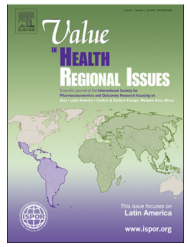

Possibility of Database Research as a Means of Pharmacovigilance in Japan Based on a Comparison with Sertraline Postmarketing Surveillance

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ABSTRACT

Background: Many pharmacoepidemiologic studies using large-scale databases have recently been utilized to evaluate the safety and effectiveness of drugs in Western countries. In Japan, however, conventional methodology has been applied to postmarketing surveillance (PMS) to collect safety and effectiveness information on new drugs to meet regulatory requirements. Conventional PMS entails enormous costs and resources despite being an uncontrolled observational study method. This study is aimed at examining the possibility of database research as a more efficient pharmacovigilance approach by comparing a health care claims database and PMS with regard to the characteristics and safety profiles of sertraline-prescribed patients. **Methods:** The characteristics of sertraline-prescribed patients recorded in a large-scale Japanese health insurance claims database developed by MinaCare Co. Ltd. were scanned and compared with the PMS results. We also explored the possibility of detecting signals indicative of adverse reactions based on the claims database by using sequence symmetry analysis. Diabetes mellitus, hyperlipidemia, and hyperthyroidism served as exploratory events, and their detection criteria for the claims database were reported by the Pharmaceuticals and Medical Devices Agency in Japan. **Results:** Most of the characteristics of sertraline-prescribed patients in the claims database did not differ markedly from those in the PMS. There was no tendency for higher risks of the exploratory events after exposure to sertraline, and this was consistent with sertraline's known safety profile. **Conclusions:** Our results support the concept of using database research as a cost-effective pharmacovigilance tool that is free of selection bias . Further investigation using database research is required to confirm our preliminary observations.

Keywords: database research, health care claim, pharmacovigilance, postmarketing surveillance, sertraline.

Introduction

Pharmacoepidemiologic studies have recently attracted attention as a means of evaluating the safety and effectiveness of drugs in clinical practice. In Western countries, various types of databases have been available for pharmacoepidemiologic studies, and numerous investigations have been conducted using these databases [1]. In Japan, the Ministry of Health, Labour, and Welfare mandates that postmarketing surveillance (PMS) of new drugs be conducted by pharmaceutical companies to collect safety and effectiveness information in clinical practice. PMS started with the enforcement of the drug re-examination system in 1980, and surveillance of 10,000 subjects was conducted at the time [1]. In 1991, the report by the "Study Group on Implementation Method of Post-marketing Drug Use Surveillance" was compiled, and it was established that PMS of 3000 subjects should be conducted to capture at least 1 subject developing an adverse reaction with an incidence of 0.1% with a probability of 95%. The requirement of PMS for 3000 subjects was deleted from the guideline after the introduction of early postmarketing phase vigilance in 2000. The Guideline on Pharmacovigilance Planning (International Conference on Harmonisation [ICH]-E2E) based on international consensus was officially released in 2004 [2], and that guideline advocated nonconventional methods of pharmacovigilance. However, conventional methodology continues to be applied to PMS regardless of the safety issues of each drug, and this remained the case even after the guideline was released. Under these circumstances, there is a growing need for advancing database research for pharmacovigilance. Various issues associated with conventional PMS, such as huge costs and resource

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expenditures, selection bias, difficulty in interpreting the data of observational research without a control group, and the possibility of "prescription only for PMS," have been pointed out [3–5]. The results of a questionnaire survey of 74 pharmaceutical companies in Japan showed that some information was obtained from approximately 40% of a total of 359 postmarketing drug use surveillance studies and that approximately half of them led to revisions of the package inserts. However, most revisions pertained only to the incidence of adverse reactions. No actions were taken regarding the approximately 30% of the postmarketing drug use surveillance studies that had obtained potentially relevant findings [6]. Considering these results, more efficient methods of utilizing databases should also be considered from the perspective of drug risk management in addition to conventional PMS. Thus, this study aimed to examine the possibility of database research as a more efficient pharmacovigilance approach, for application in Japan, by comparing the characteristics and safety profiles of sertraline-prescribed patients between a health care claims database and PMS.

Sertraline is a selective serotonin reuptake inhibitor and is widely prescribed all over the world. This drug was approved in Japan for the indications of depression/depressive symptoms and panic disorder in 2006. The postapproval re-examination period for this drug expired in 2014, and analysis of the PMS results has already been completed. Furthermore, the health insurance system in Japan covers all of the citizens. Against this background, we compared the health insurance claims database and PMS with regard to data from sertraline-prescribed patients.

Methods

We scanned the characteristics of sertraline-prescribed patients in a large-scale Japanese health insurance claims database developed by MinaCare Co. Ltd. and compared them with the PMS results. This database included about 2.8 million employees and their dependents' anonymized data from claims and annual health checkups (the maximum age was 74 years). In this study, cases where sertraline was prescribed at least once during the period from February 2008 to September 2013 were extracted from the claims database (pharmacy claims, medical claims, and diagnostic procedure combination claims) as of March 2014. Among these, cases that were in the database for 6 months prior to the first prescription record of sertraline were defined as the analysis set for comparison with the PMS population. This definition was chosen to allow us to extract cases similar to those in the PMS where prescribed sertraline for the first time. On the basis of the claims database, we also explored the possibility of detecting signals indicative of adverse reactions by using sequence symmetry analysis (SSA), which is a self-controlled study design [7,8]. Diabetes mellitus, hyperlipidemia, and hyperthyroidism served as exploratory events, and their detection criteria for the claims database were reported in a validation study of the Medical Information for Risk Assessment Initiative (MIHARI project) by the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan [9]. The PMDA selected these events because preventive therapy is unlikely to be provided, clear diagnostic guidelines are available, and laboratory data are also important for making an accurate diagnosis. For the patients who experienced both exposure (prescription of sertraline) and the exploratory events, the numbers experiencing post-sertraline and pre-sertraline events were compared. Patients whose first exposure (prescription of sertraline) and events occurred within the same month were excluded. The adjusted sequence ratio (ASR) and its 95% confidence interval (CI) for each event were calculated.

PMS, compared with the claims database, included two forms of surveillance—the postmarketing drug use surveillance (observation period 16 weeks) and special drug use surveillance on long-term use (observation period up to 52 weeks) in patients who had completed a 16-week observation period. Both forms of surveillance were conducted from December 2006 to November 2010.

Results and Discussion

Among patients prescribed sertraline at least once in the claims database, 6513 were identified in the analysis set. The safety analysis set in the PMS of sertraline included 2156 patients. Patient characteristics and concomitant medications prescribed for central nervous system disorders and conditions are shown in Table 1.

The proportion of female patients was slightly lower in the claims database (52.7%) than in the PMS (59.8%). The safety profile of sertraline did not differ between male and female patients [10] to the extent that the difference in the proportion of female patients was not likely to have exerted an influence on the safety evaluation in this study. The mean age was slightly lower in the claims database (37.9 years) than in the PMS (44.1 years). Since the claims database of MinaCare Co. Ltd. mainly provides data on those covered by employment-based health insurance (employees and their dependents) [11], mean age is likely to be lower than that in the PMS because of the characteristics of the insured persons. The diagnosis in most patients was depression/depressive state (claims database: 68.9%; PMS: 86.7%), and almost all were outpatients (claims database: 98.5%; PMS: 93.2%). The lower proportion of patients with a diagnosis of depression/depressive state in the claims database could be attributed to the insurance claims codes not always being in accordance with the International Classification of Diseases (ICD)-10 codes and the disease names not always being in accordance to with the ICD-10. In contrast, the proportion of patients prescribed concomitant central nervous system medications [12] was slightly higher in the claims database (91.4%) than in the PMS (84.0%). The higher proportion of patients with concomitant medications in the claims database suggests that this database does reflect clinical practice rather well because all prescriptions of medications covered by health insurance are recorded. The mean daily dose of sertraline was lower in the claims database (40.9 mg/day) than in the PMS (55.2 mg/day). One likely reason is that patients who revisited medical institutions within 4 weeks after starting the administration of sertraline (i.e., continuing patients) were involved in the PMS.

As a result of signal detection aimed at identifying adverse reactions, in the claims database, the numbers of patients who experienced post-sertraline and pre-sertraline events were 38 and 112 for diabetes mellitus, 139 and 310 for hyperlipidemia, and 5 and 26 for hyperthyroidism, respectively. The ASR (95% CI) was 0.893 (0.601–1.301) for diabetes mellitus, 0.871 (0.708–1.067) for hyperlipidemia, and 0.747 (0.224–1.976) for hyperthyroidism. Since the 95% CI included "1" for all of these events, the results can be interpreted as indicating that there is no tendency for a higher risk of these events after exposure to sertraline.

No diabetes mellitus, hyperlipidemia, or hyperthyroidism events were reported as adverse reactions in the postmarketing drug use surveillance (observation period 16 weeks) or special drug use surveillance on the long-term use (observation period up to 52 weeks) of sertraline. Since the results of the claims database were similar to those of the PMS, these results can be taken to support the existing information [10], indicating that sertraline does not pose a potential risk for the development of these diseases.