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Original Research

Investigation of the boxed warnings in package inserts of prescription medicines for medical professionals in Japan

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Abstract

Objective: In the Japanese Pharmacists Act, article 25-2, revised in 2013, it states that pharmacists shall provide the necessary information and guidance to the patient based on pharmaceutical knowledge and experience for ensuring the proper use of the medicine dispensed. The package insert is one of the documents to be referred to when providing the information and guidance. The boxed warnings in package inserts that include the precautions and responses are the most significant parts, however, the suitability of boxed warnings for pharmaceutical practice has not been evaluated. The aim of this study was to investigate the boxed warning descriptions in package inserts of prescription medicines for medical professionals in Japan. **Methods:** Package inserts of prescription medicines listed in the Japanese National Health Insurance drug price list on March 1st 2015 were collected one by one by hand from the website of the Japanese Pharmaceuticals and Medical Devices Agency (https://www.pmda.go.jp/english/). Package inserts with boxed warnings were classified according to the Standard Commodity Classification Number of Japan based on the pharmacological activity of each medicine. They were also compiled according to their formulations. The boxed warnings were divided into the precautions and responses parts, and their characteristics were compared among medicines. **Results:** The number of package inserts found on the website of the Pharmaceuticals and Medical Devices Agency was 15,828. Boxed warnings were present in 8.1% of the package inserts. A description of adverse drug reactions accounted for 74% of all precautions. Most of the precautions were observed in the warning boxes of antineoplastic agents. Blood and lymphatic system disorders were the most common precaution. Responses in the boxed warnings directed toward medical doctors, pharmacists, and other healthcare professionals accounted for 100, 77, and 8% of all package inserts with a boxed warning, respectively. Explanations for patients were the second most frequent response. **Conclusions:** The majority of boxed warnings request therapeutic contribution by pharmacists, and the descriptions of these explanations and guidance by pharmacists to patients were found to be consistent with the Pharmacists Act.

Keywords: boxed warning; Japanese Pharmaceutical Act; package insert; precaution part; response part

INTRODUCTION

Package inserts have been adopted in many countries and are employed in clinical practice.[1-3] Information on the external packaging and the label are complementary to the package insert.[4] Package inserts and labels are also used in Japan. Boxed warnings are included in package inserts in Japan for drug safety management purposes. The Japanese Pharmaceuticals and Medical Devices Agency (PMDA) has constructed a package insert notification system,[5] which requires the verification of package inserts for medical professionals by the drug manufacturer. A study of the characteristics of package inserts is needed in order to maintain the validity of the descriptions and to ensure that they successfully comply with clinical practice.

In article 25-2 of the Japanese Pharmacists Act, revised in 2013, it states that pharmacists shall provide the necessary information and guidance to the patient based on their pharmaceutical knowledge and experience for ensuring the proper use of the medicine dispensed.[6] The package insert of a prescription drug is one of the documents to be referred to when providing the information and guidance. Package inserts in Japan consist of 20 items; date of preparation or revision, Japan Standard Commodity Classification Number,[7] therapeutic category, regulatory classification, name, boxed warnings, boxed contraindications, description, indications, dosage and administration, precautions, pharmacokinetics, clinical studies, pharmacology, physicochemistry, precautions for handling, conditions for approval, packaging, references and request for literature should be made to, and name and address of manufacturer or importer. After the incidence of a drug-drug interaction between sorivudine and fluorouracil in Japan, the format of boxed warnings in package inserts was fully revised,[8]

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and resemble those in the United States. Articles 216-6, 227-4, and 228-7 of the Ministerial Ordinance for Enforcement in Japan state that boxed warnings are mandatory for drugs with fatal or serious side effects.[9] The boxed warnings consist of precautions and responses for medical staff. The precautions and responses in the boxed warnings in the package insert are the most significant parts for drug safety. However, the suitability of boxed warnings for pharmaceutical practice has not been evaluated. The validity of the Japanese Pharmacists Act, which was revised to comply with the descriptions, needs to be fully investigated. The aim of this study was to investigate the descriptions of boxed warnings in package inserts of prescription medicines for medical professionals in Japan.

METHODS

The package inserts of prescription medicines listed in the Japanese National Health Insurance drug price list on March 1st 2015 were collected from the website of the Japanese Pharmaceuticals and Medical Devices Agency.[10] The inserts were obtained one by one by hand. In Japan, medicines which have the same active components and pharmacological activity and the same formulation have the same package insert regardless of the dosage strength. Generic medicines usually have the same boxed warnings as the branded medicines, and they are regarded as the same insert.

Package inserts with boxed warnings were classified according to the Standard Commodity Classification Number of Japan[7] based on the pharmacological activity of each medicine. They were also compiled according to their formulations. Internal medicines included tablets, capsules, granules, powders, liquids and solutions, elixirs, syrups, and jellies. External medicines were troches, sprays, creams, gels, ointments, lotions, gargles, eye drops, nose drops, ear drops, patches, inhalers, mouthwashes, and suppositories. Injections included ampoules, vials, and syringes.

The boxed warnings were divided into precaution and response parts, and their characteristics were compared between medicines. With respect to the precaution part, adverse drug reactions were classified according to the System Organ Class terms of the Medical Dictionary for Regulatory Activities terminology version 18.1,[11] while for the response part, the medical interventions were classified into nine types: hospital facilities, explanation for patients, patient selection, laboratory examination, avoidance of drug interaction, precaution for patients, duration of administration, therapeutic drug monitoring, and others.

RESULTS

The number of drugs listed in the National Health Insurance drug price list was 17,042. The number of package inserts found on the website of the Pharmaceuticals and Medical Devices Agency was 15,828. The total number of the boxed warnings was 401. Boxed warnings were present in 2.5 percent of the package inserts.

Table 1 shows the number of package inserts with boxed warnings stratified by pharmacological action. Most of the boxed warnings were observed in the package inserts of antineoplastic agents. Stratified by agent form, the number of package inserts with a boxed warning was 168, 18, and 215 for internal medicine, external medicine, and injections, respectively.

There were 298 package inserts with a boxed warning describing adverse drug reactions. Descriptions of adverse drug reactions accounted for 74% of all precautions (298/401). Table 2 shows the number of adverse drug reactions described in the package inserts. The most common precautions were related to blood and lymphatic system disorders.

Table 1. Package inserts with a boxed warning classified by pharmacological activity

Pharmacological action	**n**
Antineoplastic agents	107
Other agents affecting metabolism	51
Agents affecting the central nervous system	42
Antimicrobial agents	37
Hormone preparations (including antihormone preparations)	26
Others	138
Total	401

Table 2. Type of precaution in package inserts

Adverse drug reactions described in package inserts	**n**
Blood and lymphatic system disorders	62
General disorders and administration site conditions	62
Hepatobiliary disorders	50
Metabolism and nutrition disorders	47
Infections and infestations	41
Respiratory, thoracic and mediastinal disorders	34
Psychiatric disorders	25
Cardiac disorders	23
Nervous system disorders	15
Renal and urinary disorders	14
Skin and subcutaneous tissue disorders	14
Gastrointestinal disorders	12
Pregnancy, puerperium and perinatal conditions	12
Reproductive system and breast disorders	11
Neoplasms benign, malignant and unspecified (including cysts and polyps)	10
Vascular disorders	9
Immune system disorders	8
Total	449

There were 401 boxed warnings directed at physicians, 309 for pharmacists, and 33 for other healthcare professionals. Among all package inserts with a boxed warning, 100%, 77%, and 8% of the responses in the boxed warnings were to directed to

physicians, pharmacists, and other healthcare professionals, respectively. Table 3 shows what therapeutic intervention is instructed in the package insert. Explanations for patients were the second most frequent response. Responses were also frequent in the package inserts of agents affecting cellular function. Several warning descriptions had only either a precaution or response which may be difficult to understand by healthcare professionals.

DISCUSSION

To the best of our knowledge, this is the first report on an investigation of boxed warnings in the package inserts of prescription medicines for medical professionals in Japan. The number of package inserts identified was 15,828. The total number of package inserts with a boxed warning collected using generic names was 401 (2.5%). Descriptions of adverse drug reactions accounted for 74% of all precautions. The majority of boxed warnings request therapeutic contribution by pharmacists, and the descriptions of these explanations and guidance by pharmacists to patients were found to be consistent with the Pharmacists Act. The suitability of the Pharmaceutical Act was confirmed.

This study evaluated the suitability of the descriptions in boxed warnings of package inserts for medical professionals. Boxed warnings are composed of a precaution entry and a response entry, although other descriptions including contraindications have only a response. The methodology seems to be different for assessing a boxed warning from that of other descriptions. For example, compliance with a response and its supervision seems to be significant in clinical practice. However, there is no methodology with which to evaluate the compliance with a response so further studies will be needed. This is the first study to investigate Japanese package inserts.

Antineoplastic agents have many adverse drug reactions and boxed warnings (Table 1). Stratified according to agent form, injections require the most precaution. Pharmacists usually provide explanations of internal medicines and topical medicines because their administration requires a thorough understanding of the drug. Injections, which are administered by healthcare professionals, are rarely explained to the patient by pharmacists in Japan. However, pharmacists should provide explanations about injections because they require the most precaution when administering.

Blood and lymphatic system disorders are the most commonly mentioned precaution (Table 2), and this is consistent with the results of package inserts classified by pharmacological activity. Most antineoplastic agents cause bone marrow suppression. However, the patient is usually unaware of any bone marrow suppression. Explanations of its symptoms and the requirement for regular laboratory tests are needed. Adverse drug reactions were classified using Medical Dictionary for Regulatory Activities (medDra)[11] in Japanese package inserts as well as those used by the US Food and Drug Administration. Therefore, the methodology should be applicable to other countries.

The most frequent response is that the hospital facility administering the chemotherapy should possess expertise and be able to undertake multidisciplinary treatment (Table 3). Explanations for patients were the second most frequent response. The results of the response part corresponded to the results of the precaution part. Almost all chemotherapies cause blood and lymphatic system disorders.

Table 3. Type of response in package inserts

Therapeutic intervention described in package insert	**n**
Hospital facilities	201
Explanation for patients	165
Patient selection	129
Laboratory examination	99
Avoidance of drug interaction	46
Precaution for patients	9
Duration of administration	6
Therapeutic drug monitoring	4
Others	121
Total	780

Based on these study results, typical boxed warnings are presented for injectable antineoplastic agents with adverse drug reactions that should be explained to patients. Boxed warnings in Japanese package inserts originated from the drug-drug interaction between sorivudine and fluorouracil. Sorivudine, whose trade name is Usevir, has been withdrawn from the Japanese market, and its package insert is no longer available. On the other hand, the package insert for fluorouracil describes a drug interaction with a tegafur/gimeracil/oteracil combination agent in the boxed warning.[12] Boxed warnings in Japanese package inserts properly deal with adverse drug reactions and drug-drug interactions. Some boxed warnings, however, still need to be improved.

CONCLUSIONS

Boxed warnings are useful for pharmacists in terms of providing the patient with necessary information and guidance based on pharmaceutical knowledge and experience. The validity of boxed warnings in package inserts for medical professionals should be regularly assessed.

LIST OF ABBREVIATIONS

US United States

medDra Medical Dictionary for Regulatory Activities

PMDA The Japanese Pharmaceuticals and Medical Devices Agency

DECLARATIONS

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Consent for publication

Not Applicable

Competing Interests

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Author contributions

YM analyzed the data and wrote the manuscript; TN designed the study and analyzed the data; JO collected the data; TY collected the data; JK critically reviewed the manuscript. All authors reviewed the manuscript.

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