SHORT COMMUNICATION

Drug Safety 2002; 25 (6): 441-444
0114-5916/02/0006-0441/$25.00/0



# Prescription-Event Monitoring in Japan (J-PEM)

*Kiyoshi Kubota*

Department of Pharmacoepidemiology, Faculty of Medicine, University of Tokyo, Tokyo, Japan

## Abstract

In prescription-event monitoring in Japan (J-PEM), patients are identified by prescriptions in individual pharmacies where drugs are dispensed. The methodology is somewhat different to that used by the Drug Safety Research Unit in the UK, in that two questionnaires, one to the pharmacist and the other to the doctor are sent for each patient and the method of concurrent control is employed in J-PEM. In the data analysis, the list of events reported as a suspected reaction or a reason for stopping the drug is made to generate a signal. In addition, a signal may be generated for some events with the statistically significant difference of crude rates followed by the regression analysis or a follow-up study. In J-PEM, Medical Dictionary for Regulatory Activities (MedDRA) terminology is used for data entry and data analysis. Lowest level terms (LLTs) in MedDRA are used in data entry while a signal is generated using preferred terms (PTs). However, to generate a signal effectively, some PTs may be grouped as one term. In addition, if two terms are so similar, it may be instructed that one of those two terms is normally selected in data entry to avoid confusion. Many more PEM studies could be undertaken to determine if MedDRA can be used for effective signal generation, but the usefulness of MedDRA in J-PEM is still to be determined.

Two pilot studies for prescription-event monitoring in Japan (J-PEM) were launched in 1997 and 1998 to examine the feasibility of observational studies similar to the prescription-event monitoring undertaken by the Drug Safety Research Unit in the UK (UK-PEM). In this paper, the methods of J-PEM are described. In the first part, methods of patient identification and data analysis as well as some other methodological issues of J-PEM that differ from those of the UK-PEM are described. In the second part, problems associated with the use of Medical Dictionary for Regulatory Activities (MedDRA) terminology in J-PEM are discussed.

## 1. Methods of Prescription-Event Monitoring in Japan (J-PEM)

### 1.1 Method of Patient Identification in J-PEM

In the UK-PEM, patients are identified by prescriptions collected by the Prescription Pricing Authority (PPA). In Japan, hospitals, private medical offices and community pharmacies issue monthly claims asking for a reimbursement fee for medical care including drug costs and the claims are collected by the central body for reimbursement. However, currently, the record of those claims cannot be used to identify patients in the

drug safety-monitoring scheme for several reasons. For example, according to the Ministry of Health, Labour and Welfare (MHLW), which has a strong influence on the Social Insurance Medical Fee Payment Fund (the organisation established for the reimbursement of medical fees), the MHLW cannot promote the use of monthly claims for drug safety purposes unless a satisfactory agreement is reached between relevant organisations, such as the Japan Medical Association and National Federation of Health Insurance Society and such an agreement is difficult to make. In J-PEM, patients are currently identified by prescriptions in individual pharmacies where drugs are dispensed.[1]

The biggest issue for J-PEM is how to increase the study size since only a fraction of pharmacies in Japan are currently participating in the scheme. For example, in the pilot study of J-PEM on losartan, patients monitored in the study were estimated to be only 1 to 2% of all of patients who used losartan during the study.

A new scheme of J-PEM, called as 'J-PEM 2000', is currently in progress, but the basic method of identifying patients is the same as that used in the pilot study.

### 1.2 Some Characteristics of J-PEM

Some features in J-PEM are different from those in the UK-PEM. For example, in J-PEM two questionnaires are sent for each patient, one to the pharmacist and the other to the doctor. Both the pharmacist and doctor are requested to report events that occur in the patient prescribed the test or control drug, in addition to providing other information. Another feature, which is different from the UK-PEM, is that a method of concurrent control is employed in J-PEM. In J-PEM, the pharmacist asks a patient if he/she is taking one of the specified control drugs and registers him/her as a control patient. Pharmacists in each pharmacy are instructed to register patients who are prescribed one of control drugs for the first time ever in his/her life after the index date (the date when the test drug was released to the market). If the patient has a clear idea that he/she will be using the drug for the first time ever, the patient is registered as a control patient irrespective of the age, gender and the number of patients prescribed a test drug and registered so far by the pharmacist and/or pharmacy in the study.

### 1.3 Method of Data Analysis in J-PEM

In the analysis of event data in J-PEM, the list of events reported as a reason for stopping the drug and that of events reported as a suspected reaction to the study drug are made. In addition, the crude rates of events that the patients experienced while using a study drug are calculated as the number of events divided by the corresponding patient-months and compared between test and control drugs by the likelihood ratio test.[2] The list of events for which the unadjusted event rate is significantly greater in patients taking the test drug than the control drug differs somewhat from the list of those events reported as a reason for stopping the study drug as well as from a list of those events reported as a suspected reaction to the study drug. For example, some events may be identified as events with a significant difference in crude rates even if all or most of reporters did not describe them as a suspected reaction to the drug or as a reason for stopping the drug.

Events for which the event rate is significantly greater in patients with the test drug than the control drug may be a true or false signal and further study is required to elucidate whether or not those events are likely to be an adverse reaction to the study drug. When the number of patients who had the event is large, some statistical method (e.g. the regression analysis using a multivariate model) may be of help to know whether possible confounding factors are associated with the difference in crude rates. However, when the number of patients is small, a follow-up study in which more information is obtained by asking the reporter to provide additional data on the reported event will often be useful. In conclusion, the comparison of crude rates between test and control drugs followed by the regression analysis or a follow-up study may be useful in signal generation.

## 2. Medical Dictionary for Regulatory Activities (MedDRA) for Signal Generation

### 2.1 Structure of MedDRA

MedDRA has a hierarchical 5-fold structure [system organ class (SOC); high level group term (HLGT); high level term (HLT); preferred term (PT); and lowest level term (LLT)]. The MedDRA version 2.1 (V2.1) came into use in March 1999. At the same time, its Japanese version (V2.1J) was released by Japan Maintenance Organisation, the only formal maintenance organisation located in a non-English environment.

### 2.2 Advantage of MedDRA

MedDRA has several advantages. First, it is easy to communicate when MedDRA is used because it is maintained as a global terminology. Secondly, many terms (e.g. 49 247 LLTs in V3.3) are available and most of reported terms are already included in MedDRA. Thirdly, the versions are frequently upgraded and new terms become available in MedDRA relatively quickly.

### 2.3 The Level of Terms for Data Entry

It is recommended by the Maintenance and Support Services Organisation (MSSO) that the data entry be done using LLTs. The large number of LLTs in MedDRA will facilitate exact matches with the original words in the adverse reaction case report or other documents, such as articles in medical journals, thus reducing the need for judgement in data entry. In J-PEM, LLTs are used in data entry as recommended by the MSSO. In 'Points to Consider' (PTC) for MedDRA term selection (release 2.0; 5 November 2000) provided by the MSSO, it is pointed out that judgement is sometimes needed when selecting an LLT in addition to facilitate matching the reported term with a MedDRA LLT. For example, in PTC, the following example is shown: select 'hair texture abnormal' when 'brittle hair' is reported. In general Japanese users may have to judge more than those in English-speaking environments. It is stressed that terms can be selected in any language for which MedDRA is maintained (e.g. PTC 2.5). English and Japanese terms in MedDRA can be equivalent when English and Japanese words assigned to the same term have the same meaning. On the other hand, at least currently, translation from English to Japanese is often inappropriate in 'MedDRA/J' which consists of the original MedDRA and its Japanese translation. If Japanese translation is found to be inappropriate, Japanese users may have to rely on the original English term when selecting the term and the extent of matching between the MedDRA Japanese term and the reported term may be ignored in such a case.

### 2.4 The Level of Terms for Signal Generation

The experience in J-PEM has indicated that PTs may be used for signal generation.[3] Many LLTs are synonyms or lexical variants and normally the level of LLT is not suitable for signal generation. On the other hand, HLTs are often not specific enough to generate a proper signal. Therefore, PTs are, in general, suitable for the purpose of signal generation.

### 2.5 Grouping Preferred Terms for Signal Generation

To generate a proper signal, some PTs may be grouped. If the same event or a group of events are reported and coded by different PTs and counted separately, the sensitivity may be lowered. As a result, an important problem may be missed. Similarly, the difference of crude rates may be not significant unless they are properly grouped. Terms may be grouped for a variety of reasons. First, the same event could be reported by different terms and thus coded by LLTs under different PTs with similar meanings (e.g. 'anorexia' and 'appetite decreased'). Confusion associated with two terms which have similar meanings may be augmented in MedDRA/J as Japanese translation of two similar terms can be almost identical to each other. Similarly, the same event could be reported and coded by PTs with different specificity because

one reporter may report the event in detail while the other may report using a non-specific term (e.g. 'liver function test abnormal' *vs* 'SGOT increased, SGPT increased, and ALP increased').

Related PTs may be grouped because a pathological condition could develop in several ways in different patients. For example, arthralgia may develop in a variety of joints, some conditions may develop in different patients with different intensities and may be coded by different PTs (e.g. nausea and vomiting) and a syndrome may appear as various combinations of symptoms and abnormalities. However, there seems to be no good guidelines on which PTs are to be grouped to generate a proper signal. As pointed out earlier, the currently available special search categories (SSCs) made by grouping several PTs in MedDRA are very limited in scope and it is to be hoped that the MSSO may construct new SSCs.[4]

### 2.6 Can the Process of Coding Events and Grouping Terms be Separated?

In many cases, PTs may be grouped when they are analysed after they are coded using different PTs. However, in some cases, it may be advantageous to group events while coding them. For example, one patient may have events defined by two related PTs which are grouped when analysed. If just one term is coded for such a patient, the computational process of counting events may become easier when the summary table is made. In another situation where it is considered advantageous to group events while coding them, those persons who are responsible to coding events may be frustrated when no clear instruction are given as to how to handle two similar terms. In J-PEM, those people who code events are given instructions regarding how to use a few specific terms which require careful handling. For example, if two PTs are so similar that distinction between these two terms is usually not needed, then it may be instructed that one of those two terms is normally selected. In another instruction, it may be indicated that one non-specific term (e.g. 'liver function tests raised') is coded together with specific terms (e.g. 'SGPT increased, SGOT increased and ALP increased').

## 3. Conclusion

In conclusion, the usefulness of MedDRA in J-PEM remains to be determined particularly for signal generation. There seem to be areas where many more investigations can be conducted if MedDRA is used for signal generation effectively. For example, general guidelines for grouping PTs may be given as creating new SSCs suitable for signal generation.[4]

## Acknowledgements

This study was conducted under a grant from the Ministry of Health, Labour and Welfare as a Health Sciences Research Project ('A pilot study of the Japanese version of Prescription-Event Monitoring' 1998.4-2001.3). The Japan Pharmaceutical Association (JPA), Japanese Society of Hospital Pharmacies (JSHP), and Japan Medical Association Research Institute (JMARI) are participating in this research.

## References

1. Kubota K. A design for prescription-event monitoring in Japan (J-PEM). Pharmacoepidemiol Drug Saf 1999; 8: 447-56
2. Kuobta K, Kawabe E, Hinotsu S, et al. Pilot study of prescription-event monitoring in Japan (J-PEM) comparing troglitazone with alternative oral hypoglycaemics. Eur J Clin Pharmacol 2001; 56: 831-8
3. Yokotsuka M, Aoyama M, Kubota K. The use of a medical dictionary for regulatory activities terminology (MedDRA) in prescription-event monitoring in Japan (J-PEM). Int J Med Inf 2000; 57: 139-53
4. Brown E, Douglas S. Tabulation and analysis of pharmacovigilance data using the medical dictionary for regulatory activities. Pharmacoepidemiol Drug Saf 2000; 8: 479-89

Correspondence and offprints: Dr *Kiyoshi Kubota*, Department of Pharmacoepidemiology, Faculty of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-8655, Japan.
E-mail: kubotape-tky@umin.ac.jp