ORIGINAL CONTRIBUTION

The Feasibility of Case-Control Studies Using Rezept Files of a Japanese Hospital: A Study on Thrombocytopenia

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A case-control study on thrombocytopenia with the Rezept files of Tokyo Medical and Dental University Hospital has been carried out. The study explored whether the case-control studies are feasible using files of Rezept system maintained in many Japanese hospitals for health insurance billing. Each of the 100 patients with thrombocytopenia was contrasted with one control case, matched for age, sex, in- or out-patient, consultation clinic and year of registration. Of 1,021 products of drugs registered in the files, 40 products (36 drugs) were associated with the disease. Through medical record review, low platelet count was confirmed in 94.6% of inpatients, while only in 26.9% of outpatients. Thirty-one cases of drug-induced thrombocytopenia were identified, and 29 suspected drugs were listed up. On the basis of the analysis of these data, we conclude that the Rezept files be useful in the case-control studies on adverse drug reactions similar to thrombocytopenia in inpatients. The medical records, however, must be reviewed to confirm the date of disease onset and to obtain information not included in the computerized data. J Epidemiol, 1994; 4: 147-155.

pharmacoepidemiology, databases, adverse drug reactions, postmarketing surveillance, epidemiologic methods

In recent years, the role of pharmacoepidemiology in drug evaluation has begun to be emphasized in Japan. For example, the Ministry of Health and Welfare has established the Good Post-Marketing Surveillance Practice, which came into effect on April 1, 1993. Upon performing pharmacoepidemiologic studies, computerized databases have been extensively used in the North America and in Europe. These databases have special features of promptness of data retrieval, largeness of accumulation and cost advantages, although there are still formidable difficulties in relevant usage of them. Unfortunately these types of databases are scarcely available in Japan.

Rezept files are files of the Rezept system, which is a computerized system maintained by many hospitals in Japan for health insurance billing. We have a nationwide health insurance system under which most fees for drugs and medical procedures are reimbursed by insurance agencies to medical facilities. They include information on patient characteristics, drugs dispensed, and diagnoses for nearly all of both inpatients and outpatients. Thus, the Rezept system is one of the few potential resources for pharmacoepidemiologic studies in Japan. For years, we have tried to find out the possibility of applying the data of the system in pharmacoepidemiologic studies, particularly relating to the postmarketing drug surveillance system for earlier detection of adverse drug reactions. The previous studies suggest that Rezept files can be useful in retrospective cohort studies provided that the diagnostic data are reliable to some extent.

To examine the feasibility of case-control studies using Rezept files, we tried a case-control study on thrombocytopenia with the Rezept files of Tokyo Medical and Dental University Hospital at the outset. Thrombocytopenia caused by drugs is a serious problem, and the diagnostic validity of which is objectively evaluated through laboratory findings. The present paper reports on the results of an effort to conduct retrospective case-control study on thrombocytopenia and illustrates some problems in using the files for this purpose.

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SUBJECTS AND METHODS

Data Source

The present study population was drawn from the Rezept files of Tokyo Medical and Dental University Hospital, Faculty of Medicine, for about seven years from January 1982 to November 1988. The hospital is a general hospital with about 700 beds, and consists of 18 consultation clinics. The Master File of Inpatient included data on patients admitted to the hospital, which consisted of an identification number, name, date of birth, sex, and admission and discharge dates. The Master File of Outpatient included similar data on outpatients examined and treated at the hospital.

A potential subject was defined as a patient whose diagnostic data was entered into the Master File of Diagnosis during the study period. This Master File of Diagnosis contained a record of each diagnosis with the diagnostic date, consultation clinic, and in- or out-patient. Because diagnostic data before April 1985 were very sparse, the number of potential subjects defined was 109,088 out of 177,317 patients registered in the files during the study period.

The Master File of Treatment included the records of medical procedures which could be reimbursed through the health insurance program. They consisted of drug prescriptions, anesthetizations, surgical operations, X-ray examinations, laboratory tests and so forth. Although drugs which could be reimbursed have been on the National Health Insurance Ethical Drug Tariff, during the study period, most prescription drugs had been on the Tariff, and had been filled in the hospital even for outpatients. In the previous studies, a person based longitudinal file, named the File of Each Patient's Medical History, was created for the potential subjects through record linkage (Fig. 1).

Figure 1. Flow chart of data processing.
Selection of cases and controls

We identified potential cases from the File of Each Patient's Medical History for those with thrombocytopenia. They were then examined to exclude those that had not received any medication before the first diagnostic date of thrombocytopenia (index date). A large pool of potential control patients remained. For each case of thrombocytopenia, we further drew a subgroup from the pool of potential control patients, matching for age, sex, in- or out-patient, consultation clinic and year of registration, some allowance being set for year of registration. Finally, a control case was randomly drawn from the subgroup.

Screening of drugs associated with thrombocytopenia

For each case, we identified all the drugs administered before the index date. For each drug identified, users before the index date in the case group and users during the whole study period in the control group were counted respectively. Exposure odds ratio and its 95% confidence interval were calculated of each drug. If the lower 95% confidence limit was larger than 1.0, namely, if a drug was used in the case group with a definitely higher frequency, then the drug was selected.

Medical record review procedures

We requested the relevant doctors for primary medical records and laboratory data of all cases. We identified patient characteristics and underlying or primary diseases. Presence of thrombocytopenia in the month including the index date or in the previous month or in the following month was confirmed by the finding of low platelet count less than 120,000/mm³, the lower limit of the reference interval adopted in the hospital. The medical record review was aborted if low platelet count was not found. The primary medical records of the cases of low platelet count were reviewed in detail for the followings: changes over time in platelet count and other laboratory data, complications, drugs prescribed and other treatments given including operations and radiations, and descriptions on etiology for thrombocytopenia. If recurrence was found, the records were reviewed on thrombocytopenia in the time including the same or closest date to the index date. Recurrence was defined as the returning of low platelet count exceeding the limit in 14 days or more after the recovery. The date of disease onset was decided as the first date of falling of platelet count exceeding the reference value. Descriptions on etiology for the disease were examined by one of the authors (TS). For the cases of drug-induced thrombocytopenia, we listed suspected drugs designated on the records. If only product categories of suspected drugs were mentioned, he decided which drug was to be indicated based on the time relationship of drug exposure to the onset and the course of the illness.

RESULTS

Characteristics of subjects and drugs associated with thrombocytopenia

We identified 131 patients with thrombocytopenia from the Rezept files. Of these, 100 cases had been receiving

| Groups | Drugs |
|--------|-------|
| A      | Therapeutic agents for the disease (2) | dexamethasone, heparin sodium* |
| B      | Diagnostics for the disease (0) | cefalexin, chlorpheniramine maleate, cimetidine, cyclophosphamide, cytarabine, daunorubicin hydrochloride, doxorubicin hydrochloride, heparin sodium, indomethacin, mercaptopurine, pipercillin sodium, sulfamethoxazole, trimethoprim, vincristine sulfate |
| C      | Drugs whose Japanese package inserts refer to the disease as an adverse reaction** (13) | amphotericin B, gentamicin sulfate |
| D      | Drugs except stated above whose US package inserts refer to the disease as an adverse reaction*** (2) | aluminum hydroxide, magnesium hydroxide, amikacin sulfate, L-aspartate potassium, cytochrome C, distilled water for injection, domperidone, glucose, hydrocortisone sodium phosphate, indocianine green, intravenous hyperalimentative basic solution, iodine addition products of the ethylesters of the fatty acids obtained from poppyseed oil, isotonic sodium chloride solution, metoclopamide, potassium chloride, povidone iodine, procaine hydrochloride, sissomic sulfonate, technetium phytate, thiamine hydrochloride, vitamin A |

* Classified also into C group. ** Based on Iryo-yaku Nihon-iyakuhinshu (Drugs in Japan: ethical drugs), 1993. *** Based on Physicians' desk reference, 47th ed., 1993, and 46th ed., 1992.
medication before the index date. For these cases, we selected 100 matched controls. Of both the case and control groups, 54% were men, mean age (SD) was 44.4 (21.6) years, 74% were inpatients, and 57% were the patients of the clinics of internal medicine. Examination of medical records of all cases revealed that primary or underlying diseases were malignant tumors in 49%, heart disorders in 7%, thrombocytopenic purpura in 7%, bleeding tendency or nasal hemorrhage in 4%, and others in 33%.

Of 1,021 products of drugs registered in the files, 40 products (36 drugs) were associated with the disease from the lower 95% confidence limit of odds ratios. They are tentatively classified into five groups as shown in Table 1. Fifteen drugs have been described to be liable to cause thrombocytopenia in Japanese and/or US package inserts15–17) (C and D groups in Table 1).

Accuracy of diagnostic information in the Rezept files

In Table 2 is shown the reliability of diagnosis for thrombocytopenia in the computerized files. Among 100 cases, 77 had low platelet counts. For inpatients, 94.6% (of 74) actually had thrombocytopenia, while only 26.9% (of 26) for outpatients. Then the medical records of 77 cases were reviewed in detail. We examined the agreement of the diagnostic date in the computerized files with the date of disease onset from primary record review for the disease. As shown in Figure 2, the two dates agreed in only six cases (7.8%), and in almost all of the others (76.6%), the diagnostic date was later than the date of the onset. Although the difference between the two dates ranged from -9 to 769 days, it was within ±10 days in

| Low platelet count | Inpatient | Outpatient | All cases (n=100) |
|--------------------|-----------|------------|------------------|
| No. | % | No. | % | No. | % |
| Present &superscript; | 70 | 94.6 | 7 | 26.9 | 77 | 77.0 |
| Absent | 4 | 5.4 | 17 | 65.4 | 21 | 21.0 |
| Unknown &superscript; | 0 | 0 | 2 | 7.7 | 2 | 2.0 |

&superscript; Platelet count less than 120,000/mm³ in the month including first computerized diagnostic date on thrombocytopenia or in the previous month or in the following month was confirmed.

&superscript; Platelet count was not tested or data were incompletely available.

58.4% and within ±20 days in 72.7% of cases.

Drug-induced thrombocytopenia

Through medical record review, we identified 31 cases of drug-induced thrombocytopenia diagnosed by medical doctors, and listed up 29 suspected drugs. Although two or three suspected drugs were designated for most of the cases, almost all of the drugs for each case were classified into the same product category. Of drug-induced thrombocytopenia cases, 23 (74.2%) were due to antineoplastic agents, five (16.1%) to antibiotics, one (3.2%) to antiepileptics, and two (6.5%) to drugs not classified in the same product category.

![Figure 2. Difference between the date of disease onset and the computerized date of diagnosis. On the horizontal axis, if the computerized date was later than the date of onset, a positive number represents the difference, in case of the opposite situation, a negative number represents it.](image-url)
Table 3. Comparison of the results from Rezept files and the results from medical record review.

| Drugs* (Products) | No. of exposed cases (n=100) | No. of exposed controls (n=100) | Odds ratio (95%CI) | No. of cases of drug-induced thrombocytopenia (n=100) |
|------------------|-------------------------------|---------------------------------|--------------------|---------------------------------------------|
| cytarabine       | 8                             | 1                               | 8.6 (1.1-70.2)     | 8                                           |
| (Cytocide Injection 60 mg) |                   |                                  |                    |                                              |
| (Cytocide Injection 20 mg) |                   |                                  |                    |                                              |
| cyclophosphamide | 14                            | 4                               | 3.9 (1.2-12.3)     | 6                                           |
| (Endoxan Injection 500 mg) |                   |                                  |                    |                                              |
| (Endoxan Injection 100 mg) |                   |                                  |                    |                                              |
| daunorubicin hydrochloride (Daunomycin) | 13 | 2 | 7.3 (1.7-33.4) | 5 |
| doxorubicin hydrochloride (Adriacin Injection) | 16 | 6 | 3.0 (1.1-8.0) | 4 |
| vincristine sulfate (Oncovin) | 17 | 7 | 2.7 (1.1-6.9) | 4 |
| mercaptopurine (Leukerin Powder) | 13 | 3 | 4.8 (1.3-17.5) | 3 |
| piperacillin sodium (Pentillin Injection 1 g) | 32 | 19 | 2.0 (1.0-3.9) | 1 |
| cefalexin (Keflex 250 mg Capsules) | 12 | 4 | 3.3 (1.0-10.5) | 0 |
| chlorpheniramine maleate (Polaramin Injection 0.5% 1 ml) | 27 | 14 | 2.3 (1.1-4.7) | 0 |
| cimetidine (Tagamet Injection) | 28 | 15 | 2.2 (1.1-4.4) | 0 |
| heparin sodium (Novo heparin Injection 1,000 Units) | 16 | 6 | 3.0 (1.1-8.0) | 0 |
| indomethacin (Indacin 50 mg suppositories) | 25 | 11 | 2.7 (1.2-5.8) | 0 |
| sulfamethoxazole • trimethoprim (Baktar 480 mg Tablets) | 19 | 7 | 3.1 (1.2-7.8) | 0 |

* Only the data on drugs classified into C group on Table 1 (drugs whose Japanese package inserts refer to the disease as an adverse reaction) are shown. There was no thrombocytopenia case due to drugs classified into other groups on Table 1.

Table 4. Drugs not associated with thrombocytopenia but designated as suspected drugs on medical records.

| Drugs | No. of cases |
|-------|--------------|
| methotrexate | 5 |
| cisplatin | 3 |
| etoposide | 3 |
| ampicillin | 2 |
| cefmetazole sodium | 2 |
| mitomycin C | 2 |
| sodium valproate | 2 |
| vinblastine sulfate | 2 |
| vindesine sulfate | 2 |
| L-asparaginase | 1 |
| carmofur | 1 |
| cefamandole sodium | 1 |
| enocitabine | 1 |
| fluorouracil | 1 |
| ifosfamide | 1 |
| latamoxef sodium | 1 |
| mitoxantrone hydrochloride | 1 |
| pipemidic acid trihydrate | 1 |
| procainamide hydrochloride | 1 |
| tegafur | 1 |
| tegafur • uracil | 1 |
| theophylline | 1 |

Comparison of drugs from the Rezept files and those from medical record review

Of 36 drugs associated with thrombocytopenia from the Rezept files, seven (six antineoplastic agents and one antibiotic agent) were suspected drugs from medical record review as listed in Table 3. Oppositely, of drugs not associated with the disease from the files, 22 were suspected drugs from the record review (Table 4).

DISCUSSION

The Rezept system: advantages and limitations

Rezept is a German term and means the bill for reimbursement. The Rezept system was introduced in the 1970's for the first time in Japan, and has rapidly become popular among hospitals in the 1980's. As of 1992, 76.9% of hospitals, and 41.9% of all medical facilities have maintained the system. And, 94.4% of bills from hospitals, and 68.3% of total bills were prepared by the system. Some hospitals incorporated the Rezept system into comprehensive systems for various administrative purposes. Although the codes of drugs and diagnoses and/or the data structures differ depending on the situation, every Rezept system includes similar kinds of information.

Much has been written on advantages and limitations of using computerized databases which are maintained for administrative purposes. For pharmaco-
The feasibility of case-control studies

In this study using the Rezept files of Tokyo Medical and Dental University Hospital, we found that the files are useful in the case-control studies of thrombocytopenia for inpatients but not for outpatients. This is based on the following three findings: First, obtained primary medical records of all cases proved to be highly accessible, and thus the number of cases deleted from the study due to inaccessible medical records can be small. Moreover, detail information not involved in the files is available in the medical records. This enhances the validity and efficiency of the study. Second, low platelet counts being found in 94.6% of inpatient cases, the computerized diagnostic data on the disease are highly reliable as far as inpatients are concerned. Third, it is possible that a control group drawn from the Rezept files is comparable to a case group to detect the drugs that cause the disease. As shown in Table 3, the drugs associated with thrombocytopenia at higher odds ratios were more frequently designated on medical records as suspected drugs such as cytarabine, daunorubicin and cyclophosphamide. Particularly for cytarabine, the number of cases for which the drug was suspected as the cause was close to the difference in the number of patients administered the drug between case and control groups.

Besides these findings, we have already confirmed that the Rezept data on drugs were extremely accurate in preparation form, dosage, and duration by a previous study on piroxicam, an NSAID (nonsteroidal anti-inflammatory drug) (data not published). In the present study, the computerized data on drugs which were designated as suspected drugs were also well consistent with the data in the medical records, and thus we consider that the Rezept data on drugs are of high quality.

We, however, also found several limitations of applying the Rezept files to case-control studies in addition to the limitations mentioned above. First of all, computerized diagnostic data for outpatients would not be reliable enough, as thrombocytopenia was confirmed only in 26.9% of outpatients. In a previous study on gastrointestinal disorders, in which most of the subjects were outpatients, drug-induced gastritis and gastric ulcer were confirmed at most in only 14.8% and 11.4% of the cases drawn from the Rezept files. These results indicate that the study of outpatients will not be efficient. We suggest a possible explanation of why false diagnoses were frequent in the files for outpatients: In the Japanese health insurance system, medical procedures which could be reimbursed have been exclusively treatments for a disease, and have not been for examination and prevention. Thus, getting reimbursement for medical procedures, routine blood tests to diagnose thrombocytopenia for instance, requires that a relevant diagnosis, thrombocytopenia as a temporary diagnosis, should be registered before final diagnosis. In the present study, many outpatients have evidenced bleeding tendency or nasal hemorrhage, but have not had thrombocytopenia. Likewise, it would be frequent for outpatients that a temporary diagnosis is entered into the files for billing. Existence of such “diagnosis for billing” or “Rezept diagnosis” have been tacitly understood, however, there have been very few reports on the frequency of Rezept diagnoses. In order to evaluate the effect of the Rezept diagnoses on the quality and efficiency of the studies, we need to study on many other diseases.

Diagnostic date in Rezept files did not accord with the date of disease onset, generally the diagnostic date was liable to be behind the date of disease onset. The reason for this date discrepancy can be due to a time lag period between the onset and the diagnosis, as well as the process of data input. The clerks who input data for monthly billing are not concerned with the accurate date of diagnoses. It is essential for getting reimbursement only that a
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Table 5. Confounding variables could not be controlled in this study.

| Confounding variables                                      | Drugs associated with thrombocytopenia                                      |
|------------------------------------------------------------|---------------------------------------------------------------------------|
| Therapeutic agents or diagnostics for the disease          | dexamethasone, heparin sodium                                              |
| Combined or adjuvant therapy with the drug causes the disease | aluminum hydrochloride gel • magnesium hydroxide, cytochrome C, domperidone, metoclopramide |
| Therapeutic agents or diagnostics for primary or underlying diseases | iodine addition products of the ethylesters of the fatty acids obtained from poppyseed oil |
| Adjuvant therapy for primary or underlying diseases        | glucose, high calorie infusion, thiamine hydrochloride                     |
| Severity of the disease                                   | distilled water for injection, isotonic sodium chloride solution           |
| Therapeutic agents or diagnostics for complications of primary or underlying diseases | antibiotics, antymycotics, cimetidine, indocianine green, potassium L-aspartate, potassium chloride, technetium phytate |

diagnosis which is admitted as the indication of a therapy is registered in the month when a therapy is performed. There may also be cases for which a diagnosis was not entered into the files before starting a therapy for a disease. For these cases, diagnostic date would be liable to be the entry date. The delay in the diagnostic date should be problematic in that the drugs dispensed after the onset can be counted, and this bias may come to show false-positive association. Consequently, medical records must be reviewed to confirm the date of disease onset.

It may be difficult to control such confounding variables as therapeutic agents for the disease studied and combined therapy with the drug causing the disease (Table 5). We initially meant to select controls matched for primary or underlying diseases to manage some of these confounding variables. However, automatic determination of primary or underlying diseases was too complicated to execute. Difference in the severity of primary or underlying diseases, cancer for example, might also be a confounding variable. Although we cannot evaluate the influence of these variables in this study, in which medical records for control patients were not reviewed, consideration of such confounding variables should be taken upon the analysis.

There is the limitation of the statistical power. Such antineoplastic agents commonly induce thrombocytopenia as methotrexate, cisplatin and etoposide were not detected to be associated with the disease (Table 4). This implies the size of potential study subjects may not be sufficiently large to detect even relatively common adverse reactions. The size of the study population must be large to find the relevant drugs that rarely induce the disease or are uncommonly prescribed.

Our methods in the present study have some unsatisfactory aspects to be improved to assure the quality of analysis. The patients who did not have a low platelet count, or had chronic thrombocytopenia should be excluded. The drugs dispensed after the time of disease onset and dispensed fairly before the time of the onset should also be excluded. Also a variety of codes of a drug, for which a different code is given for each product, should be put together. Since 1992, however, the computer system of the University Hospital has been changed into a new one not compatible with the old one to develop a system for more versatile services. Therefore, unfortunately we could not afford to revise the computer program and to analyze the data again when the medical record review was completed.

Apart from the limitations, mentioned above, one should be well aware of securing the privacy of study subjects. One should make arrangement for protecting the confidentiality of the data by omitting information that might lead to the identification of individual subjects or limiting access to the data31). In our case, we kept the printed data sheets in a safe with strict access control.

Perspectives

In spite of some incompleteness, the findings of the present study encourage one to conduct pharmaco-epidemiologic studies using Rezept data. For years, in many major hospitals in Japan, advanced hospital information systems32-35) are under development such as the computerized clinical laboratory system36), the prescription order entry system37, the electronic medical record system38) and the research assistance system39-41). These systems connected with the Rezept system would ensure the reliability and validity of the data on prescription as well as diagnosis. In some hospitals, for members of a health insurance cooperative association42), population based databases could be constructed using the data of hospital information systems. Thus, the use of developed systems mentioned above promises to get over the limitation of applying Rezept files of hospitals to pharmaco-epidemiologic studies. The University Medical Information Network (UMIN)43,44) and memory card systems in local communities might also strengthen the Rezept data system45-50).

In summary, our study indicates that the Rezept files of Tokyo Medical and Dental University Hospital having been useful in the case-control study of drug-induced thrombocytopenia for inpatients. Medical records, however, must be reviewed to exclude patients not aimed at, to confirm the date of disease onset, and to obtain information not included in the computerized data. We speculate that case-control studies with the Rezept files as to other diseases would also be feasible, if computerized diagnosis
data are reliable, and other types of Rezept files also would be applicable to the studies. This type of study is an effective tool to catch an early signal of adverse drug reaction.

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