Multivariate Analysis and Predictive Formula for the Etiological Factors Underlying Drug Side Effects of Antibiotics

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With the objective of determining the causative factors underlying drug side effects, a pharmacoepidemiological study was conducted using three injection drugs, cefotaxime, cefoperazone and latamoxef, which in Japan, are referred to as third-generation cephem antibiotics. An analytical investigation of 150 items, including medicated drugs and bioinformation, was conducted on the medical records of 600 hospitalized patients, all of whom had been administered one of these injection drugs.

Principal component analysis and multivariate logistic analysis were conducted on 11 factors, whose significance had been demonstrated previously by univariate analysis, to examine the degree of their association with the presence or absence of side effects from drug administration. The results of principal component analysis revealed that these 11 factors were classified into the categories of the first to the fifth factors. Combined together, these factor groups were found to be associated with the side effects of the three antibiotics under investigation. Five factors with suspected etiologic involvement in the occurrence of side effects were selected for further investigation in accordance with the Akaike-Minimum-AIC method and included the method of administration, leukocyte counts, total administration dose, existence of cancer disease, and combined use of drugs with a hemorrhage-inducing tendency. The present analysis suggested that the relative risk of developing side effects increases when these five factors are combined together, and that this closely reflects the predictive formula of side effect manifestation.

Keywords—pharmacoepidemiology, hospital-based study, drug side effects, multivariate analysis, predictive formula

Introduction

The importance of medication history has been raised recently with current opinion pointing to an apparent need to analyze and evaluate the accumulated medication history together with a variety
of bioinformation on a patient using epidemiologic techniques. Pharmacoepidemiology, which is an example of this epidemiologic approach, is a field of medical science that aims at effectively reducing the data and information obtained from observation of a patient population for application to individual pharmacotherapy1,2).

Using cephem antibiotics the authors conducted a pharmacoepidemiological investigation to elucidate the causative factors specific to a side-effect positive patient group, and have reported the results of univariate analysis elsewhere3). In the present study, several factors were considered simultaneously and a multivariate analysis was conducted in order to investigate the degree of association of these factors with the development of drug-administration side effects. Moreover, using the factors identified to have a close association with the development of drug-administration side effects, the authors derived a predictive formula of side effect manifestation to estimate the probability that side effects will occur. The authors report here the results of using the formula to estimate the probability of side effects.

**Subjects and Methods**

An analytical survey was conducted on 150 items, including the patient’s general background factors, habits, medication-related factors of the antibiotics under investigation, the status of manifestation of side effects, and the laboratory test data before drug administration documented in the hospital records of the patients who were given any of the three injection drugs, cefotaxime, cefoperazone and latamoxef, which in Japan, are referred to as third-generation cephem antibiotics, during the one-year between March 1982 and February 1983. The subjects of the analysis included 600 randomly selected patients accounting for around 50% of 1,196 hospitalized patients who had been administered one of the injection drugs under investigation. As shown in Table 1, these subjects consisted of 318 males and 282 females3).

In the present survey, signs and symptoms of the side effects which were common among the three antibiotics under investigation were checked. The side effects were seen as shock, hypersensitivity, hemorrhage, stomatitis, glossitis, candidiasis, headache, anorexia, neuritis, general malaise, diarrhea, nausea, and vomiting. These signs and symptoms of side effects occur commonly with administration of any of the three antibiotics under investigation. The authors defined side effects as the manifestation of adverse signs and symptoms that were first described in the hospital records after ad-

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>~39</td>
<td>40 ~59</td>
</tr>
<tr>
<td>Males</td>
<td>79* (24.8%)</td>
<td>146 (45.9%)</td>
</tr>
<tr>
<td>Females</td>
<td>105 (37.2%)</td>
<td>107 (37.9%)</td>
</tr>
<tr>
<td>Total</td>
<td>184 (30.7%)</td>
<td>253* (42.2%)</td>
</tr>
</tbody>
</table>

*: p < 0.05, **: p < 0.01 (Chi-square test)
Table 2. Frequency of Side Effects by Drugs

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Drugs</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cefotaxime</td>
<td>Cefoperazone</td>
<td>Latamoxef</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of positive cases</td>
<td>244 (100%)</td>
<td>118 (100%)</td>
<td>238 (100%)</td>
<td>600 (100%)</td>
<td></td>
</tr>
<tr>
<td>No. of negative cases</td>
<td>215* (88.1%)</td>
<td>79 (66.9%)</td>
<td>186 (78.2%)</td>
<td>480 (80.0%)</td>
<td></td>
</tr>
</tbody>
</table>

*: p < 0.05, **: p < 0.01 (Chi-square test)

ministration of the relevant antibiotics. The subjects under analysis were divided into two groups: a side-effect-positive group consisting of patients who manifested the above-mentioned signs and symptoms of side effects only after administration of any of the antibiotics under investigation and a side-effect-negative group consisting of patients without these signs and symptoms of side effects. Comparison of the relevant factors was made between the two groups in order to statistically identify the factors that were specific to the side-effect-positive group. As shown in Table 2, the side-effect-positive group consisted of 120 patients (20%), while the side-effect-negative group consisted of 480 patients (80%)³.

Methods of Statistical Analysis

1. Principal component analysis (factor analysis)

Among the factors that were shown to be predominant in the side-effect-positive group by univariate analysis³, the 11 highly significant factors that are listed below were used to conduct the multivariate analysis:

(1) existence of cancer disease
(2) concurrent use of drugs with a hemorrhage inducing tendency (antineoplastic agents, sulbenicillin preparations, antithyroid preparations, anticoagulants, aspirin preparations, female hormone drugs, potassium chloride, trimetadion⁴)
(3) concurrent use of antineoplastic agents
(4) abnormal leukocyte counts before administration of the drugs under investigation (normal range: 3.8 to 8.5 × 10⁹)
(5) abnormal platelet counts before administration of the drugs under investigation (normal range: 160 to 410 × 10³/mm)
(6) abnormal total cholesterol level before administration of the drugs under investigation (normal range: 120 to 230 mg/dl)
(7) abnormal GPT (glutamate pyruvate transaminase) level before administration of the drugs under investigation (normal range: 0 to 45 IU/l)
(8) intravenous injection (excluding drip administration) of the relevant antibiotics
(9) total administration dosage of the relevant antibiotics of more than 11 g (gram)
(10) administration of either cefoperazone or latamoxef of the antibiotics under investigation
11. abnormal eosinophil value before administration of the drugs under investigation (normal range: less than 450/µl).

In the present study, all of these factors were converted to binary (0, 1) variables before analysis. For instance, the side-effect-positive group, existence of cancer disease, and abnormal laboratory findings were defined as 1. The multivariate analysis was performed by principal component analysis\(^5\) and Akaike-Minimum-AIC method.

2. Akaike-Minimum-AIC method

The objective of Akaike-Minimum-AIC method\(^6\) was to prepare a model using as few representative parameters as possible, in order to explain the data observed in the actual cases. A model with a smaller AIC \(= (-2) \times \log \text{ (Likelihood)} + 2 \times \text{ (Number of parameters)}\) was considered to be superior.

3. Predictive formula of manifestation of side effects according to the multivariate logistic analysis

With the use of the factors extracted by the Akaike-Minimum-AIC method, a predictive formula of the manifestation of side effects was derived according to a multivariate logistic model to estimate the probability of side effect manifestation.

Results

1. Principal component analysis (factor analysis)

Principal component analysis was conducted to classify these 11 variables (factors). Tables 3 shows the result of this analysis. These 11 factors were classified into the categories of the first to the fifth factor (numerical values underlined in Table 3). Combined together, these factor groups were found to be associated with the side effects. Cancer disease-related factors were extracted as the first factor, host-factors as the second factor, and drug-related factors as the third factor. The types of drugs under investigation and eosinophil were respectively extracted as the fourth and the fifth factors independently.

2. Akaike-Minimum-AIC method

The following five factors were selected from the aforementioned 11 factors as representative variables from which information may be effectively obtained by Akaike-Minimum-AIC method:

(1) total administration dosage of the relevant antibiotics of more than 11 g
(2) abnormal leukocyte counts before administration of the drugs under investigation
(3) intravenous injection (excluding drip administration) of the relevant antibiotics
(4) existence of cancer disease
(5) concurrent use of drugs with a hemorrhage-inducing tendency

3. Predictive formula of manifestation of side effects according to the multivariate logistic analysis

Table 4 illustrates a predictive formula of manifestation of side effects according to the multivariate logistic analysis using the above-described 5 variables (factors) extracted by the Akaike-Minimum-AIC method. The probability of manifestation of side effects estimated from this predictive for-
Table 3. Principal Component Analysis (Varimax factor matrices)

<table>
<thead>
<tr>
<th></th>
<th>First factors</th>
<th>Second factors</th>
<th>Third factors</th>
<th>Fourth factors</th>
<th>Fifth factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Side effects&lt;sup&gt;3&lt;/sup&gt;</td>
<td>0.115</td>
<td>0.271</td>
<td>0.543</td>
<td>0.362</td>
</tr>
<tr>
<td>2</td>
<td>Cancer disease&lt;sup&gt;4&lt;/sup&gt;</td>
<td>0.583</td>
<td>0.081</td>
<td>-0.009</td>
<td>0.288</td>
</tr>
<tr>
<td>3</td>
<td>Concurrent drugs associated with the development of hemorrhagic tendency&lt;sup&gt;5&lt;/sup&gt;</td>
<td>0.762</td>
<td>0.123</td>
<td>0.105</td>
<td>-0.061</td>
</tr>
<tr>
<td>4</td>
<td>Concurrent antineoplastic agents&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.855</td>
<td>0.020</td>
<td>-0.031</td>
<td>-0.044</td>
</tr>
<tr>
<td>5</td>
<td>Leucocytes&lt;sup&gt;6&lt;/sup&gt;</td>
<td>0.141</td>
<td>0.679</td>
<td>-0.103</td>
<td>-0.025</td>
</tr>
<tr>
<td>6</td>
<td>Platelets&lt;sup&gt;7&lt;/sup&gt;</td>
<td>0.179</td>
<td>0.775</td>
<td>0.017</td>
<td>-0.062</td>
</tr>
<tr>
<td>7</td>
<td>Total cholesterol&lt;sup&gt;2&lt;/sup&gt;</td>
<td>-0.064</td>
<td>0.536</td>
<td>0.041</td>
<td>0.233</td>
</tr>
<tr>
<td>8</td>
<td>GPT&lt;sup&gt;8&lt;/sup&gt;</td>
<td>0.027</td>
<td>0.420</td>
<td>0.264</td>
<td>-0.138</td>
</tr>
<tr>
<td>9</td>
<td>Administration methods&lt;sup&gt;9&lt;/sup&gt;</td>
<td>-0.180</td>
<td>-0.151</td>
<td>0.737</td>
<td>-0.244</td>
</tr>
<tr>
<td>10</td>
<td>Total dosage&lt;sup&gt;4&lt;/sup&gt;</td>
<td>0.300</td>
<td>0.071</td>
<td>0.580</td>
<td>0.197</td>
</tr>
<tr>
<td>11</td>
<td>The drugs under investigation&lt;sup&gt;10&lt;/sup&gt;</td>
<td>0.051</td>
<td>0.003</td>
<td>0.003</td>
<td>0.862</td>
</tr>
<tr>
<td>12</td>
<td>Eosinophils&lt;sup&gt;10&lt;/sup&gt;</td>
<td>0.027</td>
<td>0.024</td>
<td>0.061</td>
<td>-0.034</td>
</tr>
</tbody>
</table>

Binary variables:
1) 1: positive, 0: negative.
2) Laboratory tests before administration of the drugs under investigation; 1: anomaly, 0: normal.
3) Administration methods of the relevant antibiotics; 1: intravenous injection (excluding drip administration), 0: intramuscular injection or drip.
4) Total administration dosage of the relevant antibiotics; 1: 11 g ≤, 0: <11 g.
5) 1: cefoperazone or latamoxef 0: cefotaxime.

mula, that is, the expected value, was consistent with the observed result. The probability of manifestation of side effects in patients having a single factor was 10.7% for cancer disease, 14.1% for the total administration dose of more than 11 g of the antibiotics under investigation, 22.9% for the abnormal leukocytes, and 23.9% for intravenous injection (excluding drip administration). When 4 factors such as cancer disease, total administration dose, leukocytes, and concurrent use of drugs with a hemorrhage-inducing tendency were combined together, the probability of manifestation of side effects was as high as 75.9%.

Table 4 shows the relative risk of developing side effects using the formula when a group free from any of these 5 factors was used as a standard. The relative risk in patients possessing a single factor was 2.9 for cancer disease, 3.1 for a total administration dose of more than 11 g of the antibiotics under investigation, 7.7 for the presence of abnormal leukocytes, and 9.6 for intravenous injection (excluding drip administration). Similarly, it was shown that the relative risk was higher with combined factors. When these 4 factors were combined, the relative risk of developing drug-administration side effects was found to be as high as 67.

**Discussion**

Using three injection drugs, cefotaxime, cefoperazone and latamoxef, which in Japan, are referred to as third-generation cepham antibiotics, the authors conducted an analytical epidemiologic
### Table 4. The Estimated Multivariate Logistic Formula for Prediction of Drug Side Effects

\[
\log \left( \frac{p}{1-p} \right) = -2.744 + 0.936X_1 + 1.528X_2 + 1.588X_3 + 0.624X_4 + 0.802X_5
\]

<table>
<thead>
<tr>
<th>( X_1 )</th>
<th>( X_2 )</th>
<th>( X_3 )</th>
<th>( X_4 )</th>
<th>( X_5 )</th>
<th>Side effect positive cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total dosage</td>
<td>Leucocytes</td>
<td>Administration methods</td>
<td>Cancer disease</td>
<td>Concurrent drugs associated with the development of hemorrhagic tendency</td>
<td>Observed</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>7(77.8%)</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>3(75.0%)</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>7(63.6%)</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>1(50.0%)</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>12(42.9%)</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4(36.4%)</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>12(36.4%)</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>13(34.2%)</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>2(33.3%)</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2(28.6%)</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>22(23.4%)</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>24(14.1%)</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>4(13.3%)</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>7(5.0%)</td>
</tr>
</tbody>
</table>

The model consisting of the above five important risk factors was selected by Akaike-Minimum-AIC method. + indicates total dosage: total administration dosage of the relevant antibiotics of more than 11 g, leucocytes: abnormal leukocyte counts before administration of the drugs under investigation, administration method: intravenous injection of the relevant antibiotics (excluding drip administration), cancer disease: positive, and concurrent drugs associated with the development of hemorrhagic tendency: positive.
study on the causative factors of drug side effects of these antibiotics by linking the patients’ prescriptions and medical records\(^3\). These three agents have been observed to induce almost identical side effects. The authors believe that clarification of the causative factors, which should be referred to as risk factors for the development of side effects, may provide useful information for the effective use of pharmacotherapy.

Investigation of the internal correlation between the highly significant factors, which were identified from the result of univariate analysis, revealed a reciprocal close relation between the factors. In our view, investigation of the correlation between individual factors (risk factors) and side effects fails to disclose the degree of association between the individual factors and the side effects. According, the authors conducted a multivariate analysis in order to analyze the relation between various factors and side effects concurrently. The result of principal component analysis (factor analysis) showed that certain groups of factors were associated with the side effects. From the result of the Akaike-Minimum-AIC method, it was revealed that the 5 factors including total administration dose, leukocyte counts, method of administration, cancer disease, and combined use of drugs with a hemorrhage-inducing tendency are the most useful in explaining the mechanism of occurrence of side effects. The authors prepared a predictive formula of side effect manifestation according to the multivariate logistic analysis using these 5 factors and used it to estimate the probability of side effect manifestation.

For example, when the aforementioned 5 factors were not applicable, such as in the case of a total administration dose of less than 10 g, normal leukocytes, drip or intramuscular injection, absence of cancer disease, and no use of drugs with a hemorrhage-inducing tendency, the estimated probability of side effect manifestation (P) was such that

\[
\log \left( \frac{P}{1-P} \right) = -2.744.
\]

Accordingly, the probability of side effect manifestation (P) was

\[
P = \frac{\exp (-2.744)}{1 + \exp (-2.744)} = 6.04\%.
\]

However, with an increase in the number of superimposed factors, the manifestation of side effects increased.

In the present study drug administration by intravenous injection, total administration dosage of more than 11 g, concurrent use of antineoplastic agent, and drugs associated with a hemorrhagic tendency were found to be the main causative factors underlying the appearance of side effects of the three antibiotics under investigation. The respective clinical dosages of the three antibiotics under investigation were equivalent. The frequency of total dosage of less than 10 g was significantly rare in the side-effect-positive group, on the contrary, total dosage of more than 40 g was significantly high in the side-effect-positive group by univariate analysis\(^3\). There was a tendency for a low frequency of intramuscular injection and drip therapy, but a high frequency of intravenous injection in the side-effect-positive group\(^3\).

The following host-related factors were also found to have a causal relationship with side effects: (1) a decrease in leukocyte counts, which possibly indicates a decrease in lymphocyte counts...
and suggests a decreased immunological capacity, (2) a decrease in the total cholesterol level may indicate a decrease in the matrix of the organic cell membrane components, various steroid hormones and bile acids, also suggesting a decreased immunological capacity, (3) a decrease in platelet counts, suggesting myelosuppression and decreased coagulability. However, the above-mentioned host-related factors can also be regarded as a reflection of the influence of cancer disease and the administration of antineoplastic agents. Considering these factors at the same time, the authors carried out a multivariate analysis.

The incidence of side effects on cefotaxime, cefoperazone, and latamoxef have been reported 2.38%, 3.59%, and 2.40%, respectively. But the incidence of side-effect-positive patients of the drugs under investigation were 11.9%, 33.1%, and 21.8%, correspondingly; indicating the fivefold to tenfold increase in this study. The authors defined side effects as the manifestation of adverse signs and symptoms that were first described in the hospital records after administration of the specific drugs under investigation and not those specified by the attending doctors as "side effects".

During the administration of a drug, it is difficult to eliminate the factors of abnormal leukocyte count and the existence of cancer disease, both of which are host factors. However, if these factors are observed in a patient, it is still possible to reduce, to some extent, the incidence of side effects if the total administration dosage and method of administration, which are drug-related factors, are taken into account on the basis of the results of this predictive formula. In the present study, the side effects induced by the drugs under investigation were considered in combination. Future investigations should also address the causative factors of side effects in accordance with their individual signs and symptoms, such as for example, the major side effect of bleeding.

In recent years, pharmacokinetics-based monitoring of blood concentration by measuring drug blood concentration has allowed patient-specific control of the optimum administration dosage. Furthermore, it has been demonstrated that with an increase in the blood concentration over a certain dose, the manifestation of adverse reactions increases, thereby raising the importance of measuring the drug blood concentration from the viewpoint of avoiding side effects. In order to safely administer a drug with an expected therapeutic effect, adequate analysis of both the host-factors and drug-factors is required. Very often in actual medical management, several drugs are used in combination, and particular caution on the drugs to be combined is needed. In this case, it is of value to analyze the accumulated bioinformation of a number of patients at Phase IV after the release of the drugs on the market, as performed in the present study. Accordingly, the authors designed the predictive formula of side effect manifestation using the host-factors and drug-factors obtained from the present study to estimate the probability of side effects occurring and allow the causative factors to be eliminated and side effects to be avoided.

In Japan, pharmacopredictology based on pharmacokinetics has been proposed recently as a new field of medicine. Pharmacopredictology is a science which deals with intra-corporeal pharmacokinetics, pharmaceutical efficacy, and side effects. It is a field of study aimed at obtaining the maximum therapeutic effect with minimum side effects through pharmaco-therapy. Similarly, pharmacoepidemiology is a region of study aimed at determining the therapeutic effects and side effects of
drugs in a subject population using epidemiologic techniques in order to administer the optimum pharmacotherapy to each patient. Pharmacoepidemiology is considered to contribute to pharmaceutical care by applying the information obtained from a population to individuals. Therefore, a tight linkage between the sciences of pharmacoepidemiology and pharmacopredictology to predict side effects may further provide therapeutic benefit to individual patients.

In the present study, the authors obtained a variety of information from patient prescriptions and medical records. However, since preexisting documents such as medical records inherently entail inconstant descriptions and omissions of some descriptions, there is a limitation to the usefulness of such documents. Currently in Japan, a consultation fee of 6,000 yen per month is approved as the health insurance medical fee for bedside medical consultation of hospitalized patients by a pharmacist. This ward activity of the hospital pharmacy is now practiced at many hospitals. In order to achieve further progress in the field of pharmacoepidemiology, an essential activity will be to build up a data base of medication history and bioinformation obtained from the ward consultations of pharmacists. An example is the Boston Collaborative Drug Surveillance Program (BCDSP) which analyzed the accumulated information of monitored medications and medical events of hospitalized patients. It is expected that in Japan, a system based on the BCDSP will be developed in the course of continuing ward activities by pharmacists.

**Conclusion**

Using antibiotics, the authors accumulated the medication history and bioinformation from patient’s prescriptions and medical records, and identified the factors specific to a side-effect-positive group of patients. Selected factors from the result of univariate analysis were closely interrelated. The authors then conducted a multivariate analysis to analyze numerous factors together at the same time. According to the Akaike-Minimum-AIC method, 5 factors were selected as the most helpful factors to explain the development of side effects of the relevant antibiotics. A predictive formula of manifestation of side effects according to the multivariate logistic analysis was derived using these 5 factors. Information obtained from an epidemiologic analysis of a patient population will contribute to pharmacotherapy in individual patients.

**References**