Clinical Implications of Phase IV Studies of Antihypertensive Agents

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Phase IV studies, which are commonly referred to as “postmarketing surveillance (PMS)” or pharmacoepidemiological studies, play an important role in evaluating the long-term safety of medicines. The system for conducting PMS in Japan consists of three components; spontaneous reporting of side effects, “reeexamination of newly marketed agents” and “reevaluation of agents used in practice.” The reevaluation is to be repeated at given intervals. However, the present system applied for PMS has many problems which must be solved. Particularly in regard to antihypertensive therapy, since most hypertensive patients are required to take antihypertensive agents for the rest of their life, scientifically sound PMS is indispensable. In this article, the present system for PMS in Japan will be overviewed, the preliminary results of prospective phase IV studies which are being conducted to evaluate the long-term efficacy and safety of calcium antagonists will be reported, and some proposals will be mentioned to improve phase IV studies, PMS, on the basis of the preliminary results which are currently available. (Hypertens Res 1992; 15: 121-126)

Key Words: phase IV study, postmarketing surveillance, antihypertensive agents, calcium antagonists, sustained-release nifedipine, nitrendipine, essential hypertension

Implications of Phase IV Studies or Postmarketing Surveillance

Postmarketing surveillance (PMS) is especially important for chronically administered drugs such as antihypertensive agents, because: (1) The number of subjects or patients who are enrolled in phase II and III studies, the results of which are submitted in the application for marketing approval to the Ministry of Health and Welfare, Japan, is usually less than one thousand. This number of patients is insufficient to detect “rare” side effects. (2) The duration of administration of new agents in phase II and III studies is usually shorter than one year. Thus, difficulty may be encountered when using data derived from these studies to predict the efficacy and safety of new agents which are administered for longer periods. (3) Clinical trials which are performed prior to marketing approval by the Ministry of Health and Welfare generally do not include elderly patients, children and adolescents, pregnant women and patients with complications such as liver disease. Accordingly, the efficacy and safety of new agents in these patient subgroups should be evaluated in PMS. (4) Although phase I to III studies are performed by specialists, newly marketed agents may be extensively used by general practitioners. Thus, PMS may help to confirm the efficacy and safety of new agents which are used under such circumstances (1).

Details of the Systems to Evaluate the Safety of Medicines in Japan

In 1967, the Ministry of Health and Welfare obliged pharmaceutical companies to survey and report the occurrence of side effects of newly marketed drugs (1,2). In the following year, the Ministry extended this obligation to drugs that were marketed before 1967 (1,2). As of September 1992, 2,910 medical institutes and 2,733 drug stores have been nominated as monitor institutes designated to report side effects of drugs to the Ministry. In 1972, Japan joined the international drug safety monitoring system organized by the World Health Organization (WHO).

In 1979, concurrently to the extensive revision of the Pharmaceutical Affairs Law, regulations for the “Reexamination of Newly Marketed Drugs” and “Reevaluation of Drugs Used in Practice” were issued. The “Reexamination” regulations oblige pharmaceutical companies to evaluate and report on the efficacy and safety of newly marketed drugs in approximately 10,000 patients and to undergo a comprehensive reexamination 6 years after launch (2). In the case of newly approved indications or formulations, reexamination is required 4 years after approval. Reevaluation has been performed for...
drugs which were launched before 1967 (First Reevaluation regulation) and for those which were launched between 1967 and 1980 (Second Reevaluation regulation). Furthermore, drugs launched after 1988 must be reevaluated at 5-year intervals (New Reevaluation regulation).

Despite a battery of regulations and guidelines, the PMS system to evaluate the safety and efficacy of drugs has failed to live up to expectations. For example, 54,404 cases of side effects were reported to the Food and Drug Administration, USA, 16,431 cases to the Committee on Safety of Drugs, UK, and 15,813 cases to the Bundesgesundheit, Germany, in 1987. However, in the same year, the number of reported cases of side effects in Japan was only 2,523 cases (2). To try to improve the situation, the Ministry of Health and Welfare, Japan, organized a Research Group (Chairman: Mitsuo Homma, MD, Professor, Keio University) to define items to be considered in PMS, prepare guidelines to ensure meaningful analyses, and to design the regulations for pharmaceutical companies to conform to when conducting PMS. Based on the final report of this Research Group (3), the Ministry of Health and Welfare has issued regulations for PMS referred to as “Good Postmarketing Surveillance Practice (GPMSP)” (1). These regulations will come into effective as of April 1993. One of the most important recommendations of GPMSP is that pharmaceutical companies establish a separate division to handle PMS independently from other functions such as development and sales promotion.

Incidence of Side Effects According to Conventional PMS in Japan

As mentioned above, when newly marketed antihypertensive agents are reexamined 5 years after launch, the results of surveys on their efficacy and side effects in approximately 10,000 patients are requested to be attached to the application for reexamination (2). However, since there have been no strictly defined guidelines or regulations available for conducting PMS, the reliability of PMS is questionable. For example, the incidences of side effects of slow-release nifedipine were 20.6% in premarketing clinical trials and 4.3% after marketing (4). The same held true for a non-selective β-blocking agent; the incidence of side effects was 4.9% before marketing, but it decreased to 0.3% after marketing (4). The lower incidence of side effects after marketing seems to have been due to lack of scientific rigor in conducting PMS, because PMS has not been required to be performed on a prospective basis so far.

Although antihypertensive agents may be uneventfully used for 3 to 4 months, some side effects may occur with a longer duration of administration. In late phase II studies, usually conducted on an open-label basis, new antihypertensive agents are tested in monotherapy and in combination therapy in 150 to 200 hypertensive patients for 8 to 12 weeks (5). In these studies, the effect and safety of longer treatment are followed up by continuing to give the agents to the same patients, who have been confirmed to respond to short-term therapy without adverse reactions, for an additional 40 to 42 weeks (for one year in total) (5). The subjects are usually registered for these long-term trials before being enrolled (5). Figure 1 demonstrates the responder rates, incidence of side effects, incidence of discontinuation due to side effects or complications and overall utility rates of 8 recently developed adrenoceptor blocking agents (aronitlol (6), nipradilol (7), terazosin hydrochloride (8), urapidil (9), doxazosin mesilate (10), bisoprolol fumarate (11), long-acting carteolol (12), and betaxolol hydrochloride (13)), 5 angiotensin converting enzyme

Fig. 1. Responder rates, incidences of side effects and complications, discontinuation rates due to side effects or complications and overall utility rates assessed for 8 adrenoceptor blocking agents, 5 angiotensin converting enzyme (ACE) inhibitors and 5 calcium (Ca) antagonists. Overall utility rate means the frequency of responders without any side effects.
Preliminary Results of Prospective PMS of Ca Antagonists

Ca antagonists are among the first line drugs for the treatment of hypertension and are widely used in Japan. A 2-year prospective PMS study was designed to assess the efficacy and safety of sustained-release nifedipine (Sepamit-R; 10-20 mg, b. i. d.) in monotherapy and combination therapy. The characteristics of this study were as follows: (1) Although complicated inclusion criteria for the subjects were not employed, participating physicians were requested to use the agent in ways that would allow for a reasonable evaluation of its safety and efficacy. (2) Participating physicians were requested to register all patients with the registrar (Naokata Shimizu, MD, Teikyo University) prior to starting treatment and to respond to follow-up inquiries submitted by the registrar every 3 months. (3) Although the protocol was concise, emphasis was placed on the detection of side effects and complications. (4) This surveillance is being performed with cooperation of general practitioners. As the period for registration was from March 1990 to January 1991, the surveillance is to be completed in January 1993.

Although 6,020 patients were initially enrolled, 31 patients were excluded from analysis because of inadequate registration. Among the 5,989 adequately registered patients, 3,153 (52.6%) were registered by medical institutes with less than 200 beds. As of August 1992, 2,208 patients (36.9%) completed the 2-year survey. 135 (2.3%) dropped out due to side effects, 89 (1.5%) dropped out due to complications, 718 (12.0%) dropped out due to non-medical reasons, and 372 (6.2%) were lost to follow-up. There were 68 deaths (1.1%). Thus, 2,399 patients were still under treatment.

Side effects which necessitated the discontinuation of treatment are summarized in Table 1. Signs and symptoms which were probably caused by vasodilation or hypotension were the most frequent cause of discontinuation. Complications which necessitated cessation of treatment were cerebrovascular disease in 20 patients, cardiovascular disease in 18, neoplasms in 16, renal failure in 6 and other diseases in 31.

Table 2 lists the number of deaths by cause, the respective mortality rates adjusted by age and sex, and the corresponding standardized mortality rates of the survey with those in the general population. If the standardized mortality rate of a given cause of death is below 100% with a confidence limit of 95%, its corresponding mortality rate was smaller in the subjects of this survey than in the general population. Although the mortality rates due to heart disease and cerebrovascular disease were possibly greater in this survey than in the general population because of the nature of the patients being treated, the mortality due to neoplasms or other diseases was lower in the survey than in the general population.

It should be emphasized that, although no deaths were reported in clinical trials performed prior to approval and in PMS which was conducted in 6,391 patients by conventional methods (24), 68 deaths occurred in the present survey. The finding that the standardized mortality rates of heart disease and cerebrovascular disease were greater in the survey than in the general population does not necessarily imply that treatment with sustained-release nifedipine accelerated or increased the incidences of these disorders, since mortality rates were not compared between treated and non-treated hypertensives.

The long-term efficacy and safety of nifedipine (Baylotensin®) in monotherapy or combination therapy (5-10 mg, once a day) were also surveyed on a multicenter basis with a similar protocol as that used for sustained-release nifedipine. The patient registration period was from July 1991 to June 1992 and the survey is to be continued for 2 years. A total of 962 patients were registered, but 4 patients were excluded from analysis because of inadequate registration procedures. Thus, 958 patients were adequately registered. Responses to a follow-up inquiry were obtained from 805 of the 958 patients. As of July 1992, 45 patients (4.7%) completed the survey, and 23 (2.9%) dropped out due to side effects, 16 (1.7%) due to complications, and 152 (18.9%) due to non-medical reasons. Five deaths (0.6%) occurred: two were caused by stroke, two by neoplasms and one by pneumonia. Thus, treatment was discontinued due to side effects or complications in 39 cases (4.1%). The discontinuation rate in this survey approximated that in phase I to III studies (3%) (25). However, no deaths occurred in the studies performed prior to marketing.
sustained-release nifedipine is the largest prospective surveillance study ever to be executed in Japan. The preliminary results of the PMS program for the two Ca antagonists demonstrated that: (1) Discontinuation due to non-medical reasons was 12 to 19%, being greater than expected; (2) The incidences of dropouts due to side effects or complications were greater than those usually seen in conventional PMS surveys, but were similar to those of the premarketing data; and (3) A sizable number of deaths occurred. These two surveys have not yet been completed. Since a fairly large number of patients are expected to drop out during follow-up, the frequencies of side effects or complications may increase when the results are finalized.

### How to Apply the Results of PMS to the Management of Hypertensives

The two studies we planned were not conventional PMS surveys but pharmacoepidemiologic studies. The purpose of pharmacoepidemiologic studies is to collect valid and interpretable information about generally available medications, including their uses and effects, and the characteristics of the treated populations, to assemble meaningful information that can be used to maximize the benefit and minimize the risk associated with treatment (26,27). The preliminary results of the two studies we are now conducting suggest that the application of demonstrable scientific rigor to the collection, assembly, analysis, and interpretation of clinical data is essential to achieve valid results.

Although the Joint National Committee, USA, recommends physicians to follow-up treated hypertensives patients at intervals that may vary from a few weeks to several months depending on clinical judgement (28), physicians usually check hypertensive patients every 4 weeks in Japan. Although a number of antihypertensive agents with unique mechanisms are presently being developed, newly marketed drugs are not permitted to be prescribed beyond 2 weeks for the first 2 years that they are on the market (Regulation No. 15, the Ministry of Health and Welfare, Japan, 1957). It may be advantageous to mitigate current restrictions on the prescription period for new drugs which are used for chronic diseases such as hypertension to facilitate prompter assessment of their long-term safety and efficacy. At the same time, care should be taken to prevent PMS from developing into a sole sales promotion tool for some drugs (27,29).

### Table 1. Classification of Side Effects Which Necessitated Discontinuation of Sustained-Release Nifedipine

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Number of cases</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs and symptoms due to vasodilatation or hypotension</td>
<td>102</td>
<td>75.6</td>
</tr>
<tr>
<td>Gastrointestinal upset</td>
<td>11</td>
<td>8.1</td>
</tr>
<tr>
<td>Rash</td>
<td>9</td>
<td>6.7</td>
</tr>
<tr>
<td>Neuro-psychotic trouble</td>
<td>6</td>
<td>4.4</td>
</tr>
<tr>
<td>Frequent micturition</td>
<td>3</td>
<td>2.2</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>2</td>
<td>1.5</td>
</tr>
<tr>
<td>Gingival thickening</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Others</td>
<td>5</td>
<td>3.7</td>
</tr>
<tr>
<td>Abnormal laboratory data</td>
<td>10</td>
<td>7.4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>135</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

(Based on the preliminary results available as of August 1992)

### Table 2. Mortality Rates Based on the Preliminary Results of the Surveillance and a Comparison with Those in the General Population (Mortality rates were adjusted by sex and age according to the indirect method)

<table>
<thead>
<tr>
<th>Type of Death</th>
<th>No. of deaths</th>
<th>Sex-and age-adjusted mortality rates (/1,000 persons year)</th>
<th>Standardized mortality rates (%) (Range of 95% confidence.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total deaths</td>
<td>68</td>
<td>4.801</td>
<td>59 (46-74)</td>
</tr>
<tr>
<td>Cardiac deaths</td>
<td>24</td>
<td>1.659</td>
<td>102 (68-152)</td>
</tr>
<tr>
<td>Stroke</td>
<td>10</td>
<td>0.690</td>
<td>56 (30-105)</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>15</td>
<td>1.032</td>
<td>44 (26-73)</td>
</tr>
<tr>
<td>Others</td>
<td>19</td>
<td>1.400</td>
<td>47 (30-73)</td>
</tr>
</tbody>
</table>

The number of observed subjects was 5,895. The number of observed persons per year was 6,867.4. The mortality rates in the general population in 1990 were used for comparison. This table was made as a favor by Toshiharu Fujita, Ph D, Department of Epidemiology, Institute of Public Health.
Acknowledgement

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