Effects of Pharmacists' Consultation on Serum Uric Acid Level in Outpatients with Hyperuricemia

Masato Shintoh*†1, Seigo Iwakawa†2, Youko Shimada‡1 and Ken-ichi Konishi†1
Department of Pharmacy, National Public Service Personnel Mutual Aid Associations, Rokko Hospital†1
Department of Pharmaceutics, Kobe Pharmaceutical University‡2

Received December 5, 2000
Accepted March 31, 2001

As part of the pharmaceutical guidance program using drug history notebooks for each patient and drug information leaflets, we gave pharmaceutical guidance to 37 outpatients with hyperuricemia chosen at random who were administered allopurinol or benzbromarone. The effects of pharmaceutical guidance on patient adherence were evaluated using changes in the serum uric acid level. The patients who were given conventional verbal explanations and shown descriptions on the drug bag were classified as the control group. Those who were given pharmaceutical guidance according to the pharmaceutical guidance program were classified as the intervention group. The baseline uric acid level and the levels 1 and 6 months after the start of pharmacist consultations were determined. Any patients who had changes in their drug prescriptions which affected their uric acid level during the investigation period were excluded. Sixteen patients in the control group and 17 in the intervention group were included in this study. There were no differences in the average value or variance of serum uric acid concentration at the baseline between the 2 groups. However, the average uric acid level decreased significantly 1 month after the start of consultations in the intervention group, while it did not change in the control group. In patients showing baseline uric acid levels over 7 mg/dL, the uric acid levels showed a significant reduction in all patients in the intervention group, while the changes were not significant in the control group. These results showed that the pharmaceutical guidance performed by pharmacists enhanced the patients' medication compliance, thus resulting in an improvement of hyperuricemia.

Keywords — pharmaceutical guidance program, hyperuricemia, drug history notebook, uric acid, pharmacists' consultation, outpatients

Introduction

Medication compliance rates have been shown to be approximately 50%1-3). About 34% of outpatients who visited a university hospital in Japan were estimated to be medication-noncompliant4).

We performed a survey of medication compliance in outpatients in June 1995, and found that about 70% patients showed complete compliance with the drug regimens prescribed by our hospital physicians5). About one in 7 patients (14%) did not accurately understand the usage and dose of drugs, and one in 3 patients (35%) did not know the effects of the main drugs used in their treatment. Furthermore, 36% patients sometimes forgot to take their prescribed drugs.

The patients surveyed were classified into 3 groups; inpatients who were given pharmaceutical guidance by pharmacists during the hospitalization period, outpatients who were given pharmaceutical guidance, and outpatients who were given no guidance. Both drug adherence and understanding of their effects were significantly better in the inpatients who were given pharmaceutical guidance during the hospitalization period than in the outpatients who were not given drug guidance. Among the inpatients who were given pharmaceut-
tical guidance during the hospitalization period, those who
often consulted with pharmacists in the outpatient depart-
ment tended to make fewer mistakes with drug intake after dis-
charge\(^6\).

These results indicated that more effective pharmaceutical
guidance for outpatients is necessary to ensure that they suf-
ficiently understand the usage and dose of drugs, their ef-
effects, the importance and aims of treatment, and what to do
should they forget to take the drugs. Therefore, we designed
a pharmaceutical guidance program for outpatients with se-
veral diseases.

Since patients with hyperuricemia have no pain until the
occurrence of complications and subjective symptoms, they
are insufficiently concerned about their disease and drugs,
similarly to other patients with chronic diseases such as hy-
pertension. According to Barlow’s survey, about 30% of
patients with gout had renal dysfunction\(^6\). Hyperuricemia
has been reported to be an independent risk factor of
ischemic heart disease and cerebrovascular disease\(^7-11\).
Therefore, it is very important to control and treat hyperu-
ricemia from its subclinical stage. To evaluate the pharma-
ceutical guidance program for outpatients, we examined the
changes in serum uric acid level as a parameter of the com-
pliance of drug intake in patients with hyperuricemia. Pa-
ients administered allopurinol, a xanthine oxidase inhibitor,
or benzbromarone, widely used as a uric acid eliminant in
Japan, were included in this study. These drugs are known
to reduce the uric acid levels in hyperuricemic patients and
have been shown to have uric acid reducing effects of over
85% for allopurinol, and over 90% for benzbromarone (50
mg/day administration)\(^12-17\).

**Methods**

1. **Subjects**

The subjects were patients chosen at random from outpa-
tients diagnosed as having gout or hyperuricemia at the in-
ternal or orthopedic departments of our hospital and who
were taking allopurinol or benzbromarone. The pharmaceu-
tical guidance program started in October 1997 and ended in
June 1998. Each patient gave their consent to participation
in the pharmacists’ consultation, which was covered by the
Japanese health insurance system.

2. **Pharmaceutical guidance program**

When drugs were dispensed, the patients were given phar-
caceutical guidance as follows, so that they could better un-
derstand hyperuricemia and the drugs used to treat their dis-
ease.

1. Explanation and confirmation of the usage and dose of
drugs.
2. Explanation of the effects of drugs.
4. Explanation of what to do should they forget to take the
drugs.
5. Preparation of a drug history notebook for each patient.
6. Leaflets explaining hyperuricemia, diet, and complica-
tions prepared by pharmaceutical companies were given
to the patients.

The drug history notebook was brought to the pharmacy
counter every visit, and the contents, usage, and doses of
prescribed drugs were described by a pharmacist. If the pre-
scribed drugs were changed, the new medicine was ex-
plained to the patient. Explanation of associated drugs was
also given to maintain the patient’s interest in drugs, in addi-
tion to descriptions of conditions of drug intake, and results
of clinical tests. Alcohol intake was also monitored.

The drug history notebook was a booklet, measuring 12
cm × 18cm, which was the same size as the health insurance
card used in Japan. It described the purpose of the hand-
book, its usage, intake directions, usage of drugs, and gen-
eral precautions. The remaining part of the notebook was for
records of consultation, prescribed drugs, injections, intake
of commercially available drugs and any allergic reaction
history. The patient brought the notebook to hospitals, clinics
and drugstores, and physicians or pharmacists recorded
and explained the prescriptions, contents and actions of the
drugs, and precautions. Medication control by medical staff
would be possible using this notebook, and any duplication
of prescriptions and interaction between drugs would be
clear at any medical institution visited by the patient.

Initially, we chose 37 patients who were given pharma-
ceutical guidance (intervention) and 29 patients who were
given no guidance (control). Patients who had changes in
prescription of drugs affecting the uric acid level during the
investigation period were excluded. Sixteen patients in the
control group and 17 in the intervention group were in-
cluded in this study who completed the initial treatment pro-
gram without changes in other medicines such as diuretics
and angiotensin converting enzyme (ACE) inhibitors that af-
fect the uric acid level or changes in their prescription ex-
cept increases or decreases in uric acid reducing drugs dur-
ing the examination period.

We measured baseline uric acid level, and the levels 1
and 6 months after the start of the guidance program in
these outpatients. Twenty patients in the intervention group
and 13 patients in the control group were excluded from this
study because they did not conform to the above criteria.

3. **Laboratory and data analysis**

Serum uric acid levels were measured by the uricase-
peroxidase method. Data were analyzed by the unpaired
Wilcoxon test, Fisher’s exact test, or Dunnet’s multiple
comparison test.

**Results**

Clinical backgrounds of the intervention and control
groups as shown in Table 1, there were little differences in background between the two groups. Ten patients had hypertension in the intervention group, while 9 had hypertension in the control group. Diuretics, which are considered to affect the uric acid level, had been administered to 5 patients (furosemide in 4 patients, indapamide in 1 patient) in the intervention group and to 3 patients (furosemide in 1 patient, indapamide in 2 patients) in the control group. ACE inhibitors had been administered to 3 patients in the intervention group (enalapril in 2 patients, delapril in 1 patient) and to 4 patients (enalapril in 4 patients) in the control group. There were no differences in the number of drugs administered between the 2 groups (Fisher’s exact test).

1. Changes in the serum uric acid level

The serum uric acid levels 1 and 6 months after the start of pharmacists’ consultation were significantly lower than the baseline level in the intervention group. In the control group, the serum uric acid level remained unchanged 1 and 6 months after the start of pharmacists consultation (Table 2). There were no significant differences in the serum uric acid level at the baseline between the two groups, but a difference was observed one month later (p=0.061). Six months later, the difference in the serum uric acid level between the two groups was significant.

2. Distribution of the serum uric acid level

Patients were classified into 3 groups based on serum uric acid level i.e. over 7 mg/dL, 5-7 mg/dL, and below 5 mg/dL, according to the previous reports by Tomita et al and the definition of the Japan Purine and Pyrimidine Metabolism Association.

The distributions of the serum uric acid level at baseline and 1 and 6 months after the start of pharmacists’ consultation in the intervention group were compared with those in the control group. No significant difference was observed in the baseline between the two groups, while the differences 1 and 6 months after the start of pharmacists’ consultation were significant (Fig. 1). Fig. 2 shows the changes in serum uric acid levels of individual patients with baseline levels over 7 mg/dL. The uric acid levels invariably showed reduction in the intervention group, while the levels showed inconsistent changes in the control group.

In the intervention group, the doses of uric acid reducing drugs were decreased in 3 patients (allopurinol: 200mg/day to 100mg/day in 1 patient, benzbromarone: 100mg/day to 50mg/day in 2 patients). On the other hand, there were no patients in whom the doses were decreased in the control group. In one patient, the dose of allopurinol was increased from 100mg/day to 200mg/day, and benzbromarone was additionally prescribed to 2 patients who had taken allopurinol alone.

Table 1. Patient Characteristics in the Intervention and Control Groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>66.3 ± 10.2</td>
<td>63.1 ± 9.9</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>6(35.3)</td>
<td>2(12.5)</td>
</tr>
<tr>
<td>Male</td>
<td>11(64.7)</td>
<td>14(87.5)</td>
</tr>
<tr>
<td>No of Drugs/day</td>
<td>4.9 ± 2.7</td>
<td>3.9 ± 2.5</td>
</tr>
<tr>
<td>No of drug intake/day</td>
<td>2.7 ± 0.8</td>
<td>2.2 ± 0.9</td>
</tr>
<tr>
<td>Uric acid reducing drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allopurinol</td>
<td>15(88.2)</td>
<td>13(81.3)</td>
</tr>
<tr>
<td>Benzbromarone</td>
<td>2(11.8)</td>
<td>3(18.7)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia, n (%)</td>
<td>14(82.4)</td>
<td>13(81.3)</td>
</tr>
<tr>
<td>Gout, n (%)</td>
<td>3(17.6)</td>
<td>3(18.7)</td>
</tr>
<tr>
<td>Complications, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperlipemia</td>
<td>2(11.8)</td>
<td>4(25.0)</td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>12(70.6)</td>
<td>10(62.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10(58.8)</td>
<td>9(56.3)</td>
</tr>
</tbody>
</table>

Table 2. Changes in the Serum Uric Acid Level in Intervention and Control Groups (mean ± SD mg/dL).

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>After 1 month</th>
<th>After 6 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>7.1 ± 1.7</td>
<td>5.7 ± 1.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.7 ± 1.2&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Control</td>
<td>6.6 ± 1.4</td>
<td>6.6 ± 1.1</td>
<td>6.7 ± 1.3</td>
</tr>
</tbody>
</table>

<sup>a</sup>Statistically significant differences when compared with baseline, analyzed by Dunnet’s multiple comparison test. Between-group comparisons of serum uric acid levels were analyzed by unpaired Wilcoxon test.

Discussion

There was little difference in male:female ratio between the intervention group and control group. So, to confirm the uric acid reducing effects of allopurinol or benzbromarone between female and male, we analyzed the changes in serum uric acid in 24 inpatients; they were first administered allopurinol or benzbromarone on admission and showed complete compliance. In thirteen female (allopurinol in 10 patients, benzbromarone in 3 patients), serum uric acid level
was significantly decreased from 9.3±1.5mg/dL before uric acid reducing therapy to 5.7±1.6mg/dL after two weeks of therapy. In eleven male (allopurinol in 9 patients, benzbromarone in 2 patients), serum uric acid level was also significantly decreased from 10.0±1.2mg/dL before uric acid reducing therapy to 6.7±2.4mg/dL after two weeks of therapy. (paired Wilcoxon test) There were no significant differences in the serum uric acid levels between fe-
male and male before or after two weeks of uric acid reducing therapy (unpaired Wilcoxon test).

Providing the patient with information about the therapeutic effects of prescribed drugs and early symptoms of their adverse effects helps them understand the effectiveness and safety of prescribed drugs, and thus encourages them to be consciously involved in their own treatment. Under such conditions, pharmacists can feel sure that the patients will take the drugs correctly according to the directions, because they have a better understanding of the prescribed drugs.

According to the pharmaceutical guidance program in this study, prescribed drugs were explained to the patients and recorded in the drug history notebook each time they visited the hospital. The patients could read the records whenever they wanted, and their interest in the drugs increased. The patients' interest in the drugs could be maintained high by repeated explanation using the drug history notebook, and this would improve compliance with drug intake. According to the survey of medication compliance in outpatients, 17.2% patients frequently asked pharmacist, 47.4% patients consulted only when they had question in pharmacotherapy, and remaining 35.4% patients had not consulted with pharmacists, and 72.2% patients showed complete compliance\(^5\). Control group patients of this study might have conversations with the patients about the results of the clinical tests, food and drinking behavior, using leaflets explaining hyperuricemia, diet, and complications.

The baseline uric acid levels determined in this study probably include those of patients who just started treatment or who received treatment for a very short period, patients who showed non-compliance, and patients whose symptoms were sufficiently controlled. Treatment of hyperuricemia usually aims at controlling the uric acid level to 5-6 mg/dL in 3-6 months. This study period was set at 6 months so that all patients would be treated over 6 months. Although the real end point of hyperuricemia is considered to be prevention of gout attack, joint disorder and renal dysfunction, the serum uric acid level as a parameter of prevention of advancement to these symptoms was used as a surrogate end point in this study.

Since Tomita reported that the relative risk of cerebrovascular disorder is significantly lower at uric acid levels below 5 mg/dL\(^{11}\), and the Japan Purine and Pyrimidine Metabolism Association defined the upper limit of normouricemia as under 7 mg/dL\(^{10}\), we classified the patients according to uric acid levels as follows: below 5 mg/dL group, 5-6.9 mg/dL group and over 7 mg/dL group. There were significant differences in the distribution of uric acid levels 1 and 6 months after the start of pharmacists’ consultation between the intervention and control groups. It was difficult to understand why the mean uric acid level and the distribution remained unchanged in the control group even though reliable drugs were administered, so we further examined the changes in uric acid level in the 2 groups in more detail. Since patients showing uric acid levels over 7 mg/dL at the baseline were expected to show greater responses to uric acid reducing drugs, the changes in the uric acid level of individual patients showing baseline uric acid levels of over 7 mg/dL were examined. In the intervention group, the uric acid levels were invariably reduced to below 7 mg/dL at 6 months, while the levels showed inconsistent changes in the control group. Although 2 patients in the control group showed reduction of the uric acid level to below 7 mg/dL, these slight decreases were canceled by the changes in the uric acid level in the other patients resulting in the absence of reduction of the mean uric acid level and changes in the distribution. The uric acid levels in the intervention group at baseline should be classified into the close to 7 mg/dL group and 9 to 10 mg/dL group. Greater reduction of uric acid level was observed in the 9 to 10 mg/dL group. The consistent reduction of uric acid level in the intervention group was probably due to the pharmaceutical guidance program.

Since the drugs used in this study showed reproducible effects, the decrease in the uric acid level observed over the 6-month period was considered to be the result of good drug compliance. This pharmaceutical guidance program by pharmacists will lead to prevention of complications and maintenance of the patients’ QOL. We have begun to use this pharmaceutical guidance program for all patients with hyperuricemia treated in our hospital since July 1998.

References

6) K.T. Barlow, L.J. Belin, Renal disease in gout, Q. J.

367


17) Torii pharmaceutical Co., LTD, Torii products information, Tokyo, 2000, pp. 204-205.