Drug Compliance in Patients with Bronchial Asthma: Relation among Compliance with Different Types of Antiasthmatic Drug and Association with Daily Administration Frequency

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ABSTRACT

Background: Not only monotherapy with inhaled corticosteroids (ICS) but also the concurrent use of other antiasthmatic agents, including leukotriene receptor antagonists (LTRA), play an important role in the management of asthma. However, few studies have focused on compliance with these drugs and on the relation between drug compliance and drug usage.

Methods: Data were derived from a survey of pharmacists dispensing antiasthmatic drugs to adults with asthma who visited participating pharmacies from October through November 2002. The patients were limited to regular users of ICS whose medication had not been changed for at least 6 months before the survey. Drug compliance and the daily administration frequency of antiasthmatic agents were evaluated on the basis of pharmaceutical records.

Results: Completed data were received for 322 patients. ICS compliance was lower than compliance with oral sustained-release theophylline (OSRT) and compliance with LTRA. ICS compliance significantly correlated with OSRT compliance and with LTRA compliance. There were no significant differences of ICS compliance among ICS alone, ICS + LTRA, ICS + OSRT and ICS + LTRA + OSRT group, while the daily inhalation frequency in ICS + OSRT or ICS + OSRT + LTRA group were higher than those in ICS alone group. Although there was a significant negative correlation between ICS compliance and daily inhalation frequency, neither OSRT compliance nor LTRA compliance significantly correlated with the tablet or capsule numbers per day. These findings indicate that OSRT may increase the compliance of concomitant ICS, and that the compliance of OSRT or LTRA is independent of the numbers of tablets taken per day.

Conclusions: These unique characteristics should be considered in the treatment and guidance of patients with bronchial asthma.

KEY WORDS
bronchial asthma, drug compliance, inhaled corticosteroid, leukotriene receptor antagonist, oral sustained-released theophylline


**Table 1** Patient background

<table>
<thead>
<tr>
<th>subgroup</th>
<th>gender (male/female/UN)</th>
<th>age (mean ±/− SD)</th>
<th>duration (mean ±/− SD)</th>
<th>PA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICS alone</td>
<td>23/41/1</td>
<td>48.7 +/− 17.9</td>
<td>15.7 +/− 14.3</td>
<td>16.9% (UN: 1.5%)</td>
</tr>
<tr>
<td>ICS + LTRA</td>
<td>5/14/0</td>
<td>53.0 +/− 15.6</td>
<td>10.6 +/− 9.8</td>
<td>15.8% (UN: 0.0%)</td>
</tr>
<tr>
<td>ICS + OSRT</td>
<td>71/66/6,* , #</td>
<td>57.7 +/− 18.4***</td>
<td>14.5 +/− 14.9</td>
<td>20.3% (UN: 2.1%)</td>
</tr>
<tr>
<td>ICS + LTRA + OSRT</td>
<td>34/58/3¥</td>
<td>57.3 +/− 17.2**</td>
<td>14.5 +/− 12.7</td>
<td>29.5% (UN: 3.2%)</td>
</tr>
<tr>
<td>all patients</td>
<td>133/179/10</td>
<td>55.5 +/− 18.1</td>
<td>14.5 +/− 13.9</td>
<td>22.0% (UN: 2.2%)</td>
</tr>
</tbody>
</table>

**Table 2-a** The compliances with ICS, OSRT and LTRA

<table>
<thead>
<tr>
<th>compliance</th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ICS compliance</td>
<td>82.3 +/− 23.6</td>
<td>(n = 322)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OSRT compliance</td>
<td>89.8 +/− 18.2</td>
<td>(n = 238)**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LTRA compliance</td>
<td>91.2 +/− 17.4</td>
<td>(n = 114)**</td>
<td></td>
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</table>

**INTRODUCTION**

Guidelines from various countries recommend inhaled corticosteroids (ICS) for the primary treatment of bronchial asthma in adults.\(^1,2\) Increased use of ICS has led to dramatic improvement in the management of asthma.\(^3\) Recently, inhaled long-acting beta 2 agonists (LABA), leukotriene receptor antagonists (LTRA), or oral sustained-released theophylline (OSRT) have been reported to be useful when added to ICS in patients with persistent symptoms of asthma that do not respond to ICS alone.\(^4,6\) Combinations of ICS with other drugs are therefore playing an increasingly important role in the management of asthma.

Drug compliance is an important determinant of the effectiveness of medical therapy in various types of disease.\(^7\) In daily clinical practice, individual patients’ disease status and compliance with prescribed medical therapy are most likely consciously or unconsciously considered, regardless of the specific disease being treated. Drug compliance is also an important factor in the design of strategies for the treatment of asthma.

Drug compliance itself can be influenced by various factors.\(^8\) The relation of compliance to daily dose and administration frequency has been studied extensively.\(^9,10\) The need for frequent daily administration generally results in poorer drug compliance. However, studies of drug compliance in patients with bronchial asthma are scare. In contrast to other common diseases, inhalation therapy has a major role in the management of asthma. Therefore, drug compliance should be assessed for both inhaled and oral drugs. Although compliance with antiasthmatic medication has been studied previously and the negative correlation was reported between the inhalation frequency and the compliance in ICS,\(^11,12\) many points remain unclear regarding the relation of the compliance of used drugs, including ICS, LTRA and OSRT, which are administrated to the same patient. Moreover, there are no established relations between the administration frequency and the compliance with OSRT and LTRA.

This study compared compliance among ICS, OSRT, and LTRA. We also analyzed the relations between compliance with each type of drug and the daily administration frequency. To analyze factors affecting compliance, we surveyed pharmacists who dispensed antiasthmatic drugs to adults with asthma who were regular users of ICS and resided in Niigata Prefecture in 2002.

**METHODS**

The survey for this study was performed from October through November 2002 under the Ethical Principles for Medical Research Involving Human Subjects, Declaration of Helsinki. The subjects were patients who regularly used ICS dispensed by the pharmacies participating in this survey. Patients 16 years or younger were excluded. None of the subjects had had any change in their prescription for at least 6 months prior to responding to the survey. Sixty dispensing pharmacies in Niigata Prefecture, Japan participated in the survey. Completed data were received for 322 patients.

The patients’ pharmacists were questioned for the daily administration frequency of drugs used to treat asthma, including ICS, OSRT, and LTRA, prescribed by each patient’s physician. The pharmacists also reported data related to drug compliance, which was calculated on the basis of the estimated total quantity of medicines prescribed during the past 6 months (QE) and the quantity of medicines actually taken back home by the patient during the same period (QA). Drug compliance was then expressed as a ratio, calculated using the following formula: QA/QE × 100 (% from 0 to 100). Drug compliance was separately calculated for ICS, OSRT, and LTRA. Any compliance score greater than 100 was expressed as 100.

The statistical significance of the differences be-
between drug compliance scores was calculated by the Wilcoxon’s signed rank test with Bonferroni’s correction. The correlation of ICS compliance with OSRT or LTRA compliance was evaluated by the Spearman’s rank-correlation test. The correlations of compliance with the daily inhalation frequency of ICS or the numbers of tablets/capsules of OSRT and LTRA administered daily were also evaluated by the Spearman’s rank-correlation test. The data were analyzed on a Macintosh computer with StatView software, version J-5.0. P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

The clinical characteristics of the subjects are summarized in Table 1. In all patients, mean age was 55.5 ± 18.1 years, and the mean duration of disease was 14.5 ± 13.9 years. As for gender, 42.6% of the subjects were male, 57.4% were female, and 0.1% was unknown. As for asthma control, 22.0% of the subjects had had asthmatic attacks during the 2 weeks prior to the study; asthma status was unknown for 2.2%. To express further details, the cases were divided into four subgroups (ICS alone group, ICS + LTRA group, ICS + OSRT group, ICS + LTRA + OSRT group). The gender ratio in the ICS + OSRT group showed a significant difference compared with that in ICS alone and the ICS + LTRA group, and the gender ratio in the ICS + LTRA + OSRT group also showed a significant difference compared with the ICS + OSRT group. Both the age in the ICS + OSRT and the ICS + LTRA + OSRT group indicated a significant difference compared with that in ICS alone.

In all patients, mean compliance scores for ICS, OSRT, and LTRA are shown in Table 2-a. The compliance rate was higher than 80% for all three types of drugs. However, the compliance with OSRT and LTRA was significantly better than compliance with ICS. And Table 2-b shows the puff or blister numbers of ICS per one inhalation time (P/Ti), the inhalation times of ICS a day (Ti/D), the puff or blister numbers of ICS a day (P/D) and the ICS compliance in each subgroup as described above. Although P/Ti, Ti/D and P/D in the ICS + OSRT group were significantly higher than those in the ICS alone group, there were no significant differences of ICS compliance among these groups. Table 2-c shows the tablet or capsule numbers of OSRT or LTRA a day (Ta/D), the dose of OSRT a day (Do/D) and the OSRT or LTRA compliance. There were no significant differences among these subgroups.

The relations of ICS compliance to OSRT compliance and LTRA compliance were examined. The results are shown in Figure 1. ICS compliance positively correlated with OSRT compliance as well as with LTRA compliance (Fig. 1).

Next, the relation of drug compliance to P/Ti, Ti/D and P/D was examined. Figure 2 shows the results for ICS. There was a significant negative correlation of ICS compliance with the P/Ti (upper panel), Ti/D (middle panel) and P/D (lower panel) of ICS, although the correlation coefficients were low. However, OSRT compliance did not correlate significantly with the OSRT Ta/D (upper panel) and Do/D (lower panel) (Fig. 3). There was also no significant correlation of LTRA compliance with the LTRA Ta/D.
Fig. 1 Correlation between ICS compliance and OSRT compliance (upper panel); and correlation between ICS compliance and LTRA compliance (lower panel). The data were evaluated by the Spearman’s rank-correlation test and were analyzed on a Macintosh computer with StatView software, version J-5.0. Significant positive correlations were detected ($P < 0.001$).

Fig. 2 Correlation between ICS compliance and the puff or blister numbers of ICS per one inhalation time (P/Ti: upper panel), the inhalation times of ICS administered per day (Ti/D: middle panel), the puff or blister numbers of ICS administered per day (P/D: lower panel). The data were evaluated by the Spearman’s rank-correlation test and were analyzed on a Macintosh computer with StatView software, version J-5.0. A significant negative correlation between ICS compliance and Ti/D, or ICS compliance and P/D was detected ($P < 0.05$).

**DISCUSSION**

Drug medications, including inhalation therapy, play pivotal roles in the treatment of patients with bronchial asthma. Drug compliance with ICS, therefore, has an important part in the management of asthma. Moreover, other oral drugs for asthma control are also considered important.4-6 Assessment of compliance with ICS as well as compliance with concomitant medication may help to delineate factors related to drug response. The present study mainly compared compliance among ICS, OSRT, and LTRA, and analyzed the relations between compliance with each type of drug and the background of the drug use, including P/Ti, Ti/d, Ta/D, using data obtained from pharmacists who dispensed antiasthmatic drugs to adults with asthma in Niigata Prefecture in 2002.
A significant correlation was not detected (P > 0.05) between OSRT administered per day (Ta/D: upper panel) and the tablet or capsule numbers of OSRT per day (Do/D: lower panel). The data were evaluated by the Spearman’s rank-correlation test and were analyzed on a Macintosh computer with StatView software, version J-5.0. A significant correlation was not detected (P > 0.05).

Fig. 3 Correlation between OSRT compliance and the tablet or capsule numbers of OSRT administered per day (Ta/D: upper panel) and the dose of OSRT administered per day (Do/D: lower panel). The data were evaluated by the Spearman’s rank-correlation test and were analyzed on a Macintosh computer with StatView software, version J-5.0. A significant correlation was not detected (P > 0.05).

In several previous studies, ICS compliance was directly evaluated by counting the number of inhalations by means of a mechanical counter attached to inhalation devices,13-17 or compliance was calculated on the basis of unused drugs returned by patients.18 However, such methods can introduce bias because many patients are aware that their drug use is being monitored during the study, which can influence their compliance. However, the pharmaceutical-record-based evaluation of drug compliance used in this study can avoid such bias.

Comparison of compliance among antiasthmatic drugs showed that compliance with OSRT was significantly better than with ICS, consistent with the results of Kelloway et al.,19 in which almost the same evaluating method for compliance had been performed. As compared with their findings, however, ICS compliance was better, and the difference in compliance between OSRT and ICS was considerably smaller. We attribute these differences to recently increased awareness among both physicians and patients of the importance of asthma control by ICS. LTRA also had better compliance than ICS, which apparently conflicts with the results of our previous study, showing no significant difference in compliance between antiallergic drugs, including histamine receptor 1 antagonists, and ICS.20 Antiallergic drugs other than LTRA have no bronchodilatory activity, whereas LTRA have bronchodilatory activity comparable to that of OSRT. These characteristics apparently resulted in similar compliance for LTRA and OSRT in the present study. We also found that ICS compliance positively correlated with LTRA compliance as well as with OSRT compliance. Given recent reports of synergism between ICS compliance and compliance with LABA,21,22 which was not available in Japan at the time of our study, it is likely that improved compliance with concomitant drugs that have bronchodilatory activity may also improve compliance with ICS. Moreover, Table 2-b showed that although the P/Ti, Ti/D and P/D in the ICS + OSRT or the ICS + OSRT + LTRA group were obviously higher than those in the ICS alone group, there were no significant differences of ICS compliance among these groups. On the other hand, the P/Ti, Ti/D and P/D in the ICS + LTRA group appeared the same as those in the ICS alone group, and the ICS compliance in the ICS + LTRA group was better but not significant (P = 0.080) than that in the ICS alone group. These results confirmed our speculation, because it was reported that the more P/Ti, Ti/D and P/D make the ICS compliance worse.11,12 although the relation between the compliance and the P/Ti, Ti/D and P/D in this
The daily administration frequency of drugs has long been considered to affect drug compliance. Studies of hypertension treatment have shown that decreased daily administration frequency improves antihypertensive-drug compliance. A study of antiasthmatic drugs found no relation between drug compliance and the daily administration frequency of ICS or OSRT. However, a recent survey indicated that increased daily administration frequency of ICS is associated with decreased compliance with ICS. Our analysis also clearly showed that increased P/Ti, Ti/D and P/D of ICS was clearly related to decreased compliance with ICS (Fig. 2). These findings suggested that increased ICS compliance due to heightened awareness of the importance of ICS in asthma treatment most distinctly affected patients with asthma who used ICS in a lower frequency of administration. Our results for OSRT compliance were consistent with Kelloway et al. As for the relation between LTRA compliance and Ta/D of LTRA, we found no previous studies in the literature and believe that ours is the first to address this issue. Although the drugs used differed among our subjects, our results indicated no relation between the number of tablets/capsules administered per day and drug compliance with LTRA. Taken together, the commonly accepted principle that the factors influencing drug compliance are similar to those for antihypertensive agents does not appear to apply, similar to OSRT and probably LTRA.

In summary, we examined the relations among compliance with drugs used for asthma management and the administration frequency of antiasthmatic agents, focusing on ICS. Data were derived from a survey of asthmatic patients' pharmacists. We conclude that interactions among compliance with OSRT, LTRA, and ICS, and the relations of drug compliance to the daily administration frequency of these drugs, such as P/Ti, Ti/D and P/D, should be considered in the treatment and guidance of patients with bronchial asthma.

REFERENCES

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