고증성지방혈증에서 fenofibrate에 대한 acipimox의 효과 비교

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Efficacy of Acipimox in Comparison with Fenofibrate for Hypertriglyceridemia

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목적: 이상지방혈증 환자의 치료는 우선적으로 저밀도지단백을 감소시키고, 저밀도지단백이 목표수치에 도달한 이후에도 증성지방이 높을 경우 nicotinic acid 또는 fibrate를 사용하도록 권장되고 있다. 본 연구는 이상지방혈증이 있는 환자에서 acipimox의 효과를 fenofibrate와 비교하여 분석하고자 시행되었다.

방법: 본 연구는 서울에 위치한 3차 대학병원의 환자를 대상으로 후향적으로 의무기록을 분석하여 시행되었다. 혈중 중성지방농도가 200 mg/dL 이상으로써 acipimox 또는 fenofibrate를 신규처방 받은 환자를 대상으로 각각의 약물이 지단백에 미치는 영향을 36주간 추적하여 비교분석하였다.

결과: Acipimox을 투여 받은 환자 41명, fenofibrate를 투여 받은 환자 62명이 모집되었으며, 각각의 약물은 복용한 환자의 기본적인 인구학적 특성은 유의하게 상이하지 않았다. 3개월 간의 약물투여 후 두 약물군 환자 모두에서 총콜레스테롤(p < 0.05) 및 저밀도지단백(p < 0.001)이 약물투여 전과 비교하였을 때 유의하게 감소하였고, 고밀도지단백은 두 환자에서 유의하게 증가하였다(p < 0.05). 한편 증성지방 감소율은 acipimox군이 fenofibrate군보다 크게 나타났다(p < 0.05). 약물유해반응의 반도는 두 약물군 간에 유의한 차이가 없었다. 결론: 총콜레스테롤, 저밀도지단백, 폴레스테롤 등을 감소시키거나 고밀도지단백 폴레스테롤을 증가시키는 효과는 acipimox와 fenofibrate가 유의하게 다르지 않았으며, 증성지방을 감소시키는 효과는 acipimox가 fenofibrate보다 우월하였다.

Key words - acipimox, fenofibrate, hypertriglyceridemia, dyslipidemia

Introduction

Dyslipidemia is associated with causing cardiovascular disease by atherosclerosis with oxidative stress, endothelial dysfunction, and vascular inflammation. Multiple evidence from epidemiologic studies and clinical trials demonstrate a direct and causal relationship between low-density lipoprotein cholesterol (LDL-C) and coronary heart disease (CHD).1-3) High triglyceride and low high-density lipoprotein cholesterol (HDL-C) are also shown to be associated with an increased risk for CHD, especially in patients with diabetes.4) In fact, hypertriglyceridemia is the most common type of dyslipidemia in patients with diabetes, as insulin plays an important role in the formation and breakdown of lipoproteins that largely contain triglyceride.5-6)

Acipimox, 5-carboxy-2-methyl-1-oxidopyrazin-1-ium, a derivative of nicotinic acid, is a triglyceride precursor
Acipimox has several advantages compared to nicotinic acid. First, while nicotinic acid suppresses the release of free fatty acid from adipose tissue for only about 90 minutes before being rebounded, acipimox inhibits the release for more than 5 hours without significant rebound because unlike nicotinic acid, acipimox does not undergo significant metabolism. Second, while nicotinic acid has frequent bothersome vasodilation-related side effects and upper gastrointestinal (GI) distress, acipimox shows significantly lower adverse effects such as flushing, thus improving patient compliance. Third, nicotinic acid has a dosage-dependent effect in increasing plasma glucose by accentuation of insulin resistance. Acipimox can safely be used in patients with diabetes or hyperglycemia as it does not interfere with glucose metabolism or increase insulin-sensitivity. Several clinical studies have reported that acipimox has positive effects on treating type II, III, IV, or V dyslipidemia when used in monotherapy or in combination with other antihyperlipidemic agents. Although acipimox is currently unapproved by U.S. Food and Drug Administration, it is widespread in Europe, South Africa, China, Japan and Korea.

This was a retrospective review of the medical and pharmaceutical records of patients who were treated with acipimox or fenofibrate for hypertriglyceridemia at a tertiary teaching hospital in Seoul, Korea. Patients received acipimox 250 mg three times daily orally whereas fenofibrate was received 200 mg once daily. Patients over 18 years old who were followed up for at least 6 months were included. Patients who had been taking other lipid-lowering agents within one month prior to the study medications, received combination therapy with other lipid-lowering drugs, or concurrently received any medications that were known to alter the lipid metabolism were excluded.

**PATIENTS AND METHODS**

This was a retrospective review of the medical and pharmaceutical records of patients who were treated with acipimox or fenofibrate for hypertriglyceridemia at a tertiary teaching hospital in Seoul, Korea. Patients received acipimox 250 mg three times daily orally whereas fenofibrate was received 200 mg once daily. Patients over 18 years old who were followed up for at least 6 months were included. Patients who had been taking other lipid-lowering agents within one month prior to the study medications, received combination therapy with other lipid-lowering drugs, or concurrently received any medications that were known to alter the lipid metabolism were excluded.

**Data Extraction**

Data were extracted from electronic and papered medical and pharmacy records. Collected records without patient names and identification numbers were stored in a Microsoft Excel file. Data extracted by one pharmacist were reviewed and confirmed by another pharmacist to ensure accuracy. Any discrepancies were resolved by mutual consent. Demographic data collected were as follows: gender, age, weight, height, body mass index (BMI), presence of diabetes, and medications administered. Lipid profile data extracted included total cholesterol, triglyceride, and HDL-C at baseline, 3, 6, and 9 months following treatment. LDL-C level was calculated using Friedewald equation when plasma triglyceride concentration was less than 400 mg/dL. In patients with diabetes, fasting blood glucose (FBG), and glycated hemoglobin (A1C) were evaluated. Changes in aspartate aminotransferase (AST), alanine aminotransferase (ALT), and GI side effects were recorded in order to assess adverse drug effects of acipimox and fenofibrate.

**Statistical Analysis**

Descriptive data were expressed in terms of the mean ± standard deviation. Paired t-test was performed to compare the differences in FLPS, glucose and A1C at different time points (3, 6, and 9-months following the treatment) using baseline value as a reference. To compare the differences in FLPS, glucose and A1C between acipimox and fenofibrate, student t-test was performed.
The Chi-square test was used to compare the differences in ordinal variables in baseline characteristics between two groups. A \( p \)-value of less than 0.05 was considered to be significant. Data were analyzed using SPSSWIN 10.0 program.

## RESULTS

### Patient Characteristics

The baseline characteristics of the patients taking acipimox and fenofibrate are summarized in Table 1. Of the 103 patients included in the study, 41 patients were administered acipimox and 62 patients were administered fenofibrate for 36 weeks. These two groups were comparable in demographic and clinical characteristics (all \( p > 0.05 \) except for AST \( p = 0.031 \)). About 70% of patients in each group had diabetes mellitus which was entirely constituted by type II for at least one year. The complications of diabetes and the use of oral hypoglycemic agents at baseline were similar between two groups (all \( p > 0.05 \)). AST, ALT, LDL-C, FBG and A1C were not obtained from the whole study participants.

### Changes in lipid profile

Patients’ mean triglycerides levels at 0, 3, 6, and 9 months following acipimox and fenofibrate are depicted in Figure 1. Both acipimox and fenofibrate group significantly decreased triglyceride after 3 months and maintained significance thereafter (all \( p < 0.001 \)). Mean triglyceride changes from the baseline after 3 months were significantly higher in acipimox than fenofibrate (\( \Delta 255 \pm 137 \text{mg/dL} \) vs. \( \Delta 219 \pm 120 \text{mg/dL} \), respectively, \( p = 0.024 \)).

The mean differences of total cholesterol, HDL-C, and LDL-C from the baseline after 3 months administering acipimox and fenofibrate are shown in Figure 2. Both acipimox and fenofibrate group significantly decreased total cholesterol from baseline (all \( p < 0.001 \)). Mean triglyceride changes from the baseline after 3 months were significantly higher in acipimox than fenofibrate (\( \Delta 255 \pm 137 \text{mg/dL} \) vs. \( \Delta 219 \pm 120 \text{mg/dL} \), respectively, \( p = 0.024 \)).

The mean differences of total cholesterol, HDL-C, and LDL-C from the baseline after 3 months administering acipimox and fenofibrate are shown in Figure 2. Both acipimox and fenofibrate group significantly decreased total cholesterol from baseline (all \( p < 0.001 \)), but no significant differences between two groups were found (\( p = 0.345 \)). A significant elevation of HDL-C was observed in

### Table 1. Baseline characteristics of the patients

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Acipimox (n=41)</th>
<th>Fenofibrate (n=62)</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Gender</td>
<td>29 (70.7)</td>
<td>39 (62.9)</td>
<td>0.632</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>55±8.5</td>
<td>55±10.7</td>
<td>0.803</td>
</tr>
<tr>
<td>Height(cm)*</td>
<td>164.4±9.0</td>
<td>164.7±7.7</td>
<td>0.857</td>
</tr>
<tr>
<td>Weight(kg)*</td>
<td>69.9±14.3</td>
<td>70.4±12.2</td>
<td>0.866</td>
</tr>
<tr>
<td>BMI (kg/m²)*</td>
<td>25.4±3.0</td>
<td>25.7±3.3</td>
<td>0.643</td>
</tr>
<tr>
<td>Patients with hypertension</td>
<td>20 (48.8)</td>
<td>29 (46.8)</td>
<td>0.885</td>
</tr>
<tr>
<td>Patients with DM</td>
<td>29 (71.8)</td>
<td>44 (71.2)</td>
<td>0.989</td>
</tr>
</tbody>
</table>

Data are shown in number (%).
*mean±SD
SD, standard deviation; BMI, body mass index; DM, diabetes mellitus. AST, aspartate aminotransferase; ALT alanine transaminase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose.

The Chi-square test was used to compare the differences in ordinal variables in baseline characteristics between two groups. A \( p \)-value of less than 0.05 was considered to be significant. Data were analyzed using SPSSWIN 10.0 program.

### Fig. 1. Fasting mean triglycerides concentrations with standard deviation for 9 months following acipimox and fenofibrate
the acipimox \( (p = 0.004) \) and fenofibrate \( (p < 0.001) \), without significant differences between two groups \( (p = 0.813) \). LDL-C reductions within and between two medications were not statistically significant (all \( p > 0.05 \)).

**Changes in A1C**

The changes of mean A1C levels for 9 months following acipimox and fenofibrate were shown in Table 2. Neither acipimox nor fenofibrate significantly decrease FBG after 9 month treatment, except in fenofibrate group at 9 months \( (p = 0.012) \) without significant difference between two medications (all \( p > 0.05 \)).

**Adverse effects**

Ten (56\%) out of 18 patients in the acipimox group and 15 (47\%) out of 32 patients in the fenofibrate group had AST or ALT levels greater than 40 IU/L during the study periods. The average AST and ALT values were 55.00±15.51 IU/L, 55.62±20.03 IU/L in ten patients in the acipimox group and 69.20±23.75 IU/L, 57.93±23.10 IU/L in fifteen patients in the fenofibrate group, respectively. No significant differences in changes of AST and ALT between two groups were detected (all \( p > 0.05 \)). With respect to GI adverse effects, one patient in acipimox group reported GI distress and one patient in fenofibrate group reported nausea.

**DISCUSSION**

Acipimox has been reported to significantly decreasing free fatty acid and cholesterol while improving HDL-C concentration, demonstrating its effectiveness for the treatment of combined hyperlipidemia.\(^8,9\) However, some discrepancies regarding the effects of acipimox on triglyceride concentration have been shown in clinical trials. A randomized, double-blind, placebo-controlled, cross-over study was performed to evaluate the effects of acipimox on lipid parameters for 12 weeks in 18 patients with mixed hyperlipoproteinemia.\(^14\) Acipimox therapy resulted in a significant decrease in total cholesterol and apolipoprotein B concentration as well as an increase in HDL-C compared with placebo. However, no significant change in triglycerides and LDL-C was present. Another two double-blind, placebo-controlled, cross-over trials were performed to evaluate hypolipidemic effects of acipimox.\(^15\) A significant reduction of LDL-C by 11\% and an increase in HDL-C up to 20\% from baseline were

**Table 2. Mean glycated hemoglobin levels with standard deviation for 9 months following acipimox and fenofibrate**

<table>
<thead>
<tr>
<th></th>
<th>Acipimox</th>
<th>Fenofibrate</th>
<th>( p )-value (^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>8.84±2.01 (n=24)</td>
<td>9.02±1.86 (n=23)</td>
<td>0.535</td>
</tr>
<tr>
<td><strong>After Treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 3</td>
<td>8.25±1.45 (n=20)</td>
<td>8.53±1.76 (n=31)</td>
<td>0.653</td>
</tr>
<tr>
<td>( p )-value (^**)</td>
<td>0.174</td>
<td>0.087</td>
<td></td>
</tr>
<tr>
<td>Month 6</td>
<td>7.95±1.23 (n=20)</td>
<td>8.31±1.48 (n=31)</td>
<td>0.568</td>
</tr>
<tr>
<td>( p )-value (^**)</td>
<td>0.221</td>
<td>0.083</td>
<td></td>
</tr>
<tr>
<td>Month 9</td>
<td>7.81±1.13 (n=18)</td>
<td>8.10±1.27 (n=30)</td>
<td>0.561</td>
</tr>
<tr>
<td>( p )-value (^**)</td>
<td>0.190</td>
<td>0.012</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD \%.  
\(^*\) between groups  
\(^**\) from baseline
observed in 10 type IIa hypercholesterolemia patients following 9 weeks of acipimox administration. A significant reduction in triglyceride level (-35%) following 4 weeks of acipimox administration in 12 patients with type IV hypercholesterolemia was also shown in this study. These inconsistent results in the literatures may be explained by the small sample size and relatively short study durations.

In the present study, acipimox at dosage of 250 mg three times daily significantly lowered triglyceride, total cholesterol, and increased HDL-C. These favorable effects of acipimox on FLPs were consistent for 9 months. The average triglyceride level at baseline in acipimox group was as high as 496 mg/dL and afterwards that was reduced by more than 50% after 3 months therapy, suggesting acipimox would be a viable treatment option in patients with severe hypertriglyceridemia. Acipimox also lowered LDL-C, which was not statically significant. LDL levels were calculated based on the other FLP values instead of direct measurement. For this reason, there were only 17 patients with evaluable LDL in the acipimox group and 29 patients in the fenofibrate group. If LDL has been available for all patients, it would have been possible to get more meaningful conclusions.

Unlike previous studies using placebo, fenofibrate was used as a control group. Fenofibrate, a third generation fibric acid derivative, reduce plasma triglyceride by 25 to 50%17-19 thus would be expected to be a good comparator in evaluating the effects of acipimox on triglyceride. We found that acipimox had similar effects to fenofibrate on reducing total cholesterol, LDL-C and raising HDL-C. Acipimox group showed a significant reduction in triglyceride level compared with fenofibrate group. There was a difference between the two treatment groups at baseline triglyceride but this was not statistically significant. In summary, acipimox is found to have not only significant reduction in triglyceride from baseline but also significantly greater reduction compared with fenofibrate.

Acipimox has a longer half-life than nicotinic acid and it does not interfere with glucose metabolism or increase insulin-sensitivity.11-13) A randomized, double-blind, placebo-controlled, crossover study with 16 Chinese non-insulin dependent diabetes mellitus patients showed that acipimox group showed similar changes to glycemic indices and insulin sensitivity from the baseline levels as that of placebo.16) It was not far from our expectation that both fasting and two-hour postprandial were elevated at baseline due to the inclusion of severe hypertriglyceridemia. More than 70% of patients in this study had type II diabetes. We assessed effects of acipimox on glucose and compared it with that of fenofibrate, and the glucose level was found to be lowered in 24 (83%) out of 29 diabetic patients in acipimox and 23 (52%) out of 44 diabetic patients in fenofibrate group. Changes from baseline in FBG were not significant and mean A1C levels decreased by about 1 % at 9 months with both medications. Our results confirmed the previous findings that acipimox can be safely used in patients with diabetes. Considering triglyceride independently predicts CHD risk and diabetes can be a secondary cause of hypertriglyceridemia,20) acipimox should be considered as a viable option of treatment to decrease triglyceride in patients with diabetes or hyperglycemia.

Treatment with acipimox was well tolerated. Elevations of liver function tests (LFTs) were transient without significant clinical symptoms. Considering that most studies defined abnormal liver function tests values as being at least 2-3 times the upper limit of normal, actual frequency of abnormal LFTs values was low in this study. GI adverse effects were not significant. As for medication adherence, there was no significant difference in medication administering frequency of three times daily comparing with once daily.21) Thus, three time daily administration of acipimox might not decrease patient’s adherence lower than once daily fenofibrate.

One limitation of our study was that we could not assess all potential risk factors for dyslipidemia such as family history, exercise, and diet due to the retrospective study design. However, all patients were provided diet and exercise education while taking medications. Even though there were more than 70% of patients with
diabetes, our patients were not categorized by diabetes or non-diabetes, preventing an accurate assessment of the effects of acipimox in these populations. Further larger randomized trials are required to determine more precise effect of acipimox on FLPs both in patients with diabetes or non-diabetes.

Hypertriglyceridemia has significantly increased the risk of metabolic syndrome, diabetes and cardiovascular disease. Acipimox has beneficial effect in its ability to improve dyslipidemia and insulin resistance. In the present study, we demonstrated the positive effect of acipimox on FLPs in Korean patients, which was comparable to fenofibrate.

CONCLUSIONS

Present study of Korean patients with dyslipidemia revealed that there were no significant differences between acipimox and fenofibrate in reducing total cholesterol, LDL-C and increasing HDL-C. Acipimox showed better effect on reducing triglyceride than fenofibrate.

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