Comparison of Traditional Herbal Medicine and Standard Western Medicine in the Management of Dyslipidemia

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Abstract
A comparison of a traditional herbal and standard western medicine for dyslipidemia was conducted in 316 Thai patients. Therapeutic equivalence of five brands of gemfibrozil available in Thailand and the therapeutic efficacy of gemfibrozil compared with safflower were studied using a randomized controlled double-blind design. The purpose of this study was to evaluate the efficacy and safety of gemfibrozil or safflower on plasma lipid profiles. The therapeutic outcomes were demonstrated by measurement of the mean change in lipid profiles in terms of total cholesterol, total triglyceride, and HDL-cholesterol from baseline over a 6-month treatment period. Toxicity outcomes were monitored by assessing renal toxicity in terms of blood urea nitrogen and serum creatinine and hepatotoxicity in terms of serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase. These findings suggest that in Thai dyslipidemia patients, some effects are similar. Both gemfibrozil and safflower can safely and effectively decrease serum total cholesterol and increase HDL-cholesterol. Gemfibrozil, but not safflower, can also reduce serum total triglyceride. Cost-benefit and cost-effectiveness were analyzed to demonstrate the pharmacoeconomic evaluation of the physicians’ formulary decision-making in the management of dyslipidemia in Thailand.

INTRODUCTION
Therapeutic efficacy study of gemfibrozil was compared with safflower (Catharanthus tinctorius Linn.) tea in Thai dyslipidemic patients and pharmacoeconomics compared in the management of dyslipidemia. Therapeutic efficacy of five brands of gemfibrozil available in Thailand compared with safflower tea as the alternative therapy in Thai patients who had dyslipidemia. The main outcome measure was the lipid profile: total cholesterol, total triglyceride and HDL-cholesterol. The lifetime cost-effectiveness and cost-benefit of five brands of gemfibrozil and safflower tea for the treatment of dyslipidemia were compared. The main outcome measure was the cost per year of life saved after discounting benefits and costs by 5% annually. The lifetime cost effectiveness of gemfibrozil and safflower for the treatment of primary hyperlipidemia varied according to patient population, the effectiveness of each drug in modifying lipid levels, and price of each drug. The importance of this study was relevant for one part of the health insurance concept to manage Thai health care system.

MATERIAL AND METHODS

Subjects
Patients were recruited from the out patients department of the Sawangdandin Hospital, Sakon-Nakhon Province, Thailand. The inclusion criteria were that subjects have dyslipidemia (type IIa or type IIb), were either male or postmenopausal female aged 35-65 years without liver and kidney dysfunction and have total cholesterol of 200 to 250 mg/dL and total triglyceride 150 to 500 mg/dL.

The method and study protocol had received prior ethical approval from Charles Sturt University, Australia and Srinakharinwirot University, Thailand and Sawangdandin
Hospital, Sakon-Nakhon Province, Thailand. The study and its protocols were clearly explained to all subjects in their native language by the principal investigator. Informed consent documentation, translated into Thai, was signed and obtained from each subject prior to the start of the experiment. The number per group to detect a difference in two proportions ($p_1$ and $p_2$), with power ($1-\alpha$) and significance level ($\alpha$) was calculated using Pocock’s formula (Pocock, 1977, 1982).

$$n = \left\{\frac{p_1(1-p_1)+p_2(1-p_2)}{(p_1-p_2)^2}\{z_{\alpha}+z_{\beta}\}^2}\right\}$$

set significant level ($\alpha$) = 0.05 (two-tailed)
set power ($1-\beta$) = 0.80
$p_1$ = 0.85
$p_2$ = 0.70

All subjects followed the step I and step II diet of NCEP (The National Cholesterol Education Program, USA) guidelines. The ratio of lipid, carbohydrate and protein of the total caloric intake were approximately 30%, 55%, and 15% respectively.

**Experimental Design**

The target collection periods in the study consisted of 24-week periods, which is the usual period for evaluation of dyslipidemic therapy in Thailand. Subjects were treated with a course of therapy consisting of either safflower tea or gemfibrozil. The safflower was provided as 1 g of tea bagged by automatic packaging. The dose regimen of safflower recommended by the Primary Health Care Unit, Ministry of Public Health, Thailand is 2 g of safflower tea dissolved in one glass of hot water (240 mL) taken three times daily (total of 6 g of safflower daily).

Three hundred and sixteen subjects were recruited into a double-blind randomized controlled parallel trial involving 24 weeks of each course of therapy, either gemfibrozil 300 mg twice daily (NCEP ATP II Recommended Interventions, 1994) before meals or safflower tea 2 g three times daily after meals. Efficacy was assessed after 4, 8, 12, 16, 20 and 24 weeks on each treatment. The therapeutic period consisted of a pre-treatment 24-week diet run-in period with step I and step II diet program (NCEP, 1994). The subjects were randomized to three groups: gemfibrozil (n=149), safflower tea (n=70) and control (n=97). These three groups were matched for age, sex and risk factor profile (high TC, high TG, high BP and low HDL-C). The gemfibrozil therapy group were divided to 5 subgroups by the top five (by sales) brands name of gemfibrozil available in Thailand: Brand A (n=30), Brand B (n=30), Brand C (n=30), Brand D (n=30) and Brand E (n=29) in order to compare the local manufactured product with the innovative product (Brand A). Bioequivalence was required to be the same as Brand A® as measured by the pharmacokinetic parameters. This was determined to be not more than 20% different from the innovative product.

**The Efficacy Assessment**

Patients had their drug adherence noted in a Record Form of Assessment of Drug Adherence. Any adverse drug reactions were monitored at scheduled appointments (each monthly visit) and each time the patients were presented at the hospital (Sawangdandin Hospital, Sakon-Nakhon Province, Thailand). Treatment responses were assessed at the end of the 4, 8, 12, 16, 20 and 24 weeks by lipid profile for total cholesterol, total triglyceride and HDL-cholesterol. All data were recorded in the dyslipidemia treatment cards and data collection forms. Other measures taken were body mass index, waist-hip ratio and routine physical checkup. Evidence of toxicity was evaluated by liver function test (SGOT:serum glutamic oxaloacetic transaminase or AST:aspartate transferase) and SGPT:serum glutamic pyruvic transaminase or ALT:alanine transferase) and renal function test (SCR:serum creatinine and BUN:blood urea nitrogen) at the start and the end of therapy.
Data Analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS 7.5.1, 1996). Within treatment changes from baseline were assessed by students t-test. The significance of differences before and after treatment within the safflower tea and gemfibrozil groups were analyzed by Wilcoxon’s signed rank test. The consistency of the treatment effect was assessed using ANOVA. A stepwise regression analysis for percentage change from baseline was carried out to detect independent predictors of the efficacy of safflower and gemfibrozil.

RESULTS AND DISCUSSION

Therapeutic Efficacy Study of Gemfibrozil Available in Thailand Compared with Safflower Tea in Thai Dyslipidemic Patients

Mean age of the subjects were 50±15 years (range 35 to 65 years). The lipid profiles of the subjects during the 6-month therapy were shown in terms of total cholesterol (TC), total triglyceride (TG) and HDL-cholesterol (Fig. 1-3). The mean lipid profile by total cholesterol at baseline of the gemfibrozil, safflower therapy group and the control group were not significant among the three groups at 264.46±54.64, 258.13±49.42 and 239.21±46.61 mg/dL, respectively.

The statistical assessments using students t-test demonstrated significant difference in the lipid profile within the first 8-weeks of therapy. Gemfibrozil reduced mean TC levels from baseline by 66.24, 50.75, 57.00, 43.52, and 42.59 mg/dL for Brand A, B, C, D, and E, respectively compared with safflower and the control group (36.12 and 20.54 mg/dL, respectively, p≤0.01). Mean TG levels decreased from baseline 87.76, 80.00, 69.12, 104.15, and 81.53 mg/dL with gemfibrozil: Brand A, B, C, D, and E, respectively (p≤0.05) and only 3.54 mg/dL with safflower (p=0.90), compared with TG increase in control group (3.98 mg/dL, p=0.89). Mean HDL-C levels increased from baseline by four treatments: safflower elevated HDL-C by 7.39 mg/dL (p=0.01) whereas it was elevated 9.09 mg/dL (p=0.01) by the control group in the first 8-weeks of therapy compared with gemfibrozil group: 8.07 and 12.14 mg/dL for Brand C and D (p≤0.01) in the 12-weeks of therapy.

The statistical assessments using Analysis of Variance (ANOVA) demonstrated significant difference from baseline of lipid profile: TC and TG levels (p≤0.01), but not in HDL-C levels (p=0.74) among the seven therapy groups. Mean difference of the lipid profile: TC, TG and HDL-C compared to baseline in each group were not significantly different from the innovator’s product: Brand A (p>0.05).

Pharmacoeconomics Comparison between the Standard Western Medicine and the Traditional Thai Medicine in Management of Dyslipidemia

The controlled trial randomized all dyslipidemic out-patients of the hospital. The intent-to-treat analysis included 316 patients [73.42% (232) women; 26.58% (84) men; mean age 53.80 y, range 40-65 y] who provided post treatment efficacy data. The cost-effectiveness analysis included data on these 316 patients since the long term-study had shown that up to 60% of patients successfully treated in dyslipidemia as primary prevention for the incidence rates of cardiovascular heart disease and coronary heart disease (CHD). Adverse events were rare and not significantly different among the agents. As a result, they were not factored into the cost analysis. The percentage change in lipid parameters with treatment are summarized in Table 1. Costeffectiveness calculated as annual acquisition cost/percentage TC and TG reduction and HDL-C induction are shown in Tables 2.

Selecting optimal drug therapy may require a comparison of different agents in the same class. It is well known that the acquisition cost of a drug is only a part of the cost-effectiveness equation. More expensive agents are not always more cost effective. This is clearly the case with the standard western medicine: a fibric derivative - gemfibrozil.

The results indicate that gemfibrozil is associated with greater TC and TG
reductions compared with 6 g/d of safflower and non-pharmacological treatment. Brand C provided reduction in TC similar to or greater than all the other brands with milligram-equivalent dosages of gemfibrozil. It reduced TC by 62.09%. Brand A provided reduction in TG by 88.28% which is similar to or greater than all the other brands. The control group provided reduction in HDL-C greater than all the other pharmacological treatments. It induced HDL-C by 10.04%. Brand D was the most cost effective on TC and TG reduction at 26.44 and 18.28 Baht/year/percentage reduction respectively. Safflower 6 g/d was the most cost effective at 222.26 Baht/year/percentage HDL-C induction.

The results of other clinical trials support aggressive HDL lowering of gemfibrozil in patients with CHD (Young, 2001). Using the treated TC level of 200 mg/dL, TG level of 150 mg/dL and HDL-C level of 45 mg/dL as the treatment goals, patients with baseline TC above 200 mg/dL, TG above 150 mg/dL and HDL-C below 45 mg/dL could not achieve this goal taking the other antidyslipidemic agents.

Our study had several limitations. First, we used AWPs based on a national database (MIMS annual Thailand, 2000-2001), which may not reflect the cost to individual institutions or to patients. Determining the cost of pharmaceuticals can be difficult if contracted prices, rebates, and “bundled” or “value-added” products are involved. It has been argued that the benefit of gemfibrozil therapy in reducing mortality goes beyond just HDL-C reduction (Frick, 1993; Young, 2001). Discussion of the merits of such an argument is beyond the scope of this study. In spite of this the National Cholesterol Education Program (NCEP, 1994) expert panel recommends that LDL levels be used as the short-term treatment goal in patients taking HMG-Co A reductase inhibitors or statins. Statin dosages that achieve these goals at the lowest cost in the individual patient are preferred. At the time this trial was conducted, among seven different treatment regimens with five brands of gemfibrozil, safflower tea and non-pharmacological treatment, five brands of gemfibrozil were approved by the Food and Drug Administration (FDA) and included in the analysis. Since that time, higher dosages of gemfibrozil (900 mg/d) have been approved. In addition, a new fibrate derivative, fenofibrate has been marketed. The cost effectiveness of these regimens used need to be examined in future studies.

It can be concluded that gemfibrozil, based on the efficacy results of the Helsinki Heart Study (Frick, 1997) and using 2000-2001 AWPs, is the most effective agent in the primary prevention of the atherosclerosis and coronary heart disease (CHD) for reducing TC and TG levels in the dosage of 600 mg/d, with a cost that is justified based on comparisons with the other commonly prescribed agents in this class whereas safflower, based on the ethnobotanical results, is the most effective agent inducing HDL-C levels in the dosage of 6 g/day. It can be an effective alternative treatment of dyslipidemia for the rural Thai people as well as the urban people who prefer the natural therapy in this century.

ACKNOWLEDGEMENTS

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Literature Cited

National Cholesterol Education Program. 1994. Second report of the expert panel on

Tables

Table 1. Mean percentage changes from baseline in lipid parameters in term of TC, TG and HDL-C in 316 dyslipidemic patients (35-65 Y) taking different brands of gemfibrozil (n=149) and safflower (n=70) compared to the control group (n=97) with no treatment.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dose (mg)</th>
<th>Number of patients</th>
<th>Mean Percentage Change from Baseline&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>TC</td>
</tr>
<tr>
<td>Brand A</td>
<td>600</td>
<td>30</td>
<td>-55.57&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Brand B</td>
<td>600</td>
<td>30</td>
<td>-52.73&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Brand C</td>
<td>600</td>
<td>30</td>
<td>-62.09&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Brand D</td>
<td>600</td>
<td>30</td>
<td>-57.42&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Brand E</td>
<td>600</td>
<td>29</td>
<td>-41.38&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Safflower</td>
<td>6000</td>
<td>70</td>
<td>-28.08</td>
</tr>
<tr>
<td>Control</td>
<td>-</td>
<td>97</td>
<td>-19.39</td>
</tr>
</tbody>
</table>

<sup>a</sup> Least square mean
<sup>b</sup> statistically significant; p<0.05

Table 2. Cost-effectiveness based on Baht/year/Percentage TC reduction, TG reduction and HDL-C induction in 316 dyslipidemic patients (35-65 Y) taking different brands of gemfibrozil (n=149) and safflower (n=70) compared to the control group (n=97) with no treatment.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily Dose (mg)</th>
<th>Baht/year/TC decrease</th>
<th>Baht/year/TG decrease</th>
<th>Baht/year/HDL increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand A</td>
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<td>104.04</td>
<td>65.49</td>
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<td>Brand B</td>
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<tr>
<td>Brand C</td>
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<td>28.92</td>
<td>38.14</td>
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</tr>
<tr>
<td>Brand D</td>
<td>600</td>
<td>26.44</td>
<td>18.28</td>
<td>290.88</td>
</tr>
<tr>
<td>Brand E</td>
<td>600</td>
<td>37.05</td>
<td>26.16</td>
<td>402.36</td>
</tr>
<tr>
<td>Safflower</td>
<td>6000</td>
<td>58.49</td>
<td>66.80</td>
<td>222.26</td>
</tr>
</tbody>
</table>
Figures

Fig. 1. Mean ± SD of total cholesterol (mg/dL) versus time of visit (week) in 316 dyslipidemic patients (35-65 Y) taking different brands of gemfibrozil (n=149) and safflower (n=70) compared to the control group (n=97) with no treatment.

Fig. 2. Mean ± SD of total triglyceride (mg/dL) versus time of visit (week) in 316 dyslipidemic patients (35-65 Y) taking different brands of gemfibrozil (n=149) and safflower (n=70) compared to the control group (n=97) with no treatment.
Fig. 3. Mean ± SD of HDL-cholesterol (mg/dL) over the first 6 visit in 316 dyslipidemic patients (35-65 Y) taking different brands of gemfibrozil (n=149) and safflower (n=70) compared to the control group (n=97) with no treatment.