ORIGINAL ARTICLE

# The Effect of Pravastatin in Patients with Primary Hyperlipidaemia

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## Summary

Thirty-four (34) subjects with primary hyperlipidaemia were enrolled for this study. After low fat dietary therapy for 6 weeks, subjects whose serum total cholesterol fell to below 6.2 mmol/l (11 subjects) were excluded from the study and those whose serum total cholesterol were 6.2 mmol/l or more (23 subjects) were started on pravastatin 10 mg nocte. After 8 weeks of treatment, there was a significant decrease in the mean total cholesterol and LDL-cholesterol. However 13 of the subjects still had serum total cholesterol 6.2 mmol/l or more and their pravastatin dose was increased to 20 mg nocte. After 12 weeks, there was a significant reduction in triglyceride, total cholesterol and LDL-cholesterol. There was also a significant increase in HDL-cholesterol. The triglyceride fell by a mean of 15.7%, total cholesterol by a mean of 18.1% and LDL-cholesterol by a mean of 26.3%. HDL-cholesterol on the other hand, increased by 19.4%. The subjects whose total cholesterol fell below 6.2 mmol/l at week 8 had significantly lower total cholesterol to begin with than those whose total cholesterol failed to do so and hence were commenced on 20 mg pravastatin. This suggests that the optimum dose of the drug is dependent on the initial level of total cholesterol.

We conclude that pravastatin is effective as a lipid lowering agent.

*Key Words:* Hyperlipidaemia, Cholesterol, Triglyceride, Pravastatin

## Introduction

Hyperlipidaemia is a well known independent major risk factor for cardiovascular disease[1]. Several studies have shown that treating hyperlipidaemia leads to regression of atherosclerotic plaques and reduction in coronary mortality[2,3,4]. Inhibitors of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase have been found to be effective in reducing serum cholesterol levels by inhibiting the de novo synthesis of cholesterol. Several of these agents have been marketed and one such inhibitor which was recently approved in this country is pravastatin. This study examines its effect in patients with primary hyperlipidaemia in a local population.

## Subjects and Methods

Thirty-four (34) subjects were enrolled for this study. The subjects were selected based on their elevated serum cholesterol (> 6.2 mmol/L) in a screening program for hyperlipidaemia. Written consent was obtained from all the subjects. None of the subjects had a history of diabetes mellitus or hypertension and were not on drugs known to affect the serum lipid levels. The subjects were asked to fast overnight and

to come the following day for an examination. Blood was taken for serum triglycerides, total cholesterol, low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) determinations (week-7). The subjects were then advised on a low fat diet and asked to come for a repeat examination after 6 weeks (week-1) followed by another blood test 1 week later (week 0). At week 0, if the subjects' average serum total cholesterol at week-1 and week 0 were less than 6.2 mmol/L, they were advised to continue on the diet and excluded from the study. If the average total cholesterol of the subjects were more than or equal to 6.2 mmol/L, they were prescribed pravastatin 10 mg nocte. The subjects were then followed 4 (week 4) and 8 (week 8) weeks later. If the serum total cholesterol of the subjects were above 6.2 mmol/L at week 8, the dose of pravastatin was increased to 20 mg nocte. For those subjects whose total cholesterol were less than 6.2 mmol/L at week 8, they were continued on the 10 mg nocte dose. The subjects were then followed up 4 weeks' later (week 12). All blood was taken in the fasting state. Apart from the lipid profile, the serum levels of alanine transferase (ALT), aspartate transaminase (AST), creatine kinase (CK) and creatinine were also measured at the various points. The study design is shown in Figure 1.

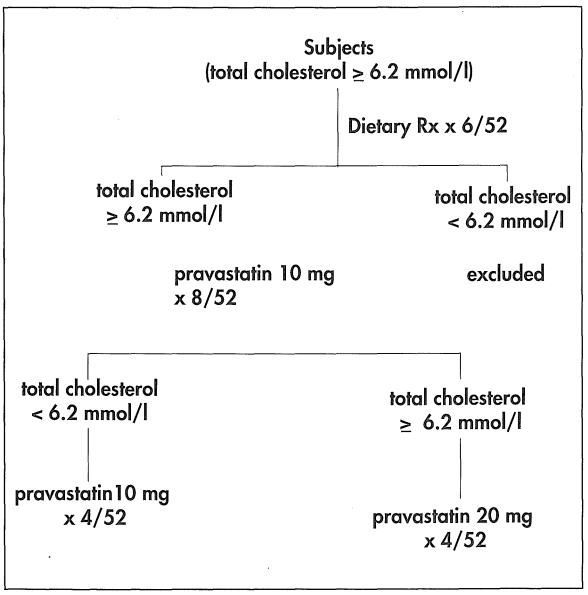


**Fig. 1: Study design**

### Assays

**Triglycerides, Total Cholesterol, High Density Lipoprotein Cholesterol** : The assays were done by enzymatic method using reagents from Bio Merieux (France) by Hitachi 705 chemistry analyser (Japan)

**Low Density Lipoprotein Cholesterol** : This was calculated by subtracting HDL-cholesterol and VLDL-cholesterol from total cholesterol.

**Alanine Transferase (ALT), Aspartate Transaminase (AST), Creatine Kinase (CK):** The assays were done by kinetic method using reagents from Bio Merieux (France) by Hitachi 705 chemistry analyser (Japan)

**Creatinine** : The assay was done by calorimetric method using reagents from Boehringer Mannheim (Germany) by Hitachi 705 chemistry analyser (Japan)

### Statistical Analysis

A non parametric test, Wilcoxon signed rank test was used to analyse paired data and Mann Whitney test was used to analyse unpaired data using Microstat statistical programme.

**Table I**
**Mean (± s.d.) age, initial serum triglyceride, total cholesterol, LDL-cholesterol and HDL-cholesterol of patients who responded and did not respond to diet**

| | Responders (N = 11) | Non Responders (N = 23) |
|---|---|---|
| Age (years) | 45.6 ± 9.8 | 47.6 ± 7.4 |
| Triglyceride (mmol/l) | 2.22 ± 0.89* | 1.66 ± 0.81* |
| Total chol (mmol/l) | 7.05 ± 0.87 | 7.33 ± 0.80 |
| LDL-chol (mmol/l) | 5.13 ± 0.96 | 5.45 ± 0.92 |
| HDL-chol (mmol/l) | 0.92 ± 0.10** | 1.12 ± 0.29** |

* $p < 0.05$
** $p < 0.01$

**Table II**
**Mean (± s.d.) serum triglyceride, total cholesterol, LDL-cholesterol and HDL-cholesterol at 0, 4 and 8 weeks of all patients treated with pravastatin (N = 23)**

| | Week 0 | Week 4 | Week 8 |
|---|---|---|---|
| Triglyceride (mmol/l) | 1.62 ± 0.79 | 1.53 ± 0.74 | 1.58 ± 0.64 |
| Total chol (mmol/l) | 6.83 ± 0.51 | 6.12 ± 0.64*** | 6.15 ± 0.69*** |
| LDL-chol (mmol/l) | 5.20 ± 0.77 | 4.28 ± 0.83*** | 4.32 ± 0.67*** |
| HDL-chol (mmol/l) | 1.03 ± 0.16 | 1.21 ± 0.37* | 1.10 ± 0.22 |

* $p < 0.05$
*** $p < 0.001$
*(compared to week 0)*

**Table III**
**Mean (± s.d.) serum triglyceride, total cholesterol, LDL-cholesterol, HDL-cholesterol, ALT, AST, CK and creatinine at 0, 4, 8 and 12 weeks of patients on 10 mg pravastatin (N = 10)**

| | Week 0 | Week 4 | Week 8 | Week 12 |
|---|---|---|---|---|
| Triglyceride (mmol/l) | 1.73 ± 1.00 | 1.55 ± 0.82 | 1.61 ± 0.66 | 1.65 ± 0.65 |
| Total chol (mmol/l) | 6.58 ± 0.26 | 5.90 ± 0.61** | 6.00 ± 0.74* | 5.34 ± 0.46*** |
| LDL-chol (mmol/l) | 4.90 ± 0.61 | 4.13 ± 1.02* | 4.14 ± 0.65** | 3.54 ± 0.57*** |
| HDL-chol (mmol/l) | 1.03 ± 0.17 | 1.23 ± 0.41 | 1.10 ± 0.25 | 1.07 ± 0.22 |
| ALT (IU/L) | 19.6 ± 10.6 | 28.6 ± 24.5 | 33.6 ± 24.8 | 24.2 ± 17.7 |
| AST (IU/L) | 26.0 ± 17.4 | 31.9 ± 19.5 | 27.3 ± 13.6 | 27.0 ± 11.0 |
| CK (IU/L) | 107.5 ± 52.8 | 143.2 ± 102.8 | 111.0 ± 48.0 | 124.6 ± 62.4 |
| Creat (umol/L) | 84.3 ± 25.3 | 87.9 ± 21.0 | 89.8 ± 22.3 | 82.0 ± 20.2 |

* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$
*(compared to week 0)*

**Table IV**
**Mean (± s.d.) serum triglyceride, total cholesterol, LDL-cholesterol, HDL-cholesterol, ALT, AST, CK and creatinine at 0, 4, 8 and 12 weeks of patients on 10 mg pravastatin from week 0 till week 8 and on 20 mg pravastatin from week 8 (N = 13)**

| | Week 0 | Week 4 | Week 8 | Week 12 |
|---|---|---|---|---|
| Triglyceride (mmol/l) | 1.53 ± 0.60 | 1.50 ± 0.70 | 1.55 ± 0.66 | 1.29 ± 0.60* |
| Total chol (mmol/l) | 7.02 ± 0.58 | 6.28 ± 0.63*** | 6.28 ± 0.65** | 5.75 ± 0.59*** |
| LDL-chol (mmol/l) | 5.43 ± 0.83 | 4.39 ± 0.67*** | 4.46 ± 0.67** | 4.00 ± 0.75*** |
| HDL-chol (mmol/l) | 1.03 ± 0.15 | 1.20 ± 0.35* | 1.10 ± 0.21 | 1.23 ± 0.43* |
| ALT (IU/L) | 28.6 ± 15.5 | 26.9 ± 18.8 | 27.9 ± 17.3 | 22.1 ± 11.9 |
| AST (IU/L) | 25.3 ± 10.9 | 29.7 ± 12.4 | 26.0 ± 11.2 | 25.9 ± 6.4 |
| CK (IU/L) | 106.3 ± 60.4 | 111.9 ± 50.5 | 117.3 ± 51.2 | 100.5 ± 38.1 |
| Creat (umol/L) | 86.9 ± 24.6 | 87.1 ± 21.1 | 98.4 ± 62.9 | 82.4 ± 6.4 |

** p < 0.05*
*** p < 0.01*
**** p < 0.001*
*(compared to week 0)*

## Results

Of the 34 subjects, 11 (32.4%) responded to dietary treatment when their serum total cholesterol fell below 6.2 mmol/L after 6 weeks. The other 23 subjects were started on pravastatin 10 mg nocte. The mean (± s.d.) age, serum triglyceride, total cholesterol, LDL and HDL cholesterol of the subjects who responded and who did not respond to dietary treatment are shown in Table I. There were no significant difference in the means of the age and total cholesterol between the responders and the non-responders but the triglyceride was higher and HDL-cholesterol was lower in the responders than the non-responders.

The mean (± s.d.) serum triglyceride, total cholesterol, LDL and HDL cholesterol of the subjects treated with pravastatin 10 mg nocte at baseline, week 4 and week 8 are shown in Table II. Of the 23 treated subjects, serum total cholesterol fell to less than 6.2 mmol/L at week 8 in 10 subjects. They were continued on 10 mg nocte whilst the other 13 subjects whose total cholesterol were more than 6.2 mmol/L were continued on 20 mg nocte. At week 12, for those on 10 mg nocte, serum total cholesterol remained below 6.2 mmol/L for all the subjects whilst for those on 20 mg nocte, serum total cholesterol fell below 6.2 mmol/L in 10 of the 13 subjects. There were no significant changes in the weight of patients on either

10 mg or 20 mg during the treatment period. The biochemical profiles for subjects on 10 mg nocte and 20 mg nocte are shown in Table III and IV respectively. Only 3 patients complained of myalgia, 1 patient complained of bloatedness and 1 patient complained of epigastric discomfort at the end of the first month of treatment. There were no significant changes in the serum AST, ALT and CK levels. They were continued on the drug and the symptoms subsided later. There was no other symptoms reported by other patients.

## Discussion

HMG-CoA reductase enzyme is responsible for the conversion of HMG-CoA to mevalonic acid in a rate limiting stage of cholesterol biosynthesis[5]. Pravastatin is a derivative of mevastatin – the first HMG-CoA reductase inhibitor[6]. In this study, 32.4 % (11/34) of the subjects had reduction in their serum total cholesterol to below 6.2 mmol/L by dieting alone showing that dieting is indeed effective in lowering serum total cholesterol. Of the subjects given pravastatin 10 mg, 10 of the 23 subjects had reduction in their total cholesterol level at week 8. Of the remaining 13 subjects given pravastatin 20 mg, another 10 subjects had reduction in their total cholesterol level at week 12. This gave an overall response rate of 87.0% (20/23) in achieving serum total cholesterol of less than 6.2 mmol/L. For those on pravastatin 10 mg, there were significant reductions in the serum total cholesterol and LDL cholesterol – 18.8% and 27.8% respectively when compared to baseline (week 0). For those on pravastatin 20 mg, there were significant reductions in the serum total cholesterol, LDL cholesterol and triglyceride – 18.1%, 26.3% and 15.7% respectively and there was also a significant increase in HDL cholesterol – 19.4% when compared to baseline (week 0). For those who responded to 10 mg pravastatin at week 8, their mean initial total cholesterol (week 0) was significantly lower than those who did not respond and was put on 20 mg pravastatin ($6.58 \pm 0.26$ vs $7.02 \pm 0.58$ mmol/L – $p < 0.05$). The findings in this study are comparable to others[7,8,9,10] – a reduction in total cholesterol of between 13 - 28% and LDL-cholesterol of between 18 - 34 %. The reduction in triglyceride was more variable ranging from non significant to 25%. The increase in HDL-cholesterol was also variable ranging from non significant to 15%. There was no significant change in the levels of serum AST, ALT, creatine kinase and creatinine before and during treatment in our patients on either 10 mg or 20 mg dose. Others had reported minor transient increase in liver function indices but major increases in serum transaminases were uncommon[11,12].

In conclusion, pravastatin is effective in lowering serum total cholesterol, LDL-cholesterol and triglyceride and increasing serum HDL-cholesterol. The drug is well tolerated and thus is a useful adjunct to dietary therapy in the management of hyperlipidaemia.

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