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ORIGINAL ARTICLE

Effects of treatment with a commercially available St John's Wort product (Movina®) on cholesterol levels in patients with hypercholesterolemia treated with simvastatin

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Abstract

Objective. To assess the effect of treatment with a St John's Wort product (Movina®) on cholesterol levels (total cholesterol, LDL-cholesterol, and HDL-cholesterol) in patients with hypercholesterolemia on treatment with a stable dose of simvastatin. *Design.* Controlled, randomized, open, crossover pharmacodynamic study. *Setting.* Two primary healthcare centres. *Intervention.* Patients were treated with Movina® one tablet (containing 300 mg of Hypericum perforatum) twice daily and control (a commercially available multivitamin tablet, Vitamineral®). The trial started with a run-in period of 4 weeks. Then the treatment order between control and active treatment was decided (randomization using sealed envelopes). The duration of each treatment period was 4 weeks and simvastatin treatment was kept unchanged during the whole study period (12 weeks). *Subjects.* Twenty-four patients with hypercholesterolemia treated with a stable dose of simvastatin (10–40 mg daily) for at least three months. *Main outcome measures.* Assessments of total cholesterol, HDL- cholesterol, LDL-cholesterol, and triglycerides were performed in the morning with the patients in a fasting condition. *Results.* All patients completed the study. LDL-cholesterol was significantly increased during active treatment compared with control. Thus, the mean LDL-cholesterol after 4 weeks' active treatment was 2.72 mmol/L compared with 2.30 mmol/L after treatment with control ($p < 0.0001$). An increase in total-cholesterol was also observed (5.08 mmol/L compared with 4.56 mmol/L, $p < 0.0001$). *Conclusion*. Products containing St John's Wort should not be given to patients with hypercholesterolemia who are on treatment with simvastatin.

Key Words: *Hypericum perforatum, hypercholesterolemia, interactions, LDL-cholesterol, simvastatin, St John's Wort*

Use of natural health products, including herbal medicines and vitamins, is widespread [1,2]. With expanding use, there is an increased focus on the possibility that these products may interact with prescribed drugs and alter their metabolism [3]. Clinical trials and case reports have found that St John's Wort (Hypericum perforatum) in particular may cause important interactions [4–7]. Movina® is a commercially available product containing hypericum perforatum (St John's Wort). Each tablet contains 300 mg of active substance and should be given twice daily. In 2005, 49 040 packs (each package containing the recommended dose for 1 month) were sold in Sweden and the total cost for this treatment was SEK 8 582 000 [8]. Movina® is used in Sweden for indications of mild depression, mild anxiety disorders, and occasional sleep disturbances. The documentation in depression is contradictory and studies where the effects seem to be poor have been published [9]. On the other hand, there are also studies suggesting a good antidepressive effect, well in line with conventional therapy [10].

St John's Wort-containing products could induce the intestinal drug transporter (intestinal P-glycoprotein/MDR1) as well as intestinal and hepatic cytocromes (CYP 3A4). These parallel inducing effects are expected to decrease intestinal absorption and to increase hepatic first-pass clearance of common P-glycoprotein/MDR1 and CYP3A4 substrates [11]. In pharmacokinetic studies a 14-day course of

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St John's Wort (Hypericum perforatum) is used in Sweden for mild depression, mild anxiety disorders and occasional sleep disturbances. Many patients are also treated with simvastatin for hyperlipidemia. This short-term study shows that:

- Combined therapy with simvastatin and St John's Wort results in a significant increase of LDL-cholesterol and total cholesterol.
- Patients treated with simvastatin should therefore, when taking drugs containing St John's Wort, be checked for their lipids more carefully, and be recommended to avoid this combination.

St John's Wort administration significantly induced the activity of CYP3A4 as measured by changes in alprazolam pharmacokinetics [12]. Long-term administration of St John's Wort may thus result in diminished clinical effectiveness for all drugs that are CYP 3A4 substrates. Simvastatin undergoes extensive first-pass metabolism, producing inactive metabolites, in the intestinal wall and liver, which is primarily mediated by P450 (CYP3A4). Thereafter, unchanged simvastatin, a lactone prodrug, is converted to its active form simvastatin hydroxy acid, by esterases or non-enzymatic hydrolysis in blood [13,14]. Pharmacokinetic studies suggest that St John's Wort-containing products decrease the plasma concentrations of simvastatin [15]. The clinical importance of these findings is, however, unclear. There are a few reports to regulatory authorities suggesting that there may be an interaction of clinical importance and that the clinical effectiveness of simvastatin thereby could be affected by concomitant medication with St John's Wort-containing products [16]. Against this background, we decided to perform a randomized, controlled, crossover study to evaluate if there were any clinically relevant pharmacodynamic interactions between a commercially available St John's Wort-containing product (Movina®) and simvastatin. Movina® was given in a fixed dose for 4 weeks to patients with hypercholesterolemia treated with a stable dose of simvastatin for at least 3 months. The effects on LDL-cholesterol, total-cholesterol, HDL-cholesterol, and triglycerides were assessed.

Materials and methods

A total of 24 patients with hypercholesterolemia on treatment with a stable dose of simvastatin (10–40 mg once daily) were included in the study. Patients also had other medications and the median number of other drugs was 2.5, with a range from 0 to 10. There were 14 males and 10 females and their mean age was 64 years, range 54–78 years. Nine patients had diabetes mellitus, 9 had cardiovascular disease and 14 patients had hypertension.

The study was approved by the Swedish Medical Products Agency and the Regional Ethical Board in Western Sweden.

The study was performed as a randomized, open, crossover study, where the approved St John's Wort-containing product Movina® was compared with an inactive control (a commercially available vitamin product named Vitamineral®). Patients were recruited from the primary healthcare centres in Mölnlycke and Landvetter in the Western region of Sweden. Eligible patients were identified by the routinely used data system at the primary healthcare centres. Patient characteristics are given in Table I. Patients were invited by an introductory letter which included information on the study. The information leaflet was approved by the regional ethical board and it was sent home to eligible patients. Those who were willing to participate signed an informed consent and were included in the study. No record was made of those patients who did not respond to the information letter.

Exclusion criteria were: unstable angina pectoris, recent myocardial infarction (within a year), recent stroke (within a year), cardiac failure, HIV, and dementia. Furthermore, patients on active treatment with drugs that could interact with St Johns Wort were excluded. Thus, treatment with birth control pills, warfarin, theophylline, cyclosporine, amitryptiline, nortriptiline, digoxin or sertraline was not allowed. The reason for these exclusion criteria were that clinically important interactions between St John's Wort products and these medical products have been clearly demonstrated.

The study started with a run-in period and at the initial visit (Week 0) the patients were informed

Table I. Study population (baseline characteristics).

Baseline characteristics	Mean ± SD
Weight (kg)	81.9 ± 17.2
Height (cm)	170 ± 8.5
Body mass index	28.3 ± 4.9
Systolic/diastolic blood pressure (mmHg)	144 ± 18.9/80 ± 8.8
Total cholesterol (mmol/L)	4.89 ± 0.82
LDL-cholesterol (mmol/L)	2.46 ± 0.59
HDL-cholesterol (mmol/L)	1.66 ± 0.58
Triglycerides (mmol/L)	1.70 ± 0.70
Dose of simvastatin (mg)	20.8
Cardiovascular disease	9
Diabetes mellitus	9
Hypertension	14

about the study, inclusion and exclusion criteria were verified, and a physical examination was performed. All blood samples were obtained in the fasting condition and analysed at the central laboratory at Sahlgrenska University Hospital in Gothenburg (total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides). The laboratory was unaware of patient treatment. Patients were then to return after 4 weeks and another physical examination was performed and blood samples as described at week 0 above were collected. At week 4, the treating physician randomized (using sealed envelopes handled by a person not involved with patients) the order of active (Movina®) and control (Vitamineral®) treatment. Thus, 50% started with active treatment and the other 50% started with control treatment and all were crossed over to the other treatment modality after 4 weeks. Assessment of total cholesterol, HDL- and LDL-cholesterol, and triglycerides were then performed at the end of each treatment period (weeks 8 and 12). Compliance was verified by pill counting at each visit. The dose of simvastatin was kept unchanged during the whole study period and all patients completed the study. The mean dose of simvastatin was 20.8 mg (range 10 mg–40 mg).

Statistics

T-test for paired samples was used for statistical analyses and a p-value <0.05 was considered significant. The primary efficacy endpoint was the difference in LDL-cholesterol at weeks 8 and 12 between active treatment and control. Secondary endpoints were the corresponding difference in total cholesterol, HDL-cholesterol, and triglycerides. Power calculations showed that participation of 20 subjects would give statistical significance. The randomization procedure was performed by a person not involved with the patients.

Results

The mean LDL-cholesterol level after 4 weeks of treatment with Movina® was significantly higher compared with 4 weeks of treatment with control. Thus, the mean LDL-cholesterol level was 2.72 mmol/L during active treatment compared with 2.30 mmol/L ($p<0.0001$ (Table II). Total cholesterol was also significantly increased during active treatment (5.08 mmol/L compared with 4.56 mmol/L, $p<0.0001$) (Table II). No significant change was observed in HDL-cholesterol (1.67 mmol/L compared with 1.70 mmol/L, $p=0.46$) (Table II), while triglyceride levels were slightly increased (1.54 mmol/L and 1.30 mmol/L, $p=0.016$) (Table II). Total cholesterol and LDL-cholesterol were significantly increased by active treatment in both males and females (Table III). Triglycerides were significantly increased in females but not in males (Table III).

Discussion

Lowering of low-density lipoprotein cholesterol (LDL-cholesterol) with statins has become part of the standard treatment regimen in patients with established coronary heart disease. The Scandinavian Simvastatin Survival Study (4 S) which was published in 1994 was the first large endpoint study showing clear beneficial effects on cardiovascular morbidity/mortality with simvastatin treatment [17]. Effect on cardiovascular morbidity/mortality has been demonstrated in patients without known coronary heart disease [18], in patients with various degrees of hypercholesterolemia and coronary artery disease, and in diabetics [19–21]. In one recently published study aggressive treatment with a statin to patients with a stroke/TIA demonstrated a significant decrease in fatal and non-fatal strokes over an observation period of five years [22].

When dietary measures are not sufficient to control hyperlipidemia, pharmacological treatment may be considered. In Sweden, simvastatin is used as first-line treatment in most patients who are considered to be suitable for drug treatment [23]. Since current guidelines recommend that treatment in the secondary preventive setting and in diabetics should be intensive, large populations of patients, especially elderly patients, are treated with statins.

It has been suggested that the magnitude of the lipid-lowering effect is of importance for the

Table II. Changes in total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides after 4 weeks of treatment with control and active product (Movina®).

	Control	Active	Difference (mean ± SD)	p-value
Total cholesterol (mmol/L)	4.56 ± 0.69	5.08 ± 0.84	0.52 ± 0.45	$p<0.001$
LDL-cholesterol (mmol/L)	2.30 ± 0.42	2.72 ± 0.62	0.42 ± 0.41	$p<0.0001$
HDL-cholesterol (mmol/L)	1.70 ± 0.54	1.67 ± 0.56	−0.02 ± 0.75	$p=0.46$
Triglycerides (mmol/L)	1.30 ± 0.64	1.54 ± 0.64	0.25 ± 0.46	$p=0.0155$

T-test for paired samples was used for statistical analyses.

Table III. Changes in total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides after 4 weeks of treatment with control and active product (Movina®) in males and females.

	Control	Active	Difference (mean ± SD)	p-value
Total cholesterol (mmol/L)				
Males (n = 14)	4.46 ± 0.68	4.97 ± 0.92	0.51 ± 0.41	p = 0.0004
Females (n = 10)	4.71 ± 0.70	5.24 ± 0.73	0.53 ± 0.53	p = 0.011
LDL-cholesterol (mmol/L)				
Males	2.39 ± 0.49	2.83 ± 0.71	0.44 ± 0.38	p < 0.0009
Females	2.18 ± 0.29	2.57 ± 0.46	0.39 ± 0.47	p = 0.027
HDL-cholesterol (mmol/L)				
Males	1.52 ± 0.41	1.51 ± 0.47	−0.01 ± 0.15	p = 0.811
Females	1.94 ± 0.62	1.90 ± 0.62	−0.04 ± 0.14	p = 0.399
Triglycerides (mmol/L)				
Males	1.26 ± 0.74	1.41 ± 0.61	0.15 ± 0.43	p = 0.216
Females	1.36 ± 0.50	1.73 ± 0.69	0.38 ± 0.49	p = 0.036

T-test for paired samples was used for statistical analyses.

progression of atherosclerosis and a more pronounced reduction of LDL-cholesterol has been shown to reduce the atheroma burden by more than a modest decrease [24]. Furthermore a more aggressive reduction in LDL-cholesterol has been demonstrated to reduce the incidence of major cardiovascular events [25]. It is not known if there is a linear relationship between LDL-cholesterol reduction and cardiovascular prevention. Based on results from large studies, it could be questioned whether there may be a threshold for the beneficial effect on cardiovascular morbidity/mortality. Thus, a small reduction in LDL-cholesterol may not result in any benefit at all. In the large ALLHAT-LLT study, pravastatin was compared with usual care in a subset of patients with hypercholesterolemia. The mean difference in LDL-cholesterol levels between active treatment and control at study end was only 0.5 mmol/L. No significant benefit was demonstrated in this large study, in which more than 10 000 patients were included [26]. In another large trial, the ASCOT-LLA study, hypertensive patients with other risk factors and non-fasting total cholesterol below 6.5 mmol/L were treated with either atorvastatin or placebo for 3 years. The difference in LDL-cholesterol between groups at the end of follow-up was 0.95 mmol/L. In this study a clear benefit regarding cardiovascular morbidity was found [27]. The discrepancy in outcome between ALLHAT-LLT and ASCOT-LLA may partly be explained by the effects accomplished on LDL-cholesterol. Thus, a more modest reduction in LDL-cholesterol (0.5 mmol/L) may not be sufficient to reduce atherosclerosis and prevent cardiovascular events. On the other hand a reduction in LDL-cholesterol in a magnitude of 1 mmol/L has been shown to have a preventive effect on cardiovascular events in many large studies. The dose of atorvastatin in the ASCOT-LLA study was 10 mg and this dose caused a reduction in LDL-cholesterol in a magnitude of 1 mmol/L. The lipid-lowering potency of different statins at different doses has been compared in the CURVES study [28]. The conclusions from this study are that 10 mg of atorvastatin has an effect on LDL-cholesterol comparable to that of 20–40 mg of simvastatin.

The patients in our trial had a mean simvastatin dose of 20.8 mg. We do not know the actual absolute reduction in our patients, since they were on stable chronic medication and we did not change their simvastatin treatment. From the results given in major studies, as mentioned earlier, it could, however, be assumed that the absolute reduction achieved for our patient population would be slightly lower than 1 mmol/L but greater than 0.5 mmol/L.

The main finding in our study was that the commercially available St John's Wort product (Movina®) at a recommended dose given for one month together with simvastatin reduced the effect of simvastatin in a clinically significant way. Thus, mean total cholesterol was increased by 0.52 mmol/L and LDL-cholesterol was increased by 0.42 mmol/L. No change in HDL-cholesterol was observed, while triglycerides were slightly but significantly increased by 0.24 mmol/L.

It could be concluded that about half of the effect of simvastatin on LDL-cholesterol was lost in our patients, when they were on concomitant treatment with the St John's Wort-containing product at a recommended dose for one month. It seems quite clear from large controlled studies that the

magnitude of LDL-reduction is of importance for the cardiovascular preventive effects observed with simvastatin and other statins. Whether there is a threshold for the preventive effect of LDL-lowering therapy around 0.5 mmol/L is not known, but if this were to be the case, then the total effect on cardiovascular prevention with simvastatin would be abolished by concomitant treatment with a St John's Wort-containing product.

Our study has limitations since it was not double-blind. Bias from expectations may have occurred and carry-over effects may be present in crossover studies. The treatment periods in our study were each 4 weeks and it would seem unlikely that any clinically important carry-over effect would be present for a short-acting product such as Movina®. Furthermore, there is no reason to believe that patients or doctors would have mismanaged the diet or lipid-lowering medication during Movina® treatment in order to achieve a less satisfactory result after active treatment. The study was randomized and the assessments of lipids were performed by a central laboratory, which was blinded to treatment regimen. Furthermore, the results as regards total cholesterol and LDL-cholesterol were robust and occurred in both males and females. The results are in line with what could be expected from a product interfering with a central metabolizing enzyme of importance for simvastatin pharmacokinetics. Simvastatin lowers the levels of triglycerides and this effect was also partly inhibited by active treatment. These results were less robust compared with the effect on cholesterol. The effect was statistically significant in the total patient cohort. When the results were analysed according to gender, only females had a statistically significant increase in triglycerides. The clinical importance of this finding is unclear. Since this was a short and small study, we cannot draw any conclusions about long-term effects on cardiovascular morbidity/mortality. Such effects could only be demonstrated in a larger prospective controlled long-term trial. If simvastatin is given together with a St John's Wort-containing product, the efficacy, as measured by LDL- and total cholesterol concentration, is diminished. This will result in difficulties in reaching recommended therapeutic goals. It could therefore be concluded that these products should not be given together.

Conflict of interest statement

The authors of this paper have no conflict of interest to declare.

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References

[1] Thomas KJ, Nicholl JP, Coleman P. Use and expenditure on complementary medicine in England: A population based survey. Complement Ther Med 2001;9:2–11.
[2] Hanssen B, Grimsgaard S, Launsö L, Fönnebo V, Falkenberg T, Rasmussen NK. Use of complimentary and alternative medicine in the Scandinavian countries. Scand J Prim Health Care 2005;23:57–62.
[3] Stjernberg L, Berglund J, Halling A. Age and gender on the use of herbal medicine products and food supplements among the elderly. Scand J Prim Health Care 2006;24:50–5.
[4] Mills E, Montori VM, Wu P, Gallicano K, Clarke M, Guyatt G. Interaction of St John's wort with conventional drugs: systematic review of clinical trials. BMJ 2004;329:27–30.
[5] Johne A, Schmider J, Brockmoller J, Stadelmann AM, Stormer E, Bauer S, et al. Decreased plasma levels of amitriptyline and its metabolites on co-medication with an extract from St John's Wort (Hypericum perforatum). J Clin Psychopharmacol 2002;22:46–54.
[6] Piscitelli SC, Burstein AH, Chaitt D, Alfaro RM, Falloon J. Indinavir concentrations and St John's Wort. Lancet 2000; 355:547–8.
[7] Ruschizka F, Meier PJ, Turina M, Luscher TF, Noll G. Acute heart transplant rejection due to Saint John's Wort. Lancet 2000;355:548–9.
[8] Pharmacy information in Western Sweden (LUPP, Läkemedelsupplysningen i Västra Sverige, lupp.su@vgregion.se).
[9] Shelton RC, Keller MB, Gelenberg A, Dunner DL, et al. Effectiveness of St John's Wort in major depression: A randomized controlled trial. JAMA 2001;285:1978–86.
[10] Szegedi AS, Kohnen R, Dienel A, Kieser M. Acute treatment of moderate to severe depression with hypericum extract WS 5570 (St John's Wort): Eandomised controlled double-blind non-inferiority trial versus paroxetine. BMJ 2005;330:503–6.
[11] Durr D, Stieger B, Kullak-Ublick GA, Rentsch KM, Steinert H, Meier PJ, Fattinger K. St John's Wort induces intestinal P-glucoprotein/MDR1 and intestinal and hepatic CYP 3A4. Clin Pharmacol Therapeut 2000;68:598–604.
[12] Markowitz JS, Donovan JL, DeVane CL, Taylor RM, Ruan Y, Wang JS, Chavin KD. Effects of St John's Wort on drug metabolism by induction of cytochrome P450 3A4 enzyme. JAMA 2003;290:1500–4.
[13] Vickers S, Duncan CA, Chen IW, Rosegay A, Duggan DE. Metabolic disposition studies of simvastatin, a cholesterol-lowering prodrug. Drug Metab Dispos 1990;18:138–45.
[14] Christians U, Jacobsen W, Floren LC. Metabolism and drug interactions of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in transplant patients: Are the statins mechanistically similar? Pharmacol Ther 1998;80:1–34.
[15] Sugimoto KI, Ohmori M, Tsuruoka S, Nishiki K, et al. Different effects of St John's wort on the pharmacokinetics of simvastatin and pravastatin. Pharmacol therapeut 2001; 70:518–24.
[16] Medical Products Agency. http://www.lakemedelsverket.se
[17] Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease. Lancet 1994;344:1383–8.

[18] West of Scotland Coronary Prevention Study Group. Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study (WOSCOPS). Circulation 1998;97:1440–5.

[19] The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998;339:1349–52.

[20] Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet 2003;361:2005–16.

[21] Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes. The MIRACL Study: A randomized controlled trial. JAMA 2001;285:1711–8.

[22] The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) investigators. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006;355:549–59.

[23] Förebyggande av aterosklerotisk hjärt-kärlsjukdom (Prevention of atherosclerotic cardiovascular disease). Information from Läkemedelsverket 2006;17:16–97.

[24] Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, et al. for the REVERSAL Investigators. Effect of intensive compared with moderate lipid-lowering therapy on prognosis of coronary atherosclerosis: A randomized controlled trial. JAMA 2004;291:1071–80.

[25] LaRosa JC, Grundy SM, Waters DD, Shear C, et al. for the Treating to New Target (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005;352:1425–35.

[26] Major outcomes in moderately hypercholesterolemic hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid- Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA 2002;288:2998–3007.

[27] Sever PS, Dahlöf B, Poulter NR, Wedel H, et.al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial. The Lipid Lowering Arm (ASCOT-LLA): A multicenter randomized controlled trial. Drugs 2004;64:43–60.

[28] Jones P, Kafonek S, Laurora IL. Hunninghake D for the CURVES investigators. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin and fluvastatin in patients with hypercholesterolemia (The Curves Study). Am J Cardiol 1998;81:582–7.