

Pantethine, a derivative of vitamin B₅ used as a nutritional supplement, favorably alters low-density lipoprotein cholesterol metabolism in low–to moderate–cardiovascular risk North American subjects: a triple-blinded placebo and diet-controlled investigation

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Abstract

Safety and efficacy of a biologically active derivative of vitamin B₅ (pantethine) on total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) metabolism was studied in North American subjects at conventional low to moderate cardiovascular disease (CVD) risk. A total of 120 subjects initiated a therapeutic lifestyle change (TLC) diet 4 weeks before randomization (baseline) and maintained the diet throughout a 16-week study period; at baseline, subjects were randomized in a triple-blinded manner to either pantethine (600 mg/d, baseline to week 8, and 900 mg/d, weeks 9–16) or identically labeled, nonbiologically active placebo (n = 60 per group). We hypothesized that pantethine would lower TC and low-density lipoprotein in low–CVD-risk North American subjects in a similar manner as reported in high–CVD-risk subjects studied mainly in Italy and Japan. While sustaining a TLC diet and in comparison with placebo, pantethine demonstrated significant ($P < .005$) and sustained reductions (from baseline to week 16) in TC (6 mg/dL, 0.16 mmol/L, 3%), LDL-C (4 mg/dL, 0.10 mmol/L, 4%), and apolipoprotein B (4 mg/dL, 0.04 g/L, 5%). Our data suggest that pantethine supplementation for 16 weeks (600 mg/d for weeks 1–8 then 900 mg/d for weeks 9–16) is safe and significantly lowers TC and LDL-C over and above the effect of TLC diet alone. Although the absolute magnitude of these effects was small in these low- to moderate-risk North Americans (4–6 mg/dL), the results are noteworthy as prior studies have shown that, for each 1 mg/dL (0.026 mmol/L) reduction in LDL-C, there is a concomitant 1% reduction in overall future CVD risk.

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Abbreviations: AE, adverse event; ALT, alanine aminotransferase; Apo-B, apolipoprotein B; ATP, Adult Treatment Panel; AST, aspartate aminotransferase; CK, creatine kinase; CoQ10, coenzyme Q10; CVD, cardiovascular disease; FRS, Framingham Risk Score; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

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1. Introduction

Total cholesterol (TC) and its primary lipoprotein components (low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], and triglycerides [TGs]) are well-established factors contributing to cardiovascular disease (CVD) risk across all national and ethnic subgroups [1]. The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) in 2001 [2] was a seminal publication on management of high blood cholesterol and related disorders and is a valuable guide to the practicing clinician. All ATP reports have identified LDL-C (and associated parameters including non-HDL-C and apolipoprotein B [Apo-B]) as the primary and initial target of cholesterol-lowering/risk-reduction therapy. The introduction of a variety of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor pharmaceutical therapies (ie, the “statins”) has demonstrated LDL-C reduction as a primary therapeutic goal that can lower risks of future cardiovascular events by one thirds or greater as compared with placebo [3].

The ATP III report in 2001 (reinforced by a 2004 update [4]) reviewed multiple studies showing the benefits of statin monotherapy on reducing future CVD risk, defined “target goals” for LDL-C, and set a clinical paradigm of when to initiate statin therapy guided by the number of nonlipid CVD risk factors (ie, men >45 years, women >55 years, hypertension, smoking history) and/or calculated Framingham Risk Scores (FRSs).

The ATP III recommended that the initial approach for an individual with abnormal LDL-C commences with a more intensive lifestyle intervention known as the therapeutic lifestyle change (“TLC”) diet. Thereafter, these individuals, categorized by their risk-factor profile and/or FRS, were considered candidates for statin therapy if subsequent LDL-C levels were above a specific “goal” (ie, group 1: >160 mg/dL [4.14 mmol/L] for low FRS [<10% per decade] or 0-1 nonlipid risk factors; group 2: >130 mg/dL [3.36 mmol/L] for moderate FRS [>10% but <20% per decade] or 0-2 nonlipid risk factors; group 3: >100 mg/dL [2.58 mmol/L] for high FRS [>20% per decade] or >2 nonlipid cardiovascular risk factors including known CVD and/or diabetes).

Prior data have confirmed that lowering LDL-C by 1 mg/dL (0.026 mmol/L) in any individual could lower individual CVD 10-year risk by at least 1% [4,5]. This fact underlies the significance that lowering LDL-C, no matter what the initial risk level, can provide long-term benefits in lowering future CVD events.

Pantethine is metabolized in the body from pantothenic acid (vitamin B₅) as the biologically active substance. In conjunction with an intermediary, the aminothioliol cysteamine, they inhibit acetyl-Coenzyme A (CoA) carboxylase and HMG-CoA reductase with subsequent salient effects on TG synthesis and lipoprotein metabolism. Pantethine increases CoA levels in cells [6] and favorably modifies

lipoprotein metabolism [7,8]. Pantethine has a mild anti-platelet aggregation property [9] that can also modify the membrane fluidity of cells and platelets. These multiple mechanisms of action can contribute to the effects of pantethine in decreasing CVD risk. A prior published randomized, placebo-controlled, multicenter trial in Japan of 201 high-CVD-risk individuals demonstrated that 600 mg/d (given orally in 3 divided doses over 16 weeks) of pantethine lowered LDL-C by 15%, lowered TG by 14%, and raised HDL-C by 17% from baseline [10].

A similar well-controlled trial of pantethine and its effect on blood cholesterol and other lipometabolic factors has not been previously performed on low- to moderate-CVD-risk Western North American subjects. It has also not been established that higher doses of pantethine above 600 mg/d would provide incremental or proportional changes in serum lipid levels. Pantethine is regarded as a well-tolerated agent as described in the survey results of its clinical trials with a median pantethine dosage of 900 mg/d to be 1.4 adverse reactions per 100 subjects, most of which being classified as gastrointestinal complaints of mild severity [11]. A more recent review on the medical aspects on pantethine states that the frequency of its side effects is very low and mild [12]. Oral pantethine has been shown to be safe and effective, and an identical prescription product (Pantosin, a proprietary formulation of highly absorbable and biologically active pantethine) has been used in Japan for more than 30 years. Oral pantethine is considered a nutritional supplement in the United States (Pantesin, a proprietary formulation of highly absorbable and biologically active pantethine for North Americans) and is considered grandfathered for safe, over-the-counter use. Based on these facts regarding the efficacy of pantethine in high-CVD-risk subjects and its good tolerability, we hypothesized that pantethine would improve cholesterol metabolism in North American subjects with low CVD risk and also causes no serious adverse events (AEs) in these subjects. More specifically, our objective to test this hypothesis was to clarify the benefit of oral pantethine for subjects who are clinically less serious in terms of CVD risk but, instead, need to have particular awareness and practices for proper diets, dietary supplementation, and exercise rather than taking nonnaturally occurring potent medicines that are mainly prescribed for high-CVD-risk patients.

The purpose of this investigation was to determine the effect of 2 dosing schedules of pantethine vs placebo on blood cholesterol values over a 16-week treatment period for North American subjects in ATP III CVD risk groups 1 and 2 (initially nonstatin candidates) immediately following a 4-week TLC diet lead-in.

2. Methods and materials

2.1. Study objectives

The primary outcome was tracking changes from baseline in fasting (standard 12 hours) LDL-C levels over a subsequent

16-week study period. Additional lipoprotein parameters included fasting TC, HDL-C, TG, very-low-density lipoprotein (VLDL), lipoprotein (a), and Apo-B. Cardiometabolic outcomes included anthropomorphic measures (weight, waist circumference, skin folds [Yuhasz skinfold test]), vital signs (heart rate, blood pressure), and laboratory tests for efficacy and safety (complete blood count including platelets, high-sensitivity C-reactive protein, AST [aspartate aminotransferase], ALT [alanine aminotransferase], homocysteine, CK [creatinine kinase], and CoQ10 [coenzyme Q10]).

2.2. Study design overview

The study was performed in compliance with International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice and according to the guidelines laid down in the Declaration of Helsinki. All procedures involving human subjects were approved by Institutional Review Board Services (Aurora, Ontario, Canada) on December 22, 2008. All subjects provided consent for the study. The study was a randomized, triple-blinded, placebo-controlled trial with a 4-week diet lead-in followed by a 16-week treatment period. It was conducted at KGK Synergize, London, Ontario, Canada, and SIBR Research, Bradenton, Fla.

On April 27, 2009, a clarification to the protocol pertaining to subject inclusion was reinforced to encompass low risk (FRS 10-year risk <10%) and LDL-C less than 160 mg/dL (4.14 mmol) or moderate risk (FRS 10-year risk >10% but <20%) and LDL-C <130 mg/dL (3.36 mmol/L). A total of 152 subjects were initially enrolled and administered the TLC diet. Of the 152 subjects, 32 subjects (n = 16 per group) were enrolled under the original criteria, and 120 subjects (n = 60 per group) were found to be eligible under the clarified criteria.

Lipid profiles were measured at each study visit along with secondary outcomes and blood chemistries. Adverse events were assessed at each study visit after screening.

2.3. Subject selection

Men and women older than 21 years were recruited by advertisement or existing databases from the 2 research locations. At the initial screening visit, each potential subject was provided with an informed consent; once the consent was signed, eligibility was assessed as determined by the inclusion/exclusion criteria (Table 1). Female subjects were required to have a negative pregnancy result (serum human chorionic gonadotropin [HCG]) regardless of child-bearing potential. Each subject had a medical history and standard physical examination (excluding prostate and/or gynecologic examination) that included height, weight, waist circumference, skinfolds, heart rate, and blood pressure. Fasting blood work (12 hours) included complete blood count, TC, HDL-C, LDL-C, TG, AST, ALT, glucose, creatinine, CK, and CoQ10. Upon receipt of the screening laboratory results, the subject's information was used to

Table 1
Study subject inclusion and exclusion criteria

Inclusion criteria
Male or female aged ≥ 21 years
If female, must either not be of child-bearing potential or currently using approved methods of birth control throughout the study length and negative pregnancy test at study initiation
Meets nonstatin candidate LDL-C target goals for ATP III low risk (category I) or moderate risk (category II) after diet lead-in
Provides voluntary, written, informed consent to study participation
Exclusion criteria
Pregnancy, breast-feeding, or planning to become pregnant during the course of the trial
Currently meets ATP-III criteria for moderately high to high risk (category III)
History of gastrointestinal surgery
Current use of statins or any other prescription medication used to treat hyperlipidemia
Individuals on a diet high in soy or other food/natural products known to reduce cholesterol as a dietary supplements within 12 weeks before study entry
Use of systemic corticosteroids (oral or injectable) unless on a stable dose for >12 weeks before study entry
Planned surgery during the course of the trial
Individuals who have followed the TLC diet within 12 weeks before study entry
Alcoholic beverage consumption >2 servings per day
Individuals with any known CVD
Individuals with uncontrolled or untreated hypertension defined as systolic pressure >160 mm Hg or diastolic pressure >100 mm Hg
History of diabetes (type 1 or 2)
History of concurrent renal and/or liver disease
History of alcohol or illegal drug use within the past 1 year
History of an unstable psychiatric disorder
Immunocompromised individual or history of HIV
History of hemoglobinopathy (sickle cell, thalassemia, sideroblastic anemia)
Participation in a clinical research trial within 30 days before randomization
Use of prescribed medication or over the counter supplements for weight loss within 12 weeks before randomization
Allergy or sensitivity to investigational product ingredients
Anemia or significantly abnormal liver function (AST/ALT >2-fold above upper limit of normal)
Individuals who are cognitively impaired and/or who are unable to give informed consent
Any other condition that, in the investigator's opinion, may adversely affect the subject's ability to complete the study or its measures or that may pose significant risk to the subject

assess their ATP-III CVD risk category. In the event that a subject was in the ATP-III category of high risk (group 3), they were referred to their primary care provider for appropriate follow-up. Subjects who were overall healthy as determined by laboratory, medical history, and physical examination and who fell into ATP-III groups 1 and 2 were invited to begin the 4-week diet lead-in.

2.4. Dietary intervention and diet lead-in

Eligible subjects completed a TLC diet lead-in period of 4 weeks (defined as "baseline") to isolate and evaluate the

primary outcome (effect of pantethine on fasting LDL-C) and minimize any potential contributions from variable diets between subjects. Instruction on the TLC diet was provided by a registered dietician. The option for adding 10 to 25 g/d viscous fibers and/or 2g/d plant stanols/sterols and/or soy protein was not included in the prescribed diet during the course of this trial. A 3-day food record was provided, and subjects were instructed to complete this for any 2 weekdays and 1 weekend day before the next visit. Completed food records were returned and analyzed for average energy intake per day for protein, fats, carbohydrates, and fiber. Subjects were instructed to be fasting (12 hours) for their next and all additional study visits.

2.5. Randomization and blinding

Four weeks after starting the TLC diet, subjects were randomized in a 1:1 ratio at each site to receive either placebo or pantethine. A blocking factor was used for randomization.

Subjects randomized to either pantethine or placebo took 1 tablet 3 times per day throughout the course of the study period (baseline to week 16). The number of subjects included in the research trial at each visit and the study medication taken at each visit for subjects in the Pantestin and placebo groups is detailed in Fig. 1. All study tablets were supplied in identical blister packs at specified times during the investigation. Tablet packs could only be identified by their randomization sequence numbers. The list of identifiable sequences was maintained in a secure, locked location by the study coordinators. During subsequent study visits, subjects were required to return all blister packs dispensed at the prior session. An investigator assessed the subject's adherence to the protocol through a review of the blister packs.

2.6. Follow-up schedule

Randomized subjects returned to the clinic for follow-up at weeks 2, 4, 8, 12, and 16. Visits at weeks 2 and 4 occurred

within ± 1 day from the projected date. Visits at weeks 8, 12, and 16 occurred within ± 2 days from the projected date. Subjects were instructed to be fasting (12 hours) for all study visits.

2.7. Investigational product

The pharmaceutical grade, proprietary product Pantestin HF55 (Daiichi Fine Chemicals Co, Ltd, Takaoka, Japan) was chosen as the active investigational product (ie, pantethine) for several reasons. The most important reason was to assure consistency of the amount of pantethine in each tablet (300 mg active ingredient) and the ability to manufacture a nonactive placebo control tablet with an excipient mix identical to the active product.

The active investigational tablets (pantethine) and the identically appearing nonactive placebo tablets were manufactured by Eagle Nutritionals, Carlstadt, NJ. Subsequently, blister packs were constructed by Generic Pharmaceutical Services, Hauppauge, NY, and consisted of 2 active ingredient tablets and 1 placebo (600 mg/d dosing for weeks 1-8), 3 active ingredient tablets (900 mg/d dosing for weeks 9-16), or 3 identical placebo tablets. The investigational blister packs were labeled according to ICH-Good Clinical Practice and applicable local regulatory guidelines. The investigational blister packs were provided to KGK Synergize (London, Ontario, Canada) by Daiichi Fine Chemicals.

2.8. Safety and monitoring

Each subject was interviewed, examined, and had assessment of blood laboratories according to the predefined protocol. Adverse event was considered to be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study medication, whether it was considered related to that item. Preexisting conditions exacerbated during the study were also reported as AEs.

Participants recorded AEs in their subject diary throughout the investigation. The occurrence of any AE was assessed at each visit, documented in the study record, and classified according to the description, duration, intensity, frequency, and outcome. The investigators assessed AE and decided on the causality relationship of investigational product to the AE as most probable, probable, possible, unlikely, or unrelated. A serious adverse effect was defined as any experience that suggested a significant hazard, contraindication, major side effect, or precaution.

2.9. Statistical analyses

Required sample size was determined based upon prior published results using pantethine [10,13-16]. A minimum of 60 subjects were required to detect a difference of 10% in LDL-C between placebo and pantethine with 80% power at 5% level of significance (2 sided). Allowing for a 20% loss

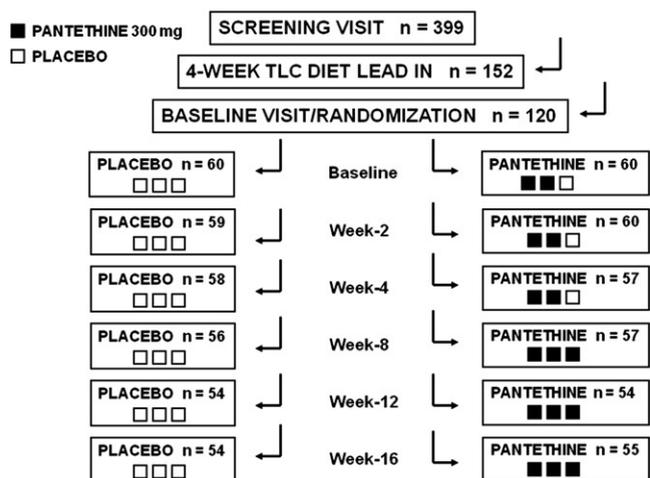


Fig. 1. Protocol flow chart.

Table 2
Baseline demographics in subjects randomized to pantethine vs placebo

Characteristic	Placebo (n = 60)	Pantethine (n = 60)	P
Age (mean ± SD)	47.3 ± 12.3	46.7 ± 11.5	NS
Sex (%)			
Female	83.3	85.0	NS
Male	16.7	15.0	NS
Race (%)			
White	93.3	96.7	NS
Other	6.7	3.3	NS

to follow-up, the per-group requirement was 75 for a total recruitment sample size of 150 subjects.

Subjects in the 2 treatment arms were compared descriptively with respect to demographic and baseline characteristics. Demographic and baseline characteristics were compared between groups using an unpaired *t* test, Fisher exact test, or χ^2 test, as appropriate, for the parameters compared. For comparison of study end points, between-group analyses were performed using a covariate adjustment. Where baseline values were missing, the value from the screening visit was used as the baseline, where applicable. The proportion of subjects in the 2 study arms withdrawing before completion of the study was tabulated and compared using a χ^2 test for comparing proportions.

Between-group comparisons of percentage compliance and the proportion of subjects at least 80% compliant were analyzed using an unpaired *t* test and a χ^2 test, respectively. For subjects who withdrew from the study, compliance was assumed to be zero subsequent to withdrawal.

Descriptive statistics were calculated for primary end points, secondary end points, and safety parameters by treatment group for each study assessment. Between-group comparisons were made using analysis of covariance, with covariance adjustment for the baseline. Where the variances were found to be heterogeneous according to Levene's test, either a simple transformation to improve homogeneity of the variances was used or, where a suitable transformation could not be found, between-group comparisons were made using Wilcoxon 2-sample tests. For between-group statistical comparisons, data missing subsequent to week 2 (visit 4) were imputed using the last-value-carried-forward technique using the last available postrandomization observation. When applicable within-group statistical comparisons were conducted using a paired *t* test. Last-value-carried-forward method was used for data missing subsequent to week 2.

The number of AEs was summarized by treatment group with counts and percentages, a between-group comparison of the proportion of subjects experiencing AEs was made using a χ^2 test, and between-group comparison of counts was performed using Wilcoxon 2-sample test.

SAS version 9.1 (SAS Institute Inc. Cary, NC, USA) was used to perform the statistical analysis, and probability values < .05 were considered to be statistically significant.

3. Results

There were no significant differences in baseline demographics between subjects randomized to pantethine or placebo; however, women represented 83% to 85% of the study population, and 93% to 97% of the participants were white (Table 2).

3.1. Effects on lipid parameters

There was some reduction in all subjects for TC and LDL-C from screening to baseline during the 4-week TLC diet lead-in (Fig. 2). By week 2 after randomization, there was a significant lowering of TC, LDL-C, and Apo-B in subjects taking pantethine as compared with placebo; this was sustained up to the end of the active study period (16 weeks). However, the magnitude of the LDL-C reduction in the pantethine group was greatest at week 2 (7%), drifting to a total of 4% reduction at week 16. It was observed (Fig. 2) that there was a trend toward higher LDL-C in both the pantethine and placebo groups from weeks 2 to 16 with values being maintained at a

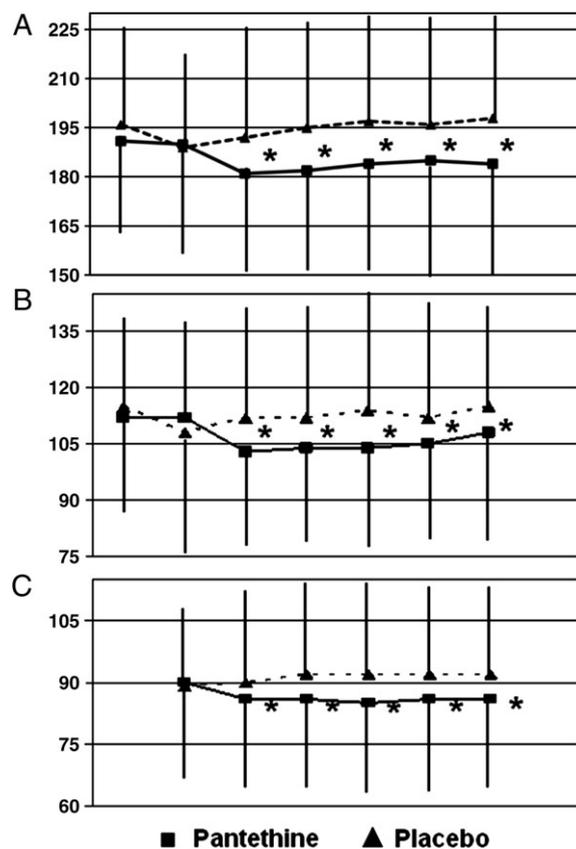


Fig. 2. Changes in serum TC, LDL-C, and Apo-B levels during the study period. Serum TC levels (panel A), LDL-C (panel B), and Apo-B (panel C) at screening, baseline, and weeks 2, 4, 8, and 12 of the study period. Data are in milligrams per deciliter, means ± SD. Triangles indicates placebo; squares, pantethine; asterisk, *P* < .05 (between-group statistical comparisons were conducted using analysis of covariance, adjusting for baseline as a covariate).

higher level in subjects on placebo during the 16 weeks of the study. The increase in dose of pantethine from 600 to 900 mg/d from weeks 8 to 16 did not appear to produce additional changes in LDL-C. From baseline to week 2 and up to week 16, there were no significant changes in TC, LDL-C, or Apo-B in the placebo group. In comparison from baseline to week 16 in the pantethine group, there was a reduction in TC of 6 mg/dL, 0.16 mmol/L, or 3%; a reduction in LDL-C of 4 mg/dL, 0.10 mmol/L, or 4%; and a reduction of Apo-B of 4 mg/dL, 0.04 g/L, or 5%.

After 16 weeks of study medication, there was a nonsignificant ($P = .064$) reduction in serum TGs in the pantethine group (105 ± 44.6 mg/dL) compared with placebo (120 ± 62.3 mg/dL). At the termination of the study period, there was no statistical difference in HDL-C between placebo and pantethine (59 ± 17.7 mg/dL vs 55 ± 11.5 mg/dL, respectively). Lipoprotein (a) was also found to be unchanged regardless of whether the subject was taking placebo or pantethine ($P = .655$).

The TC/high-density lipoprotein (HDL) ratio and non-HDL-C (TC – HDL-C) were significantly and consistently lowered in subjects on pantethine vs placebo ($P = .007$ and $P < .001$, respectively).

3.2. Effects on anthropomorphic parameters and blood chemistries

There was no statistical difference between systolic blood pressure at baseline or at the end of week 16 for subjects randomized to placebo vs pantethine (109 ± 13.9 mm Hg vs 110 ± 12.3 mm Hg, respectively; $P = .219$). There were also no statistical differences between body mass index or waist circumference at baseline or at the end of 16 weeks for subjects randomized to placebo vs pantethine (28.2 kg/m² and 94.0 cm vs 27.8 kg/m² and 93.1 cm, $P = .190$ and $P = .380$, respectively).

High-sensitivity C-reactive protein values were not statistically different at week 16 between placebo and pantethine (2.44 ± 2.54 and 2.93 ± 4.40 , $P = .427$, respectively). Likewise, serum AST, ALT, and CK were not statistically different after 16 weeks of placebo vs pantethine (21.9 ± 7.1 U/L vs 19.8 ± 9.2 U/L, $P = .423$; 24.0 ± 14.6 U/L vs 20.3 ± 10.8 U/L, $P = .440$; 98.5 ± 46.9 U/L vs 96.2 ± 52.3 U/L, $P = .820$, respectively). There was no difference between subjects on placebo and treatment in the levels of CoQ10 with values increasing in both groups from baseline to week 16.

3.3. Adverse events

A total of 14 symptoms potentially attributable to study medication were found in 12 subjects in the placebo group, and a total of 9 symptoms potentially attributable to study medication were found in 8 subjects in the pantethine group. A single and resolved episode of neutropenia was found in a placebo subject. Headache was reported twice in placebo subjects and not reported in any of the pantethine subjects.

Bloating/heartburn/nausea/loose stools/upset stomach was reported 8 times in the placebo group and 8 times in the pantethine group ($P =$ not significant [NS]); however, loose stools accounted for only 1 of these symptoms in the placebo group but 6 times in the pantethine group. All but 1 subject reporting loose stools/diarrhea regardless of treatment arm recovered spontaneously and remained in the study. One subject on pantethine reported severe symptoms and was withdrawn from the study.

4. Discussion

To our knowledge, this is the first reported placebo-controlled and diet-controlled investigation into the potential lipid altering abilities of oral pantethine in North American subjects. The purpose of the TLC diet lead-in phase was to “level the playing field” so that we could eliminate or minimize any concerns of dietary influences on our results between the 2 treatment groups.

The results of our study confirmed the hypothesis that pantethine lowers TC and low-density lipoprotein in low-CVD-risk subjects in North America with statistical significance. The comparison of our study results with other results reported on high-CVD-risk subjects may not be discussed precisely because of the inconsistent results and study designs including dosages in those small-scale studies.

The primary conclusion of this investigation in low- to moderate-CVD-risk subjects is, over and above a TLC diet, that pantethine produced a significant decrease in TC, LDL-C, TC/HDL ratio, non-HDL, and Apo-B documented at week 2 after randomization that was sustained throughout the 16-week study period. The increase from 600 mg/d in weeks 1 to 8 to 900 mg/d from weeks 9 to 16 did not appear to provide any additional or measurable benefit with respect to lipid parameters. This would suggest that the optimal benefit in low- to moderate-risk subjects is achieved at a 300-mg twice-per-day dosing schedule. The “drift” from the maximum pantethine benefit at week 2 of a 7% reduction in LDL-C to only 4% at week 16 is unclear; however, the trend for this drift upward of LDL-C was noted in both the placebo and pantethine study subjects and is likely due to a similar (but not consistently documented) relaxing of the TLC diet adherence with time. Alternatively, this could represent a level of tachyphylaxis to pantethine at 600 mg/d, and it remains uninvestigated whether this could have, with time, been overcome by the higher doses of pantethine.

A prior investigation in Japan [10] had noted additionally significant increases in HDL-C and significant decreases in TG with the same pantethine dosing schedule used in the current investigation; however, this investigation did not observe similar magnitudes for changes in these lipid parameters. There is no immediate biochemical explanation for these differences, although it is noted that the baseline HDL-C and TG values in our study subjects (since they were already in the low- to moderate-CVD categories) were nearly

optimal at baseline (>55 and <120 mg/dL, respectively, for all 120 subjects at the time of randomization), and our study was powered only to define a hypothesized effect of LDL-C only (which has been demonstrated). The magnitude of the therapeutic responses to pantethine for all lipid parameters may be in proportion to the magnitude of the abnormality above the clinical target.

Any AE potentially attributed to study medication was minimal, appearing in 13% of the placebo group and 13% of the pantethine group. The most common events were gastrointestinal with 8 instances in each group during the 16-week active treatment period. Although diarrhea/loose stools appeared to be a more prominent AE in the pantethine group, it was mild/moderate in all but 1 subject, and all recovered. Only 1 subject on pantethine had severe diarrhea and requested exit from the study. The AE we observed coincides well with many other reports described as gastrointestinal complaints of mild severity [10]. The subject size of our study is not sufficient for quantitative speculation for the tolerance of pantethine, but the accumulated reports on the clinical studies on pantethine, as reviewed recently, have shown pantethine as a well-tolerated agent, and the frequency of its side effects is very low in dosages of 600 to 1200 mg/d [10,11].

Although the current investigation and other prior investigations using pantethine have demonstrated its biological effectiveness toward favorable changes in serum lipid parameters, there remains a controversy as to whether these effects are directly related to pantethine or its in-vivo hydrolysis and production of the aminothiol compound cysteamine, which can inhibit HMG-CoA reductase in vitro [17]. However, in vitro and in vivo experiments have suggested that both may be effective, independently [18]. Regardless, it is interesting that, during our investigation, the levels of CoQ10 did not change. HMG-CoA reductase inhibitors (collectively called the statins) clearly not only lower LDL-C to a significant degree but also can lower CoQ10 production by the liver [19], and thus, some of the AEs, in particular, the dose-related myalgias, may be related to concomitant lowering of in vivo CoQ10 production. Although it was not the subject of our investigation, our results suggest that the LDL-C-lowering effects of pantethine (and cysteamine) act via a different metabolic pathway than do the statins. Further research is warranted on the combined use of low-dose statins and pantethine for a potential synergistic lowering of LDL-C (and perhaps maintenance of a lower incidence of myalgia side effects).

The final discussion point is the clinical implication of the current investigation. There are no published data on the use of pantethine for lowering subsequent CVD events—but meta-analyses of a variety of statin trials, which looked at both lipid-lowering and future cardiovascular events, have demonstrated that, for each 1% lowering of TC/LDL-C, there is a concomitant lowering of global CVD by at least 1%. This investigation in low- to moderate-CVD-risk individuals showed a final lowering of LDL-C by about 9%, including

benefits of the TLC diet. A recent review of the “get with the guidelines” database analysis of more than 136 000 individuals admitted to hospital with coronary artery disease showed the average admission LDL-C to be 104 ± 40 mg/dL [20]; furthermore, the baseline LDL-C value was less than 130 mg/dL in three quarters—supporting the notion that lowering LDL-C by any amount, regardless of perceived “risk,” would be beneficial.

Although we confirmed in this study that pantethine lowers TC and LDL-C in these low-CVD-risk subjects in North America, there are several limitations of this study. Even after 16 weeks of administration of pantethine, the measured parameters did not plateau or reach a constant level, which makes it difficult to predict the outcome of long-term administration of pantethine. Pharmacokinetic data such as blood levels of pantethine during the course of 600 or 900 mg of pantethine administration are limited in this study. The precise understanding of the mechanisms of actions of pantethine and the optimum dosage determination requires further investigation.

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References

- [1] Verschuren WMM, Jacobs DR, Bloemberg BPM, Kromhout D, Menotti A, Aravanis C, et al. Serum total cholesterol and long-term coronary heart disease mortality in different cultures: twenty-five year follow-up of the seven countries study. *J Am Med Ass* 1995;274:131-6.
- [2] Third Report of the National Cholesterol Education Program (NCEP) Expert panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-421.
- [3] LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *J Am Med Ass* 1999;282:2340-6.
- [4] Grundy SM, Cleeman JI, Merz CNB, Brewer R, Clark LT, Hunninghake DV, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adults Treatment Panel III Guidelines. *Circulation* 2004;110:227-39.
- [5] Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *BMJ* 1994;308:367-72.

- [6] Branca D, Scutari G, Siliprandi N. Pantethine and pantothenate effect on the CoA content of rat liver. *Int J Vitam Nutr Res* 1984;54: 211-6.
- [7] Prisco D, Rogasi PG, Matucci M, Paniccia R, Abbate R, Gensini GF, et al. Effect of oral treatment with pantethine on platelet and plasma phospholipids in IIa hyperlipoproteinemia. *Angiology* 1987;38:241-7.
- [8] Gensini GF, Prisco D, Rogasi PG, Matucci M, Neri Serneri GG. Changes in fatty acid composition of the single platelet phospholipids induced by pantethine treatment. *Int J Clin Pharmacol Res* 1985;5: 309-18.
- [9] Hiramatsu K, Nozaki H, Arimori S. Influence of pantethine on platelet volume, microviscosity, lipid composition and functions in diabetes mellitus with hyperlipidemia. *Tokai J Exp Clin Med* 1981;6:49-57.
- [10] Hata Y, Goto Y, Ide H, Tsuji M, Takahashi S, Itakura H, et al. Effects of pantethine on serum lipids and apoproteins—I. Results of a multi-center cooperative study. *Geriatr Med* 1986;24:1139-50.
- [11] McRae MP. Treatment of hyperlipoproteinemia with pantethine: a review and analysis of efficacy and tolerability. *Nutr Res* 2005;25: 319-33.
- [12] Horváth Z, Vécsei L. Current medical aspects of pantethine. *Ideggyogy Sz* 2009;62:220-9.
- [13] Avogaro G, Bittolo BG, Fusello M. Effect of pantethine on lipids, lipoproteins, and apolipoproteins in man. *Curr Therap Res* 1983;33: 488-94.
- [14] Gaddi A, Descovich GC, Nosedà G, Frangiaco C, Columbo L, Craveri A, et al. Controlled evaluation of pantethine, a natural hypolipidemic compound, in patient with different forms of hyperlipoproteinemia. *Atherosclerosis* 1984;50:73-9.
- [15] Bertoline S, Donati C, Elicio N. Lipoprotein changes induced by pantethine in hyperlipoproteinemic patients: adults and children. *In J Clin Pharm Ther Toxicol* 1986;24:630-7.
- [16] Carrara P, Matturri L, Galbussera M. Pantethine reduced plasma cholesterol and the severity of arterial lesions in experimental hypercholesterolemic rabbits. *Atherosclerosis* 1984;53:255-64.
- [17] McCarty MF. Inhibition of acetyl-CoA carboxylase by cystamine may mediate the hypotriglyceridemic activity of pantethine. *Medical Hypotheses* 2001;56:314-7.
- [18] Wittwer CT, Graves CP, Peterson MA, Jorgensen E, Wilson DE, Thoene JG, et al. Pantethine lipomodulation: evidence for cysteamine mediation in vitro and in vivo. *Atherosclerosis* 1987;68:41-9.
- [19] Ghirlanda G, Oradei A, Manto A, Lypa S, Uccioli L, Caputo S, et al. Evidence of plasma CoQ10 lowering effect by HMG-CoA reductase inhibition: a double-blinded, placebo-controlled study. *J Clin Pharm* 1993;33:226-9.
- [20] Sachdeva A, Cannon CP, Deedwania PC, LaBresh KA, Smith SC, Dai D, et al. Lipid levels in patients hospitalized with coronary artery disease: an analysis of 136,905 hospitalization in Get With The Guidelines. *Am Heart J* 2009;157:111-7.