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Case Report

Modulating Serum Lipids with Berberine in Naturopathic Clinical Practice

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Abstract

Medical intervention to reduce the risk of atherosclerosis using lipid modulating medications has been a target for reducing cardiovascular risk for over 40 years. Lipid lowering medications, HMG-CoA reductase inhibitors (Statin's), and more recently PCSK9 inhibitors (PCSK9i (protein convertase subtilisin/kexin type 9 inhibitors) are now and in the future will be the main stay therapy for reducing Atherosclerosis. However, the uncertainty of statin induced myalgia and other bad publicity via the media and internet reports has caused many patients to opt out of statin therapy. Berberine and is quinoline alkaloid has had several clinical trials demonstrating potential in managing cardiovascular disease risk. Berberine is a safe and natural alternative for modulating circulating lipids including LDL-C, however possible drug interactions, due to its effects on P450 enzymes, does indicate some caution should be exercised.

Introduction

Dyslipidemia and cardiovascular disease have been identified by the World Health Organisation as the number one cause of death globally, and high levels of LDL cholesterol [1] are a major risk factor contributing to this. Numerous studies have identified cardiovascular medications as the best way to achieve this goal. A meta-analysis by Baigent etal in 2010 reviewed 26 cholesterol clinical trials which included 170,000 participants1. Their results showed a relative risk reduction in total mortality of 10% per 1 mmol/L reduction in LDL-C with a P value< 0.0011. In their review a significant reduction in deaths from coronary disease and a further reduction in major vascular events which equated to a 22% reduction per 1 mmol/L of circulating LDL-C. Current clinical data supports [2] the belief that LDL-C is the real target for reducing CVD risk [2]. Another cross-sectional CVD study in the Netherlands, involving 1249 patients with heterozygous familial hypercholesterolemia (heFH), only 21 % of patients achieved an LDL-C target of 2.5 mmol/L considered to be a safe target level for these patients3. A similar failure is found in severe primary hypercholesterolemia patients, including those with familial hypercholesterolemia. Familial [3] hypercholesterolemia (FH) is an autosomal dominant disorder involving mutations in the LDL receptor gene leading to defective plasma LDL-C catabolism and increased levels of circulating LDL-C 4,5.

Berberine In Cardiovascular Therapy

Myalgia still remains the most common adverse [4] event reported with statin therapy. Statin -myositis is associated with muscle symptoms and a in severe cases a substantially elevated serum creatinine kinase (CK). In rare circumstances statin-associated myopathy is found to occur at a 1 in 1000 to 1 in 10,000 people on statin treatment 6. In contrast, statin-associated muscle symptoms (SAMS) in which CK concentrations are normal or only slightly elevated, are [5] much more common and have prevalence of 7–29 %6. The most promising natural product that results in cholesterol lowering, based on recent clinical trials, is Berberine, and is quinoline alkaloid, commonly found in several medicinal herbs including Copts sentences, Hydrates canadensis and Rhododendrons amongst others 7. Most recently Berberine has been shown to be a natural inhibitor of PCSK9 (protein convertase subtilisin/kexin type 9), acting in a similar fashion as other PCSK9 Inhibitors Eg Vedolizumab, a monoclonal antibody targeting PCSK9 in hyperlipidaemia which often lowers LDL below 1.5mmol/L8. Interestingly, Berberine has also [6] been demonstrated to lower fasting triglyceride (TG) levels and in a clinical trial, reduced body weight as well as improve dyslipidemia in high fat diet-fed (HFD) rats. Hence, the understanding the cardiovascular protective effects of Berberine appears to be mounting [8]. In several recent clinical trials Berberine has shown significant reductions in LDL-C.

One study found total cholesterol to drop from 5.4mmol/l to 4.6mmol/L after 18 weeks with the LDL-C concentration dropping from 3.5 mmol/L to 2.7mmol/L 9. Also, a systematic review, in 2013 examining [7] Berberine supplementation, evaluated eleven randomized controlled trials (including a total of 874 participants) the review identified a significant reduction in total cholesterol, triglycerides and LDL-C except for HDL-C which was increased across the 11 trials with an average LDL-C reduction of 0.65mmol/L10.

An important consideration when using Berberine is its drug interactions. A study examining the effect of longterm administration of 900mg a [8,9] day of Berberine identified significantly decreased CYP2D6 activity with mild modification of CYP2C9 and CYP3A4 activities, but no effect on CYP1A2 and CYP2C19 function11. The CYP2D6 enzyme metabolizes a quarter of all prescribed drugs. It is recognised that 5-10% Individuals homozygous for two inactive copies of CYP2D6 are known as poor metabolisers resulting in higher plasma concentrations of the substrate drugs when compared to the wild type CYP2D6 alleles. Individuals heterozygous for one inactive allele of CYP2D6 are known as [10] intermediate metabolisers, and homozygous individuals with active copies of active CYP2D6 alleles are known as ultrarapid metabolisers. Thus, in any population a number of individuals given prescribed Berberine doses of 1500mg/day will possibly have drug interactions with their other prescribed medications if they are modified by CYP2D6. My data with [11] Berberine administered to eight (8) adult individuals for 12 weeks at 500mg of Berberine three times a day, showed an avrage reduction in LDL-C of 0.65mmol/L (reported in Table 1. Seven out of the eight (8) individuals had varying reductions of LDL-C over 12 weeks. One patient who had no reduction in LDL-C had an adverse reaction with the Berberine. He exhibited [12] total inhibition of his Hydroxyurea being administered for controlled Essential Thrombocythemia. There had been no reported adverse effects reported for Hydroxyurea and CYP2D6. This observation requires further investigation. Vacuumed is a human monoclonal antibody that inhibits PCSK9 binding to the LDL-C receptor on the hepatocytes and disrupts LDL-C / PCRK9 receptor complex increasing [13] LDL-C receptor recycling to the surface of the hepatocyte and its removal of LDL-C.

Table 1: Case reports for an uncontrolled group of volunteers four (4) females and four (4) males, aged 50 to 70 years, given 500mg of Berberine, 3 times a day with meals for 12 weeks. The average reduction with LDL-C was 0.65mmol/L. This reduction was in line with the metaanalysis completed in 2013[10]. Case 9 is a patient given biweekly injections of 140 mg/mL of evolocumab, for 12 weeks

	Total Chol	Tigs	HDL	LDL	LDL change mmol/L
Case 1					
Week 1	6.3	2.1	6.6	4.56	0.46
Week 12	5.4	1.6	1.07	3.73	
Case 2					
Week1	6.7	0.8	1.82	4.27	0
Week 12	6.6	1.2	1.75	4.27	
Case 3					
Week1	6.2	1.6	1.11	4.34	0.89
Week 12	5.8	1.1	1.16	3.86	
Case 4					
Week 1	7.3	0.6	2.03	4.34	0.77
Week 12	7.2	0.7	2.25	4.32	
Case 5					
Week 1	7.1	1.1	1.5	5.08	0.35
Week 12	6.7	0.8	1.63	4.74	
Case 6					
week 1	7.9	1	2.08	5.43	0.56
Week 12	7.8	1.1	2.05	4.77	
Case 7					
Week 1	7.1	1.5	1.62	4.63	0.93
Week 12	6.3	1.4	1.57	3.79	
Case 8					
Week 1	5.1	1.1	0.77	3.79	1.27
Week 12	4.1	1	0.67	2.52	
Case 9					
Week 1	5.2	1.12	1.2	3.5	2.06
Week 12	3.6	1.4	1.2	1.44	

Another important [14] consideration with Berberine is that it is poorly absorbed into circulation with most of an oral Berberine dose accumulating in the gut. Its absorption depends on the conversion of Berberine to dihydroberberine which requires the enzyme nitro reductase for this to occur12. Hence, an important factor in Berberine absorption is the intestinal microbiota, the metabolite dihydroberberine has been shown to have a 5-10-fold higher absorption rate than Berberine. In the absence of Nitro reductase producing bacteria this conversion does not occur. Enterococcus faecium [15] and Bacteroides fragilis have both been shown to produce nitro reductase enzymes and in culture have been shown to convert Berberine to dihydroberberine. Animal data supports dehydroarene possesses a stronger lipid-lowering effect, indicating that the gastrointestinal tract is a potential target for increasing the hypolipidemic effect of Berberine12. Both Berberine and dihydroberberine have recently shown to have anti-inflammatory effects modulated by NF-κB and MAPK signaling pathways [13] and this effect adds to their use in cardiovascular disease.

Conclusion

Berberine is a useful for lowering LDL-C, but the degree is variable. The effectiveness of the biological effect is linked to the gut biome and the presence of nitro reductase enzyme producing bacteria. The probable adverse reaction with other prescription medicines via P450 enzymes especially CYP2D6 may limit its use in many circumstances and the observed inhibition of Hydroxyurea by Berberine needs to be confirmed.

The PURE study showed that socioeconomic factors play an important role in CVD and stroke14. So, lifestyle change with better dietary choices and frequent exercise, should be part of our recommendations for reducing CVD risk. There is enough evidence to recommend combinations of complementary medicines like Bergamot, Berberine, phytosterols, Niacin and fibre add additional approaches to lifestyle change to improve lipid profiles and deliver more available and appropriate CVD risk reduction measures. It is important to remember that changes in circulating lipids do take time and it would be unrealistic to expect significant change in LDL-C and its atherogenic subfractions with Berberine in less than 6 months of intervention [15].

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