Development of Novel Water-Soluble Phytostanol Analogs: Disodium Ascorbyl Phytostanyl Phosphates (FM-VP4): Preclinical Pharmacology, Pharmacokinetics and Toxicology

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Keywords: Cholesterol — FM-VP4 — Hypolipemic drugs — Phytostanols.

ABSTRACT

FM-VP4 is a novel inhibitor of cholesterol absorption that has lipid lowering and body weight reducing properties. In vitro and in vivo studies were performed to investigate the lipid-lowering effects, mechanism of action, pharmacokinetics, and toxicity of FM-VP4. FM-VP4 decreased cholesterol accumulation in Caco-2 cells by approximately 50%; its activity appeared to be independent of pancreatic lipase, p-glycoprotein, or cholesterol incorporation in micelles. In animal studies, FM-VP4 was added to the diet or drinking water and the following results were obtained. In gerbils 2% FM-VP4 produced mean 56 and 53% reduction in total cholesterol (TC) after 4 and 8 weeks, respectively. This reduction was entirely due to the loss of the low-density lipoprotein (LDL) pool, which was reduced to undetectable levels at either time point. At 8 weeks, high-density lipoprotein (HDL) concentration had risen by a mean of 34% whereas total triglyceride (TG) concentrations had decreased by a mean of 60%. FM-VP4 also had a profound effect on body weight in these animals. At 8 weeks, the mean body weight was in the 4% FM-VP4 treatment group 25% lower than in the control group. No hepatic or renal toxicity was associated with these changes. In Apo E-deficient mice, after 4- and 8-week treatments FM-VP4 caused a significant decrease in both TC and TG concentrations compared to controls. After 12 weeks, the areas of atherosclerotic lesion involvement in the aortic roots were decreased by a mean of 80% in the 0.5, 1, and 2% FM-VP4 treatment groups compared to controls. Taken together, these results suggest that FM-VP4 is a potential new drug with lipid-lowering and weight loss potential, without apparent toxicity.