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Impact of co-administration of protonated nanostructured aluminum silicate (cholesterol absorption inhibitor) on the absorption of lipid soluble vitamins D_3 and K_1: An assessment of pharmacokinetic *and in vitro* intraluminal processing

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ABSTRACT

Protonated nanostructured aluminum silicate (NSAS) is a protonated montmorillonite clay that was shown to be effective as an inhibitor of intestinal cholesterol absorption. The effect of NSAS on the intestinal absorption of nutrients is unknown. An *in vitro* lipolysis model was adapted to test the intraluminal processing of vitamin D_3 and K_1 in the presence of various amounts of NSAS. Additionally, vitamin absorption was assessed in male Sprague-Dawley rats randomized in the following treatment groups: IV administration of 0.1 mg/kg vitamin D_3 and 1 mg/kg vitamin K_1, and a single-dose gavage of 1 mg/kg vitamin D_3 and 5 mg/kg of vitamin K_1 in peanut oil with various doses of NSAS slurry, 2% NSAS-fortified diet, or 50 mg/kg stigmastanol. The solubilized fraction of vitamin D_3 in the lipolysis medium was reduced from 70% to 46% upon the addition of 120 mg NSAS. In contrast, the solubilized fractions of vitamin K_1 were not significantly affected. Although the NSAS-fortified diet did not significantly affect the absorbed fraction of both vitamins, NSAS slurry decreased the absorption of vitamin D_3 as compared to the control. These results indicate that NSAS may be incorporated in diet to treat hypercholesterolemia; however, vitamin D_3 monitoring may be required.

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1. Introduction

In recent years, sodium and calcium montmorillonite clay (MMT) has gained attention for its high adsorption capacities as well as swelling and colloidal properties and thus has been used for modulating absorption and drug delivery (Park et al., 2008). MMT is composed of layers of aluminum octahedral sheets which are sandwiched between two silicon-oxygen tetrahedral layers (Fig. 1). Substitution of the aluminum inner layer, silicon outer layer, or the exchangeable cations between the montmorillonite platelets with inorganic ions, surfactants or amino acids alters the clay's adsorption properties and changes its swelling and expansion capacities (Bhattacharyya and Gupta, 2008; Chin et al., 2001; Shen, 2001, 2002; Uddin, 2008). MMT clay and its modified forms have been found to be relatively safe for oral consumption (Baek et al., 2012; Wang et al., 2008). Several modified forms of montmorillonite were used to reduce acute watery diarrhea in children (Mujawar et al., 2012). The adsorption capabilities of MMT could interfere with the absorption of nutrients and other compounds from the intestine (Ma et al., 2004, 2009; Zhang et al., 2009). Moreover, *in vitro* intercalation of vitamins B1 and B6 with MMT resulted in reduction of their concentration in solution by 64% and 87%, respectively. The adsorbed amount of vitamins B1 and B6 was released over 10 h in intestinal fluids. These observations suggest that co-administration with MMT could result in impaired absorption of vitamins (Joshi et al., 2009a, 2009b).

Nanostructured aluminum silicates are commercially available particles of MMT in the nano-size range (Gershkovich et al., 2009). It was previously reported that the oral administration of protonated nanostructured aluminum silicates (NSASs) resulted in a significant inhibition of cholesterol absorption in rats (Gershkovich et al., 2009). Moreover, NSAS resulted in a reduction in plasma cholesterol and atherosclerotic lesions in apolipoprotein-E deficient mice (Sivak et al., 2009). To investigate the underlying mechanism of the reduction of cholesterol absorption by oral

Abbreviations: NSAS, protonated nanostructured aluminum silicate; MMT, montmorillonite clay.

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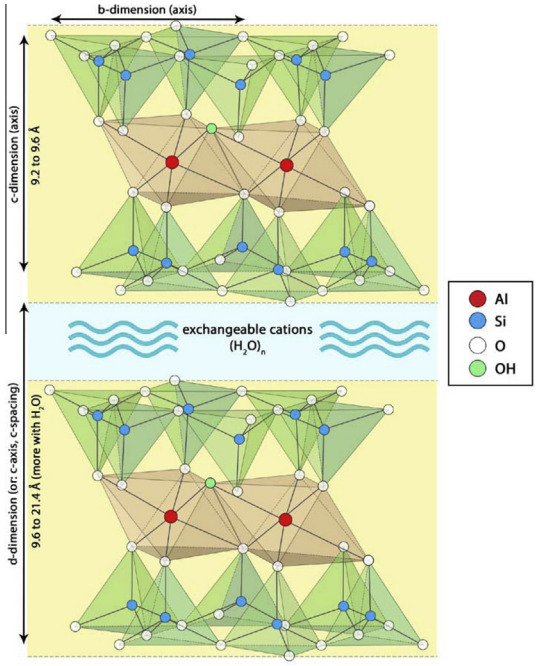

Fig. 1. Structure of montmorillonite clay.

administration of NSAS, an *in vitro* lipolysis model was adapted to simulate the intraluminal processing of triglycerides and cholesterol in the presence of NSAS. It was reported that NSAS inhibited the absorption of cholesterol either by direct or indirect binding to cholesterol leading to its precipitation and excretion with feces (Gershkovich et al., 2012).

The use of NSAS as an inhibitor of intestinal cholesterol absorption may affect the absorption of other nutrients such as lipid soluble vitamins. The incomplete absorption of vitamins could lead to serious health issues that could be avoided if sufficient vitamin supply is maintained. The purpose of this work is to investigate the impact of the co-administration of NSAS (as a cholesterol absorption inhibitor) on the absorption and pharmacokinetic profiles of vitamins D_3 and K_1. Vitamin D_3 has similar structure (Fig. 2) and common absorption pathways to those of cholesterol (Goncalves et al., 2011). This structural similarity may result in preferential interference of vitamin D_3 absorption by NSAS. In contrast, vitamin K_1 does not share any structural similarity with cholesterol and the impact of NSAS on the absorption of vitamin K_1 could be different from that of vitamin D_3.

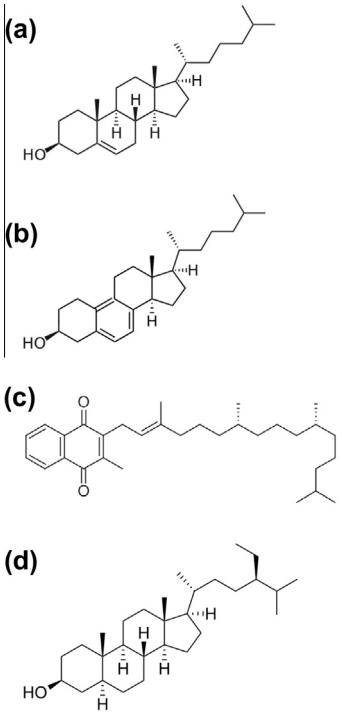

Fig. 2. Chemical structure of (a) cholesterol, (b) colecalciferol (vitamin D_3), (C) phylloquinone (vitamin K_1) and (d) stigmastanol.

2. Materials and methods

2.1. Materials

Tris maleate, taurocholic acid sodium salt hydrate, L-α-phosphatidyl choline, cholecalciferol (vitamin D_3), phylloquinone (vitamin K_1), peanut oil, sodium carboxymethyl cellulose, Tween®-80, stigmastanol, porcine pancreatin powder and probucol were purchased from Sigma–Aldrich (St. Louis, MO, USA). Protonated nanostructured aluminum silicate (NSAS) slurry (3% w/v), was protonated by ion exchange column and provided by AMCOL International Corp. (Hoffman Estates, IL, USA). All other chemicals were of analytical grade and all solvents were of HPLC grade unless noted otherwise.

2.2. Methods

2.2.1. Preparation of vitamin formulations

The oral formulation was composed of a mixture of vitamin D_3 (1 mg/ml) and vitamin K_1 (5 mg/ml) dissolved in peanut oil. The intravenous formulations were composed of 1 mg/ml vitamin K_1 in a mixture of propylene glycol:ethanol (9:1) and 0.1 mg/ml of vitamin D_3 in a mixture of PEG-400:ethanol (8:2).

2.2.2. Stigmastanol suspension preparation

Stigmastanol, a phytosterol with similar structure to cholesterol that interferes with cholesterol absorption, was used as a positive control in this study. Stigmastanol suspension (50 mg/ml) was prepared using a previously reported method (Gershkovich et al., 2009). Stigmastanol was wetted with Tween-80 (1%w/v) and suspended in sodium carboxymethyl cellulose (2% w/v). The suspension was sonicated using the Branson 3150 Sonifier® at room temperature and stirred with a magnetic stirrer for 2 h until the mixture appeared homogenous.

2.2.3. In vitro simulation of intraluminal processing of vitamins

2.2.3.1. Preparation of pancreatic lipase/colipase solution. One gram of porcine pancreatin was added to 5 ml of lipolysis buffer which was composed of 50 mM tris maleate, 150 mM NaCl and 5 mM $CaCl_2$. The mixture was stirred for 15 min and centrifuged at 4500 rpm for 15 min at 5 °C. The supernatant was collected and kept on ice.

2.2.3.2. In vitro lipolysis. The procedures of lipolysis were followed as described previously with minor modifications (Dahan and Hoffman, 2007; Gershkovich et al., 2012; Ibrahim et al., 2012). The composition of the lipolysis buffer (35.5 ml) was modified to simulate fed state conditions (Sek et al., 2001) by increasing the content of the phospholipid and bile components in the medium. 1.5 ml of the vitamin solution in peanut oil was added to the lipolysis buffer. Next, water (as a negative control), stigmastanol suspension (as a positive control) or NSAS slurry was added and the mixture was stirred for 15 min to homogenize. After equilibration, 3.5 ml

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