Introduction

Fumonisins are a group of naturally occurring mycotoxins produced by the fungus Fusarium verticillioides (previously moniliforme). Fumonisin B₁ (FB₁), is the most common toxin produced. Fumonisins alter sphingolipid biosynthesis, induce hepatotoxicity, and elevate serum cholesterol concentration in all species studied including pigs, calves, lambs, mice, rats, mink, and broiler chicks. A major concern for humans ingesting fumonisin contaminated food is the cardiotoxicity and hypercholesterolemia observed in swine and nonhuman primates. In swine, the heart is the primary target organ of fumonisin toxicity, with lethal pulmonary edema (PPE) occurring secondary to heart failure (Smith et al., 1996a and b; Haschek et al., 2001; Constable et al., 2000; Smith et al., 2000). Hypercholesterolemia was reported as the earliest detectable change in serum of swine following ingestion of fumonisin B₁ at concentrations as low as 1 ppm (Rotter et al., 1996). Fumonisin B₁ does not change cholesterol secretion (Merrill et al., 1995) but may change lipid metabolism (Rotter et al., 1997). FB₁ alters sphingolipid biosynthesis by inhibiting sphingosine N–acyltransferase and sphinganine N–acyltransferase and results in increases in the sphingoid bases, sphinganine and sphingosine, and depletion of complex sphingolipids (Wang et al., 1991, Yoo et al., 1996). It has been hypothesized that the mechanism of action of fumonisin is through these alterations in sphingolipid biosynthesis.

Swine were selected based on their utility as animal models and because FB₁ induces spontaneous disease in this species. Thirty five Sinclair minipig barrows were randomly divided into five groups. One group served as the control and four were fed 0.5 ppm, 1.0 ppm, 2.0 ppm, and 10 ppm (positive control) fumonisin FB₁, respectively, daily. Pigs were weighed weekly and bled every two weeks. No significant changes were present in the 10 ppm group after 18 weeks so the fumonisin level was increased to 30 ppm. During the study period we examined the effects of fumonisin B₁ on serum lipids, cholesterol, hepatic enzymes, electrolytes, blood counts, and sphingoid bases, as well as cardiovascular functions, tissue sphingolipids, and pathology.

Objectives

To determine if chronic fumonisin B₁ ingestion causes:

1. A dose-dependent increase in serum cholesterol concentration and a change in the serum lipid profile.
2. Chronic cardiovascular disease resulting in pulmonary hypertension.

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Results

The body weights for the 0.5 and 10-30 ppm groups, but not the 1.0 or 2.0 ppm groups, were significantly lower relative to the controls. There was no significant difference in backfat thickness in the treated groups as compared to the controls. Statistically significant differences in the concentrations of cholesterol, triglycerides, LDL, and HDL were not detected in fumonisin B1 treated groups as compared to the control group during the 6 month study. Nor were significant differences detected in the activities of hepatic enzymes, concentrations of BUN, serum creatinin and electrolytes, or complete blood counts. An increase in both tissue sphingosine and sphinganine was observed in the kidney, heart, and aorta of the 10-30 ppm fumonisin group. In the lung and liver, sphinganine, but not sphingosine, concentrations were elevated significantly, while neither was elevated in the brain and serum of the 10-30 ppm fumonisin group.

There were no differences in heart rate, cardiac output, stroke volume, maximal rate of change in left ventricular pressure (dp/dt_{max}, an index of cardiac contractility), left ventricular end-diastolic pressure, tau (an index of left ventricular relaxation), dp/dt_{min} (another index of left ventricular relaxation), mean aortic pressure, mean aortic diastolic pressure, mean aortic pulse pressure, mean pulmonary artery pressure, pulmonary artery wedge pressure, mean central venous pressure, systemic vascular resistance, and pulmonary vascular resistance between control and the 10-30 ppm fumonisin group. Mean systolic aortic pressure was significantly lower (P = 0.039) in fumonisin treated pigs (112 ± 16 mm Hg) than control pigs (131 ± 9 mm Hg). Thus pulmonary hypertension was not detected.

Major organs including the kidney, liver, heart, lung, pancreas, aorta, renal artery, cardiac arteries (left coronary, left circumflex, right interventricular, and right coronary), carotid artery, spleen, intestines, thyroid, and thymus were examined. Fumonisin treated pigs did not differ from controls. Selected vessels were stained with Verhoff’s elastin stain and periodic acid schiff (PAS) stain to detect fibrous and elastin changes associated with the tunica intima and tunica media. No significant changes were identified.

Summary

The doses used in this study bracketed the recently published FDA recommended maximum levels of 2 to 4 ppm FB1 in human foods and were below the recommended maximum level of 20 ppm (no more than 50% of diet) for swine (USFDA, 2001). The only significant change induced by FB1 was at the 10-30 ppm dose and it consisted of an increase in sphingoid bases in kidney, liver, lung, aorta, and heart as compared to control. These results support the earlier assumption that alteration in sphingoid bases is the earliest detectable biochemical change induced by FB1, and indicates that the no observable effect level (NOEL) for FB1 lies between 2 ppm and 30 ppm. This suggests that the FDA recommended maximum levels of 2 to 4 ppm FB1 for humans and 20 ppm for swine are above the NOEL, based on the percentage of corn based products in the diet.

Chronic low level fumonisin B1 ingestion did not cause an increase in serum cholesterol.
concentration or a change in the serum lipid profile. Chronic cardiovascular disease resulting in pulmonary hypertension was not observed. Therefore the concern for humans ingesting fumonisin contaminated food of cardiotoxicity and hypercholesterolemia, potentially leading to atherosclerosis, is unwarranted.

References


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