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**Case 1**

**A 52-year old ophthalmologist had mixed dyslipidemia (total cholesterol 199, HDL 32, triglycerides 120, and LDL 143mg/dL). The APO B: LDL ratio was 1.05, signifying the presence of dense LDL. The glucose was 82 mg/dL and thyroid function was normal. Baseline liver enzymes included an AST of 18 (17 to 59), ALT of 33 (21 to 72), and an alkaline phosphatase of 62 (38 to 126) U/l. He started a timed niacin preparation (Niaspan®), 1000mg in the evening, which raised his HDL to 37 and lowered his LDL and triglycerides to 130 and 75mg/dL, respectively. Five months later, his liver enzymes rose to an AST of 54, an ALT of 148, and an alkaline phosphatase of 211. The bilirubin remained normal.**

**Hepatitis A IgG and IgM were negative and hepatitis C antibody were absent. He had been immunized for hepatitis B. Abdominal ultrasound showed no fatty liver. He did not feel ill during the interval of the high liver enzymes. Niacin was discontinued and one month later his AST (15), ALT (40), and alkaline phosphatase (79) returned to normal.**

**Two 24-hour urines were collected. The first was collected while he was on niacin 1000 mg, before the rise in liver enzymes, and the ratio of 6-beta hydroxy cortisol to free cortisol was 1.66 (range of 95% of values 1.5-20.6)<sup>(1)</sup>. A second 24-hour collection was conducted two months after the niacin was stopped. The ratio was 1.40. He did not use grapefruit juice in any quantity.**

**DISCUSSION:**

**Many drugs, including hypolipidemics and antihypertensives, are degraded by the cytochrome P450/3A4 system. These drugs include some statins (simvastatin and atorvastatin), gemfibrozil, niacin, some antihypertensive drugs (all calcium blockers, and the selective aldosterone receptor blocker eplerenone), and a multitude of other drugs including antianxiety agents (alprazolam, buspirone). The activity of cytochrome P450/3A4 can be estimated by measuring the ratio of free 6-beta hydroxy cortisol to free cortisol, as this enzyme system is responsible for the conversion of cortisol to its product. This test is available through Nichols Laboratory. Values below the normal range could indicate prospective difficulty with cytochrome P450/3A4 dependent drugs, or help in adjusting dosages.**

If a 24-hour urine is not available, a randomly voided specimen can still be used to give a ratio of 6-beta hydroxy cortisol to cortisol since the two compounds have a parallel diurnal fluctuation <sup>(2)</sup>.

In this patient what likely happened was a dose related adverse event (hepatotoxicity) from an increase in serum niacin levels due to slow metabolism reflected by the low 6-beta hydroxyl cortisol to cortisol ratio.

**References:**

- 1) Caufield, M. (Nichols Laboratory). Personal communication.
- 2) Tran, J. Q., et al. Morning Spot and 24\*hour Urinary 6 beta hydroxy cortisol to cortisol ratios: Intra individual Variability and Correlation under Basal Conditions and Conditions of CYP3A4 Induction. J. Clin. Pharm 1999; 39: 487-494.