JOURNAL ARTICLE

MON-357 Recurrent Adrenal Crises in a Cytochrome P450 Ultra-Rapid Metabolizer

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Abstract

Background The cytochrome P450s (CYPs) are a superfamily of oxidative enzymes of which the CYP3A subfamily is responsible for the metabolism of approximately 50% of all drugs. This includes exogenous and endogenous steroids. Over 20 polymorphisms of CYP3A4 have been described with three metabolic phenotypes: ultra-rapid, extensive and poor metabolizers. The CYP3A4*1B has an allelic frequency of 2-9% in Caucasians and is associated with increased enzymatic activity. **Clinical Case** This is a 49-year-old Caucasian female with a known history of Addison's disease for 2 years, Hashimoto's thyroiditis, Osteoporosis, Celiac disease, Vitamin D deficiency and Pernicious Anemia, who presented to the ER after a syncopal episode following 3 days of nausea and vomiting. On arrival, she was hypothermic, hypotensive and tachycardic with a BP of 57/40 mmHg, pulse of 112 BPM. On exam she looked cachectic with tanned skin, dark palmar creases and pigmented oral mucosa. Initial labs showed normal CBC, low sodium (125, n 135 - 148 MEQ/L), hyperkalemia (5.8, n 3.5 - 5.3 MEQ/L), normal blood glucose and renal function. Further testing showed low AM cortisol <1.0 ug/dL (n 6.7-22.6 ug/dL), high ACTH (1010, n 6-50pg), TSH 7 (n 0.35 - 4.94 UIU/ML), Free T4 0.70 (n 0.70 - 1.48 NG/DL), TPO antibodies 759.06 (n<5.61 IU/ML), low aldosterone level <1.0 (n 3 - 16 ng/dL), and high renin activity 19.53 (n 0.25 - 5.82 ng/mL/h). After IV fluids resuscitation and IV steroids, she became hemodynamically stable and was

transitioned to oral hydrocortisone 20 mg AM, 10 mg PM, and fludrocortisone 0.1 mg daily. Five days later, she returned to the hospital with adrenal crisis. Despite adherence to her medications, she had several crises per month. Home regimen was adjusted to 100 mg hydrocortisone PO every 6 hours without resolution. During one of her hospitalizations, plasma cortisol was undetectable one hour after 100 mg hydrocortisone PO dose. EGD showed normal mucosa, thus malabsorption from celiac disease unlikely. Her frequent adrenal crises and undetectable levels of serum cortisol despite compliance, prompted evaluation of Cytochrome P450 genotype which revealed CYP3A4 Genotype B, allele 22, not detected. Patient was diagnosed as a CYP3A4 ultra-rapid metabolizer. She is currently being treated with Hydrocortisone 100mg IM every 4 hours and fludrocortisone 0.2mg PO every 4 hours. Since these adjustments, her adrenal crises are less frequent. **Conclusion** Variability in the expression of CYP3A4 can cause unpredictable interindividual drug responses. Exogenous steroids are not exempt. In this patient with Addison's disease, pharmacogenomic testing helped us individualize her maintenance dose to one that is intramuscular, and a higher dose and frequency, than what would be suggested in the current literature.

Issue Section: Adrenal Pathology