Predicting and managing hypertension and hypokalemia in Cushing's syndrome during mifepristone therapy.

Richard J. Auchus[1,2] Michael J. McPhaul[2], James W. Findling[3], Coleman Gross[4]
[1]Division of Metabolism, Diabetes, & Endocrinology, University of Michigan, Ann Arbor, MI; [2]Division of Endocrinology & Metabolism, University of Texas Southwestern Medical Center, Dallas, TX; [3]Endocrinology Center and Clinics, Medical College of Wisconsin, Milwaukee, WI; [4]Corcept Therapeutics, Menlo Park, CA

Hypertension and hypokalemia are frequent manifestations of Cushing's syndrome (CS), because cortisol activates both the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR). We analyzed blood pressure (BP) and potassium (K) data from the SEISMIC trial of 50 CS patients treated with the GR antagonist mifepristone (MIFE, 300-1200 mg/d) to determine prevalence, predictive factors, and approaches to management.

At baseline, 5 and 18 patients required spironolactone or K supplements, respectively, to maintain normokalemia, as specified by the protocol. During the trial, spironolactone was administered to 14 patients (25-400 mg/d) and K supplements to 33 (10-420 mEq/d) for hypokalemia. One or more episodes of hypokalemia were noted in 20 participants, 16 of whom were normokalemic at final study visit (80%). Those who required treatment for K wasting had higher urinary free cortisol (UFC) values at baseline as well at peak (week 10) than those who did not.

Baseline
Mean±SD = 1371±3523 vs 317±228 nmol/24h [497±1277 vs 115±83 μg/24h]
Median [range, IQR] = 289 [59-19739, 155-1017] vs 266 [85-1032, 229-324] nmol/24h
Wk 10
Mean±SD = 3668±6094 vs 1103±1003 nmol/24h [1330±2209 vs 400±364 μg/24h]
Median [range, IQR] = 938 [41-23480, 286-4417] vs 749 [32-2630, 312-2131] nmol/24h
(p=NS for all)

Patients who required K treatment prior to starting MIFE had higher UFCs than those treated after starting MIFE (mean±SD = 2194±4654 vs 383±387 nmol/24h [795±1687 vs 139±140 μg/24h], p=0.03). Baseline UFC was >500 nmol/24h (180 μg/24h) in 14/35 participants who required treatment for hypokalemia but only 2/17 participants who did not.

Systolic BP (SBP) rose during the trial in 18 participants, 10 of whom had clinical evidence of mineralocorticoid excess. Overall, the mean change in SBP was -2.5 mmHg during the trial (p=NS) in the 40 patients with hypertension, but changes in antihypertensive therapies among 19 diabetic subjects confounded analysis of predictive factors. In repeated measures mixed models, UFC was positively correlated with SBP and negatively correlated with serum K (p = 0.02 for both).

We conclude that hypertension and hypokalemia are common in CS patients requiring GR antagonist therapy with UFC >500 nmol/24h. These patients require concomitant treatment with a MR antagonist and/or K supplements, which control BP and K in the majority of cases. Clinical findings of MR activation are less predictable in patients with UFC <500 nmol/24h.