Need to Pause Hydrocortisone? Physiologic Replacement Does Not Affect AM Serum Cortisol, Bedtime Salivary Cortisol or UFC in Cushing Syndrome Patients on Block and Replace Treatment

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Background:
Hydrocortisone (HC) is detected by all cortisol assays, as it is the pharmaceutical name of the same compound. In patients (Pts) receiving HC as glucocorticoid (GC) replacement for adrenal insufficiency (AI), ≥1 dose(s) is often held before cortisol is measured due to concerns for test interference.

Objective:
To assess HC interference in cortisol assay results based on time between dose and sample collection, and determine whether 24-hour urine free cortisol (UFC) can exclude excess cortisol exposure during physiologic HC replacement. We used a phase 2a study of the novel oral melanocortin receptor 2 (MC2R) antagonist atumelnant (ATU) in Pts with ACTH-dependent Cushing syndrome (ADCS) as a block-and-replace model. Once-daily ATU blocks ACTH action at the adrenal cortex MC2R, rapidly achieving endogenous cortisol levels requiring GC replacement (<5mcg/dL) in all Pts studied so far.

Methods:
7 Pts (Cushing disease n=6, ectopic ACTH syndrome n=1) received ATU at an 80 (n=6) or 120 (n=1) mg dose once daily at 08:00 for 10 days. In all subjects, pre-dose morning serum cortisol (AM F) reached <5 mcg/dL and physiologic HC was started at a dose (8-12 mg/m^2/day) based on body surface area (BSA). AM F and bedtime salivary cortisol (Sal F) were measured daily by chemiluminescent immunoassay and liquid chromatography-tandem mass spectrometry (LC-MS), respectively. UFC was measured by LC-MS every 3 days starting on Day 1 (D1). Pts were screened for AI symptoms with daily questionnaires.

Results:
HC was started on D2 (n=3), D3 (n=3) or D11 (n=1) at 20-30 mg/day in 2-3 daily doses. The last daily HC dose (2.5-10 mg) was given by 17:00. In Pts receiving HC and ATU (D2-D10), AM F peaked at 5.2 mcg/dL in 1 Pt and stayed <5 mcg/dL in others. Sal F was mostly below the upper limit of normal (ULN, 100 ng/dL); 3 Pts had 1 value >ULN, range 1.84-4.45xULN, without additional HC doses after 17:00. Most UFCs were <ULN (45 mcg/d); 2/3 and 1/3 levels in 2 Pts were 1.13-1.36xULN. AI symptoms of dizziness (3/6), anorexia, nausea (2/6), headache, fatigue and malaise (1/6) all improved with HC.

Conclusion:

Consistent with its short half-life (up to ~2 hours), BSA-adjusted HC given by 17:00 did not alter AM F levels the next day. Even Sal F, sampled within 8 hours of PM doses, was largely unaffected. Thus, to promote Pt well-being, afternoon replacement HC need not be held if AM F was documented previously as low. Additionally, physiologic HC doses produce mostly normal UFC levels. Based on these data, UFC measurement during HC replacement can be useful in monitoring for iatrogenic CS in Pts with primary or secondary AI, and for recurrence in those with treated CS.