Using Mifepristone to Differentiate Cushing's Disease from Cushing's Syndrome

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Endogenous hypercortisolism (Cushing's syndrome [CS]) results from excessive pituitary ACTH secretion, ectopic ACTH synthesis, overproduction of cortisol by an adrenal tumor, and rarely by extra-hypothalamic CRH production. Identifying the cause of excess cortisol production is based upon pituitary ACTH secretory response to pharmacological agents such as dexamethasone. We hypothesized that mifepristone administration, by blocking glucocorticoid receptors, might distinguish patients with pituitary-dependent hypercortisolism (Cushing's disesase [CD]) from those with Cushing's syndrome due to ectopic ACTH production.

We retrospectively reviewed previously collected data from the SEISMIC study, a study of the safety and efficacy of mifepristone in CS (Fleseriu 2012), on ACTH and cortisol responses in patients with CD or ectopic ACTH. In this analysis, CD patients (N=41) had prior transphenoidal surgery; 18 of 41 patients had also received pituitary radiation therapy. There were 4 patients with CS secondary to ectopic ACTH secretion. Patients received mifepristone 300 mg po once daily. ACTH and cortisol were measured as close to 8 AM as possible using a centralized laboratory (Quest Diagnostics, Collegeville, PA.) at baseline and 14 days after commencing mifepristone therapy.

Patients with CD who had not received radiation therapy had a 2.13 ± .96 fold rise in ACTH versus a 1.4 ± .45 fold rise in patients with CD who had received pituitary irradiation ($p = .003$). Patients with CD who had not received radiation therapy had a 1.56 ± .6 fold rise in cortisol versus a 1.24 + .23 fold rise in cortisol observed in patients with CD who had received pituitary irradiation ($p=0.02$). Patients with ectopic ACTH showed a non-statistically significant change in fold rise in ACTH (1.75 ± .71, $p=0.08$) or cortisol (1.21 ± .28, $p=0.25$) following mifepristone therapy. There was no statistically significant difference between the rise in ACTH or cortisol between ectopic ACTH patients and CD patients as a group or in those who had pituitary irradiation.

These data indicate that, after short term mifepristone treatment, ACTH and cortisol rise to a greater extent in radiation naïve postoperative CD patients than those who have had received pituitary radiation therapy. Although the numbers of ectopic ACTH patients were small, the findings suggest further study of mifepristone to test the integrity of the pituitary-adrenal axis is warranted.