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Adrenal Disorders

PREVENTION OF SECONDARY ADRENAL INSUFFICIENCY WITH PRESURGICAL USE OF MIFEPRISTONE IN PATIENTS WITH AUTONOMOUS CORTISOL-SECRETING ADENOMAS

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ABSTRACT

Background: Autonomous cortisol secretion from a functional adrenal adenoma (AA) can suppress the HPA axis and may lead to functional suppression of the normal adrenal tissue. Unilateral adrenalectomy in ~65.3% of AA patients leads to postsurgical secondary adrenal insufficiency (AI) and often requires intraoperative and postsurgical glucocorticoid replacement until the HPA axis recovers.

Herein are two cases describing patients with cortisol-secreting AA treated with mifepristone (MIFE), a competitive glucocorticoid receptor (GR) antagonist. In addition to clinical improvement, MIFE reduces the negative feedback on the HPA axis caused by excess cortisol, and increased ACTH and DHEA-S levels. These assays are good tools to assess recovery of HPA axis function prior to surgery helping to potentially avoid postsurgical AI.

CASES

Patient 1: A 70 yo man with a unilateral AA and poorly controlled type 2 diabetes (A1c 9.1% on Lantus, Humalog, Prandin, glimepiride, Januvia and metformin), hypertension (155/84 mmHg on metoprolol, eplerenone, Micardis HCT, amiloride, clonidine, and spironolactone), ACTH of 17.9 pg/mL and DHEA-S of 29.3 µg/dL [nl:28-175]), and unsuppressed 1-mg overnight DST 1.98 µg/dL. After 6 months of treatment with MIFE (600 mg/d final dose), ACTH increased to 141.4 pg/mL, DHEA-S increased to 69.1 µg/dL, illustrating HPA axis recovery. Diabetes greatly improved as A1c decreased to 7.4% with discontinuation of all antidiabetic medications except metformin. BP was unchanged, but all antihypertensive medications were discontinued and replaced with valsartan 80 mg monotherapy. After unilateral adrenalectomy, ACTH and DHEA-S normalized to 54.2 pg/mL and 37.3 µg/dL, respectively. Since there was no postoperative AI (cortisol 11.7 µg/dL), he did not require steroids.

Patient 2: A 44 yo woman with bilateral AA presented with prediabetes (FBG 104 mg/dL), insulin resistance (HOMA-IR=7), hypertension (156/85 mmHg), undetectable ACTH, DHEA-S of 54.6 µg/dL [nl: 32-240], and unsuppressed 1-mg overnight DST of 2.66 µg/dL. After 5 months of MIFE therapy (600 mg/d final dose), ACTH (30.3 pg/mL) and DHEA-S (62 µg/dL) increased, FBG (86 mg/mL) and insulin resistance (HOMA-IR=1.4) normalized. After a partial bilateral adrenalectomy, ACTH (16.3 mg/mL) and DHEA-S (18.4 µg/dL) normalized. A postop ACTH stim test showed no AI; thus no steroid therapy was provided. Postoperative DST was 1.16. BP normalized to 119/82 mmHg and the patient is no longer prediabetic.

Conclusions: Mifepristone treatment of two patients with adrenal cortisol-secreting adenomas prior to adrenal surgery improved metabolic parameters, restored HPA axis function, and prevented postsurgical AI. These results suggest that response to MIFE was associated with a positive postsurgical outcome.

INTRODUCTION

- Approximately 30% of incidentally found adrenal adenomas are estimated to be cortisol-secreting[1]
- Depending on the degree of cortisol excess secreted by adrenal adenomas, suppressed ACTH secretion alters diurnal cortisol rhythm and can cause atrophy of normal adrenal tissue in both the affected and contralateral gland
- In patients with suppressed ACTH, adrenal surgery generally leads to lasting adrenal insufficiency (AI), even after a unilateral adrenalectomy (AI in approx. 65.3% of patients), requiring glucocorticoid replacement until the HPA axis recovers 6-18 months or more later[2]
- Postsurgical AI with glucocorticoid replacement therapy is not benign and can have lasting impacts on cardiovascular and metabolic clinical outcomes[3,4] as well as on the patient's quality of life[5]
- Mifepristone (Korlym®, Corcept Therapeutics), a FDA-approved medical therapy for Cushing's syndrome,[6] modulates the effects of cortisol by acting as a competitive antagonist at the glucocorticoid receptor (GR)
  - By antagonizing the GR in the hypothalamus and pituitary gland, mifepristone interferes with the negative feedback mechanism that regulates cortisol production
  - Mifepristone has the potential to restore the HPA axis preoperatively and reverse cortical atrophy in addition to improving the clinical manifestations of cortisol excess
  - Restoration of the HPA axis preoperatively may obviate postsurgical AI and the need for glucocorticoid replacement[7]
- We report on two very different cases of adrenal Cushing's syndrome (one unilateral adrenal adenoma and one bilateral) with mild hypercortisolism who were treated with mifepristone preoperatively

CASE 1

PRESENTATION

- 70-year-old man with unilateral adrenal adenoma
- 10 years of poorly controlled:
  - Type 2 diabetes (A1c = 9.1%) despite maximal doses of antidiabetic agents (Lantus, Humalog, Prandin, glimepiride, Januvia, and metformin)
  - Hypertension (155/84 mmHg) despite maximal doses of antihypertensives (metoprolol, eplerenone, Micardis HCT, amiloride, and clonidine)
- Obesity (201 lbs, BMI = 30.17)
- Poor sleep
- Absent typical cushingoid appearance

SUSPICION

- Left adrenal adenoma (3 cm, **Figure 1**) might be hormonally active and causing metabolic disturbances

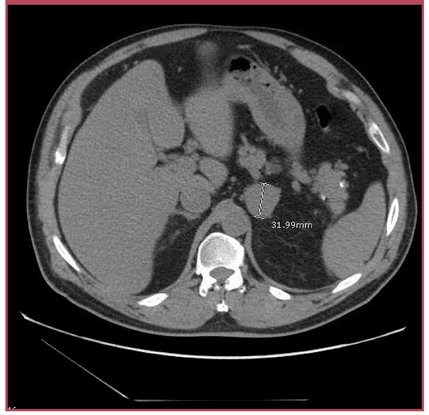
ENDOCRINE WORKUP

- DST was not suppressed (1.98 µg/dL)
- ACTH (17.9 pg/mL [normal range, 7.2-63.3]) and DHEA-S (29.3 µg/dL [normal range: 30.9-295.6]) were low normal
- Random cortisol was normal at 12.23 µg/dL (normal range: 3.09-22.4)

PLAN

- Adrenalectomy was ruled out because the involvement of the functional adenoma could not be definitely confirmed because of equivocal laboratory results
- Medical therapy with mifepristone was chosen to assess the contributions of excess cortisol to the patient's clinical picture

Figure 1. Left Adrenal Adenoma



RESULTS

- During mifepristone treatment
  - Patient developed hypothyroidism requiring thyroid replacement
  - Eplerenone was temporarily used to antagonize the mineralocorticoid receptor activation while on mifepristone
- After 6 months of treatment with mifepristone (600 mg/d final dose)
  - A1c decreased and the patient discontinued all antidiabetic medications except metformin (**Figure 2**)
  - All blood pressure medications were discontinued and replaced with valsartan 80 mg monotherapy
  - ACTH and DHEA-S increased, suggesting HPA axis recovery (**Figure 3**)
- After unilateral adrenalectomy
  - ACTH and DHEA-S normalized (**Figure 3**)
  - DST cortisol suppressed to 0.96 µg/dL
  - Patient did not require steroid replacement therapy
- Postoperative cortisol was 11.7 µg/dL and patient did not have signs or symptoms of AI

COMMENTS

- Type 2 diabetes and hypertension were largely driven by cortisol excess
- Nine months after surgery, the patient's glucose tolerance and blood pressure remained well-controlled with minimum intervention

Figure 2. Change in A1c With Mifepristone

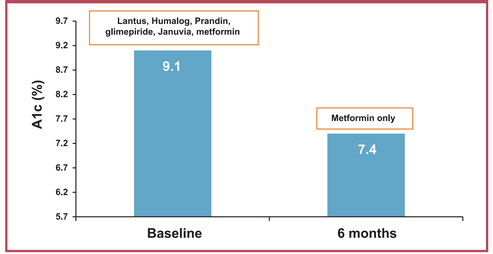
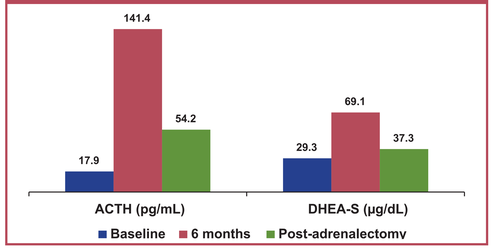


Figure 3. Changes in ACTH & DHEA-S With Mifepristone and After Adrenalectomy



CASE 2

PRESENTATION

- 44-year-old woman with bilateral adrenal adenomas
- Prediabetes (fasting blood glucose [FBG] 104 mg/dL), FB insulin = 27.2 µIU/mL, insulin resistance (HOMA-IR = 7 [normal <1])
- Hypertension (156/85 mmHg)
- Headaches, chest pain, palpitations (with negative cardiac evaluation); dizziness, vertigo with presyncope
- Facial hirsutism, depression, sleep disruption
- Referred by a surgeon for left-sided flank pain that showed bilateral adrenal masses (right 2.42 cm, left 2.08 cm) on CT imaging (**Figure 4**)
  - In retrospect, the masses were visible on imaging 9 years earlier

SUSPICION

- Many of the patient's symptoms and metabolic disturbances could be due to cortisol-producing adrenal adenomas even though her only cushingoid feature was facial hirsutism

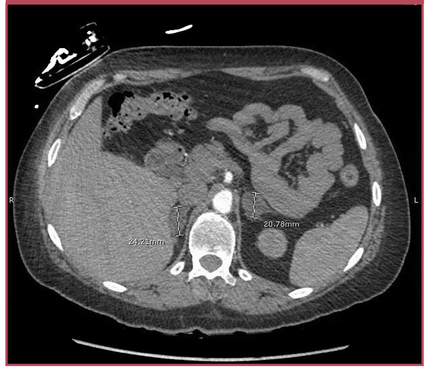
ENDOCRINE WORKUP

- Unsuppressed DST of 2.66 µg/dL
- ACTH was undetectable (normal range: 7.2-27 pg/mL)
- DHEA-S was low normal at 54.6 µg/dL (normal range: 41.2-243.7)

PLAN

- Since the patient was already in jeopardy of losing her job because of absenteeism, a bilateral adrenalectomy with a lifetime of glucocorticoid replacement therapy could not be supported unless cortisol dysregulation was demonstrated to be the cause of her medical problems
- Medical therapy with mifepristone was selected

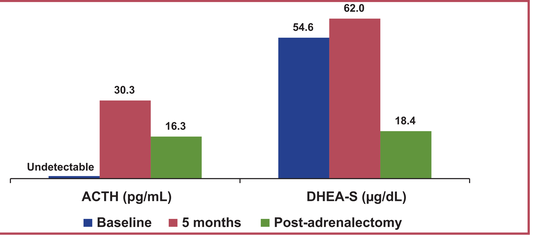
Figure 4. Bilateral Adrenal Adenomas



RESULTS

- During mifepristone treatment the patient developed a rash on her legs that spontaneously resolved
- After 5 months of mifepristone therapy (600 mg/d final dose)
  - FBG (86 mg/mL) and insulin resistance (HOMA-IR = 1.4) normalized
  - Blood pressure normalized (119/82 mmHg)
  - The patient felt well, with increased energy and better sleep
  - ACTH and DHEA-S increased (**Figure 5**)
- Given that the patient's HPA axis was restored, she was sent for a partial bilateral adrenalectomy at NIH (complete removal on the left side and partial removal on the right side), leaving intact adrenal tissue
- After partial bilateral adrenalectomy
  - A postoperative ACTH stim test showed no AI and thus no glucocorticoid replacement therapy was warranted
  - ACTH and DHEA-S normalized (**Figure 5**)
  - DST was normal at 1.16 µg/dL
  - One year later she remains normotensive (127/87 mmHg) and euglycemic (FBG = 86 mg/dL, FB insulin = 6.6 µIU/mL, A1C = 4.9%)

Figure 5. Changes in ACTH & DHEA-S With Mifepristone and After Adrenalectomy



DISCUSSION

- Mifepristone is FDA-approved for the management of glucose intolerance in patients with endogenous Cushing's syndrome who are not candidates for surgery or have failed surgery
- Due to its mechanism of action (competitive antagonism of glucocorticoid receptors), mifepristone has the potential to alter the treatment paradigm of patients with mild Cushing's syndrome caused by adrenal adenomas
- Glucocorticoid receptor antagonism reverses HPA-axis suppression as manifested by gradual normalization of ACTH, which in turn stimulates restoration of steroidogenesis and normal adrenal tissue
- Five to 6 months of treatment with mifepristone in these two patients with cortisol-secreting adenomas significantly improved their metabolic parameters, made them better candidates for adrenalectomy, and allowed them to avoid postsurgical AI and long-term glucocorticoid therapy

CONCLUSION

- Mifepristone treatment of adrenal adenoma patients with mild cortisol excess has the potential to improve morbidity prior to adrenal surgery and to prevent postsurgical AI and long-term glucocorticoid therapy by restoring the HPA axis

REFERENCES

1. Chiodini I. *J Clin Endocrinol Metab.* 2011;96:1223-36.
2. Di Dalmazi G, et al. *J Clin Endocrinol Metab.* 2014;99:2637-45.
3. Johannsson G, Ragnarsson O. In Granata R, Isgaard J (eds): Cardiovascular Issues in Endocrinology. Basel: Karger, 2014; Vol 43:p33-44.
4. Johannsson G, et al. *Clin Endocrinol.* 2015;82:2-11.
5. Forss M, et al. *BMC Endocr Disord.* 2012;12:8-15.
6. Flesiru M, et al. *J Clin Endocrinol Metab.* 2012;97:2039-49.
7. Dehal H, et al. Presented at ENDO 2016. Poster SUN455.

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DISCLOSURES

JCP: Consultant, Corcept.
JJS: Employee, Corcept.

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