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Mifepristone (RU-486) in the Treatment of Refractory Cushing's Disease

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Background

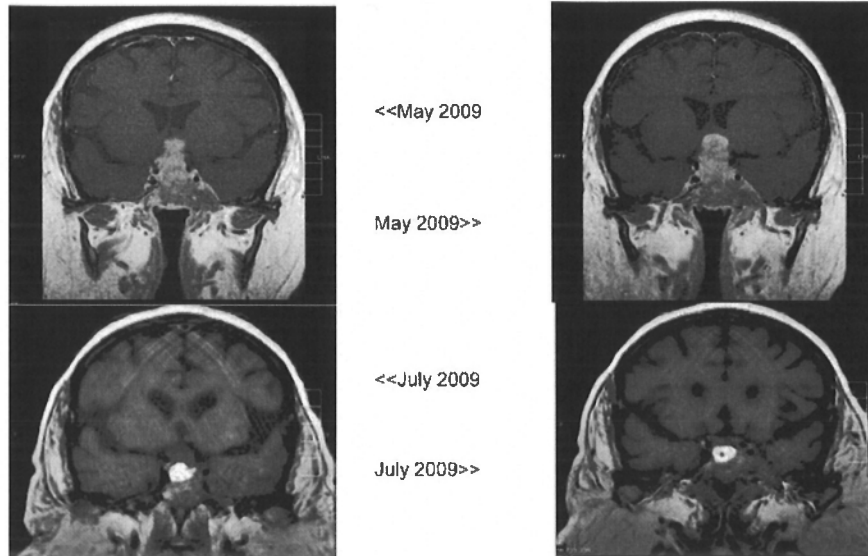
Optimal management of Cushing's Disease (CD) consists of surgical resection with a cure rate estimated between 70-80% (1). Persistent hypercortisolism is associated with elevated mortality. For these patients, chemical adrenalectomy using dopamine agonists (cabergoline) and 17 α -hydroxylase inhibitors (ketoconazole) are variably successful. Such tumors may also exhibit progressive growth and compromise neighboring neuroanatomy making further attempts at resection technically difficult. We describe a case of a woman with refractory CD and use of a novel agent, mifepristone.

Presentation

A 47 year old Hispanic female with historically well-controlled Type 2 diabetes mellitus on oral agents presented with two weeks of progressive weakness, fatigue and exertional dyspnea. She endorsed polyuria and acutely increased capillary blood glucose levels. Diabetic control had recently deteriorated as evidenced by a Hgb A1c of 13.3 mg/dL. She had decreased oral intake secondary to dysphagia and odynophagia to solids and liquids resulting in an unintentional thirty pound weight loss. She denied fevers, chills, nausea, vomiting, but described pre-syncope and orthostasis without recent falls. The remainder of her review of systems was negative. Past medical history was notable for Type 2 Diabetes Mellitus for 13 years with retinopathy, no known neuropathy or nephropathy. The remainder of the social and family history was non-contributory. Admission medications included metformin, glyburide and baby aspirin.

PE: T 35.7, HR 103, BP 144/77. General: Obese with facial plethora, appropriate and oriented to four spheres. HEENT: extraocular movements intact, no visual field cuts. Neck: no thyromegaly. CV: regular rate and rhythm. Lungs: clear bilaterally. Abdomen: central obesity, soft, non-tender without striae or masses. Extremities: +2 pitting edema. Neurologic: cranial nerves intact, reflexes normal, decreased sensation and strength in the lower extremities bilaterally. Skin: easy bruising, multiple subcutaneous nodules and superficial ulcers which cultured positive for *Mucor* and *S. aureus*.

A Brain MRI revealed a large enhancing macroadenoma in the sella with anterior extension into the sphenoid sinus and suprasellar extension into the third ventricle displacing the optic chiasm.



Hospital Course

Two months after initial presentation, the patient was hospitalized for volume overload and bilateral pulmonary infiltrates. Infectious and cardiac evaluations were negative.

Subsequently, the patient developed complications due to her relatively immunosuppressed state—first *E coli* urosepsis then cholecystitis—for which she was not felt to be sufficiently medically stable to undergo cholecystectomy.

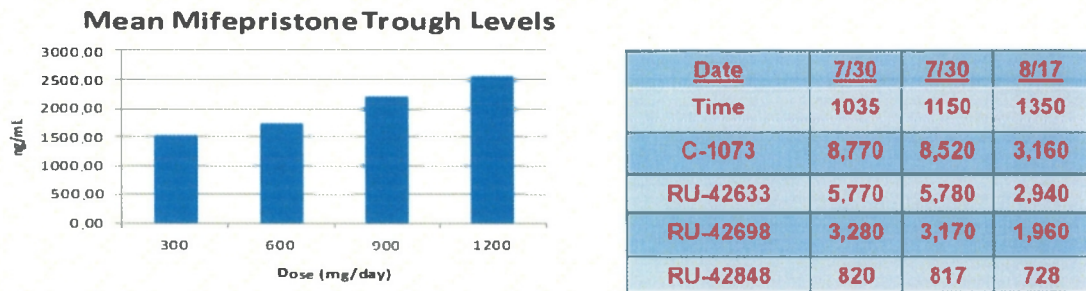
For the patient's hypercortisolism, she was started on ketoconazole and titrated to a target cortisol level of 30-35 mcg/dL. Although she initially responded well, the patient developed hypokalemia. Ketoconazole was discontinued and the patient was started on spironolactone instead to continue diuresis.

Although not originally felt to be a good surgical candidate, the patient's persistently elevated cortisol and ACTH levels prompted Neurosurgery to perform a transsphenoidal resection. Because of the extensive size and involvement of this tumor, approximately 20% residual tumor could not be resected. Postoperative, repeat MRI revealed residual tumor eroding inferiorly into the clivus and on the left into the cavernous sinus, possibly into the left Meckel's cave. She was continued on maximal doses of ketoconazole. Cabergoline was added and titrated to 1 mg/d. Stress dose steroids were given immediately following surgery, but these were discontinued when her serum cortisol level continued to increase.



Osteopenia was first noted one month prior to surgery, also attributed to hypercortisolism. CT imaging revealed anterior wedging of L2-L5 without retropulsion and diffuse osteopenia. Postoperatively she complained of hemiplegia and was found to have an irreversible cord compression and multiple thoracic and lumbar vertebral compression fractures.

Mifepristone was then added using compassionate use protocol. Owing to her other medications, a dose of 600 mg/d was used. Following initiation of treatment, the patient's insulin and hypertensive medication requirements dropped dramatically and mental status improved markedly. Potential common side effects, particularly hypokalemia, did not develop. However, after several days of treatment, the patient grew despondent, hypotensive, and hypoglycemic, requiring short-term treatment with dexamethasone.



This development of clinical adrenal insufficiency was likely exacerbated by the P450 (CYP3A4) -inhibiting properties of ketoconazole, which led to unexpectedly high levels of mifepristone and its metabolites.

Notably, even following discontinuation of mifepristone administration, the patient's insulin and anti-hypertensive requirements remained low.

Endocrine Rev, Suppl 1, June 2010, 31(3):S1201 (Endocrine Society Annual Meeting, 2010, San Diego)

	Reference	Dec-08	Feb-09	Mar-09	Apr-09	May-09	Jun-09	Jul-09	Aug-09
ACTH	6-58 pg/mL	167	294		338	267		230	
Cortisol	10-25 mcg/dL	36	69	9	>63.4	>63.4	15	51	14
Insulin-like GF-1	91-246 ng/mL	40							
Prolactin		2	7		12	22			
LH		<0.1			<0.1	<0.1			
FSH		1			0	0			
Testosterone	14-76 ng/dL	98							
HCG Quant	<4mIU/mL	<5							
Renin								4	
PTH	14-72 pg/mL	28				44		10	
TSH	0.4-4.5 mIU/mL	1	<0.1		0				1
FT4	0.8-1.8 mg/dL	1	2		1				1
FT3	2.0-4.4 pg/mL				2				
Hbg A1C	4.9-6.2%	13	9		8				
Cortisol, baseline			70						
Cortisol, poststimulation			>75.0						

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July	13	14	15	16	17	18	19	20	21
			1 st dose	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
RU486 600 mg daily									
Ketoconazole 400 tid	+	+	+	+	+	+	+	+	+
Cabergoline 1 mg q D	+	+	+	+	+	+	+	+	+
Total insulin requirement (units)				48	42	25	14	NA	NA
Hypoglycemia					To 40				
Dexamethasone 4 mg q12h									
SBP			130-140s	110s				100s	80-90
DBP			71-85	66				50-60	60s
Spirolonactone			+	+	+	+	+	+	+
Carvedilol 3.125 mg BID	+	+	+	+	+	Stop			
Hallucinations	+	+	Stop						
Depression/Lethargy	+/-	+/-	+/-	-/-	-/-	-/-	-/-	-/-	-/-
Appetite									

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