64yo Woman with Lung Cancer and Low Sodium

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Med-Peds Endo
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HPI

64yo WF

6/2008 – SOB, 5lb weight loss, pleural effusion
pleural biopsy: + mesothelioma

7/2008 – L extrapleural pneumonectomy with L hemithorax radiation x 3 months

5/2011 – imaging showed recurrent L pleural mass, 8th rib, parasplenic tissue involvement
PET with lesions throughout chest/abd
radiation to L chest

11/2011 – chemo: cisplatin→carboplatin; pemetrexed

12/2011 – progression of lesions → navelbine chemo

3/2012 – progression of disease; U of C for 2nd opinion

6/2012 – started phase I immunotherapy trial
indoleamine-2, 3-dioxygenase 1 (IDO) inhibitor

HPI Continued

- Admitted 2 weeks after starting study drug
- Nausea, fatigue, poor po intake x7d
- Wt unchanged; HR 118
- IVF (NS @ 85mL/hr → 120ml/hr)
- Hgb 8 (down from 9)
- TSH 6.7 mIU/mL
- 5am cortisol 6.6 mg/dL
- Consulted endo re: <u>hyponatremia</u>

	6/27/2012 0749
Glucose, Ser/Plasma	87
Sodium	121
Potassium, Ser/Plasma	4.8 *
Chloride	90
Carbon Dioxide	17
BUN	24
Creatinine	1.1
GFR Estimate (Calc)	50 *
Calcium	8.9
Inorganic Phosphate	3.7
Magnesium	
Total Protein	6.8
Albumin	3.0
Bilirubin, Total	0.2
Bilirubin, Conjugated	0.1
Alk Phos, Serum	79
AST (SGOT)	10
ALT (SGPT)	8
Lactic Dehydrogenase	105
C-Reactive Protein	221
Gamma Glutamyl T-Pep	61
Beta-Hydroxybutyrate	
Creatinine (Untimed)	
Uric Acid	4.2

ROS

+ nausea, - vomiting
+ fatigue
+ loose stools
+ decreased urination
+ abdominal pain
- change thirst, +less po intake
- wt loss
- confusion
- headache/visual changes
- galactorrhea

Remainder negative

PMH

1) Mesothelioma (metastatic)
2) HTN
3) Migraines
4) GERD
5) Depression
6) DJD
7) IJ thrombosis

Family/Social

Family History

Father died from aortic aneurysm

Mother died from heart disease

Sister healthy

No primary relatives with adrenal disorders, thyroid disease, diabetes

Social

Former grade school teacher

Retired age 56

Childhood home +asbestos

Allergies/Meds

Allergies: heparin, propoxyphene

Medications:

Lovenox 40mg SQ bid

Nexium 40mg po daily

Dilaudid 0.4mg IV q4h prn

Oxycodone IR 5mg po q6 prn

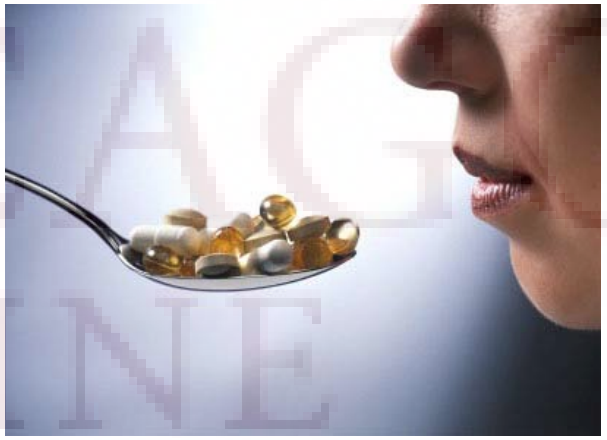
Lorazepam 1mg po qam, 1.5mg qpm

Megestrol 400mg po bid

Mirtazepine 30mg po qhs

Compazine 10mg po q6 prn

Miralax + Colace



Physical Exam

T 36.6; HR 124; BP 108/60 (95/51 at admit); RR 16; Wt 53kg, BMI 20

Gen: Awake, supine, pallor, non-cushingoid

HEENT: mouth dry

Neck: no goiter

CV: tachy, regular

Chest: no breath sounds on L, clear on R

Abd: soft, nontender, nondistended

Musc: no edema; no muscle weakness

Neurological: sensation normal

Skin: warm/dry, normal pigment

Laboratory/Radiology Review

	6/20	6/27	6/27	6/28	6/28
Na	131	121	123	124	124
Sosm			259		
Uosm			258	410	
Una			31	77	
U-SG		1.018	1.011		
FeNa			0.5%		

	6/6	6/13	6/20	6/27
TSH (0.3-4)	2.8	10.1	11	6.7
fT4 (0.9-1.7)	1.38	1.07		
T3 (80-195)	89	80		
rT3 (160-353)				

Abd/Chest CT 6/6:
+R lung with multiple nodules (2.5cm)
+mediastinal LN disease
+liver mass 5x10cm
+spleen nodules
+bowel mesentery/pelvic mass 7x5cm
Normal adrenals, pancreas

	6/6 1pm	6/13 8am	6/28 5am
ACTH	<5	<5	
Cort	6.5	5.1	6.6
FSH	5.6		
LH	0.5		
PRL	7.8	74	

Endocrine Problems

1) Hyponatremia
2) Question of adrenal insufficiency
3) Hyperprolactinemia
4) Abnormal thyroid function tests

Further Evaluation and Mgmt

1) Hyponatremia

   Volume depletion/SIADH/central AI/hypothyroidism

2) Question of adrenal insufficiency

   ACTH stim test advised; then start HC 40/20

3) Hyperprolactinemia

   Pituitary adenoma vs. drug (compazine); MRI pituitary

4) Abnormal thyroid function tests

   Possible primary hypothyroidism; check fT4,T3,rT3

   Await adrenal eval

Follow-up Labs

Cosyntropin 250mcg stimulation test

	6/28 Base	6/28 +32min	6/28 +58 min
Cortisol	9.8	22.0	22.8

Thyroid function tests

	6/6	6/13	6/20	6/27	6/29
TSH (0.3-4)	2.8	10.1	11	6.7	
fT4 (0.9-1.7)	1.38	1.07			1.41
T3 (80-195)	89	80			84
rT3 (160-353)					400

MRI of pit

Focal thickening of left posterior pituitary with similar signal/enhancement to rest of gland; unremarkable otherwise

Subsequent Hospital Course

- Started on levothyroxine 25mcg/d
- Continued on hydrocortisone 40/20, planned decrease to 20/10 then 15/5 at discharge
- Pt with gradual/partial symptomatic improvement in nausea/weakness
- Na gradually improved to 129 with 1L fluid restriction and IVF stopped
- Primary team arranged for home hospice services

Allergies/Meds

Allergies: heparin, propoxyphene

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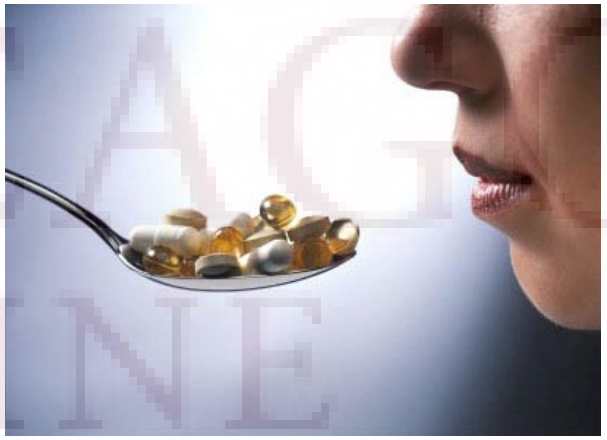
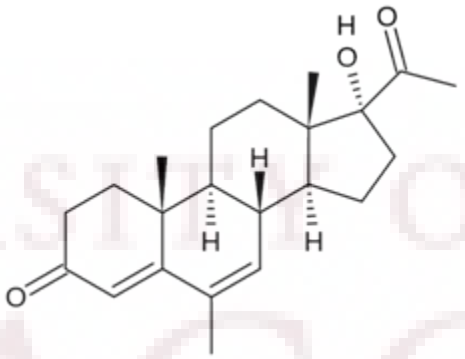


Clinical Questions

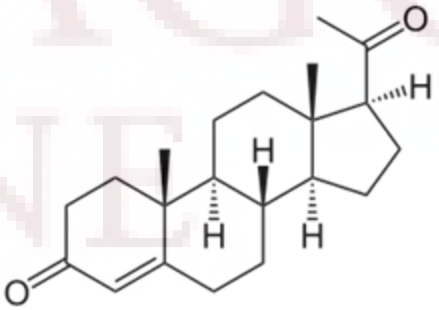
1) What is megestrol (Megace)?
2) Is megestrol (Megace) associated with adrenal insufficiency? If so, is it reversible? Do these patients need stress steroids?

What is megestrol (Megace)?

- Synthetic progestin
- Binds to PR and GR
- Blocks AR and ER
- FDA approved 1993 (ES form in 2005)
- Appetite enhancing/weight gain
- AIDS pts: 8-11 lbs in 12wks (800mg/d)
- Cancer: 2001 meta-analysis: pooled OR 2.6 (1.8-3.9) for weight gain



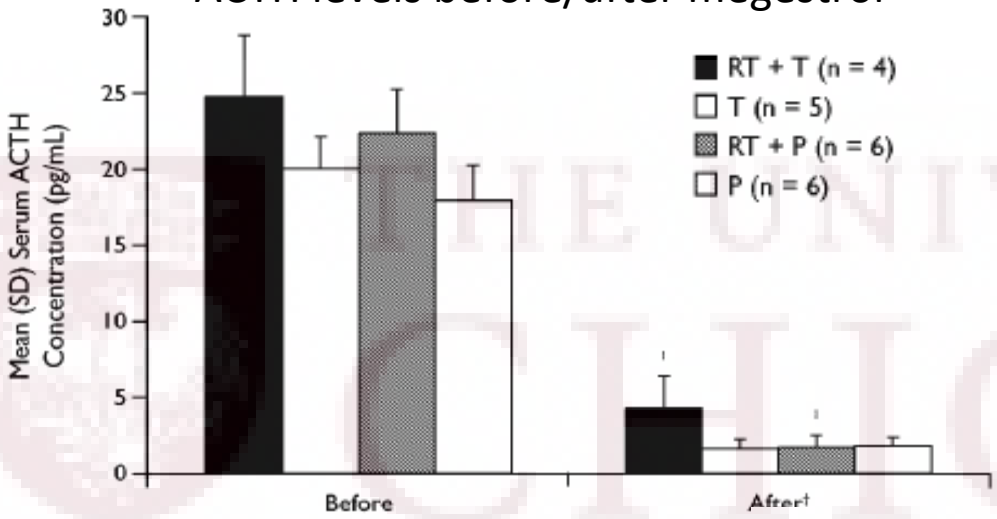
Megestrol



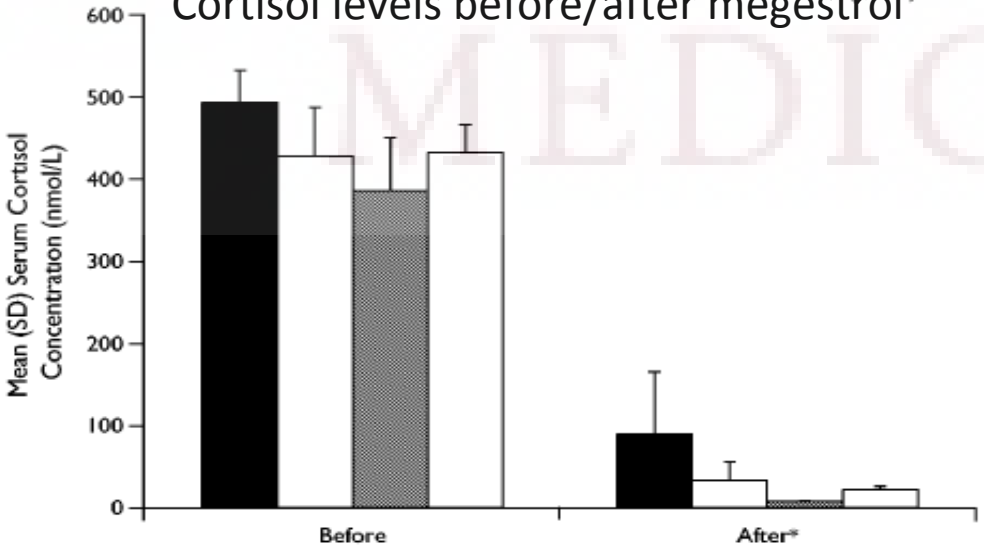
Progesterone

Megestrol and the HPA axis

ACTH levels before/after megestrol



Cortisol levels before/after megestrol



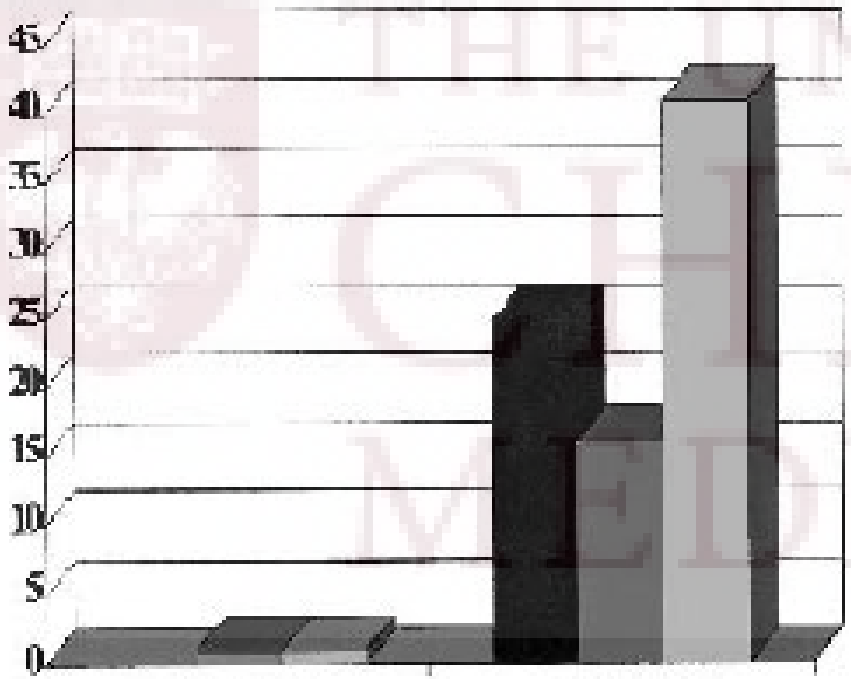
- 2005 study
21 healthy older adult males on megestrol 800mg/d x 12 weeks

- 90% decreases in ACTH and cortisol

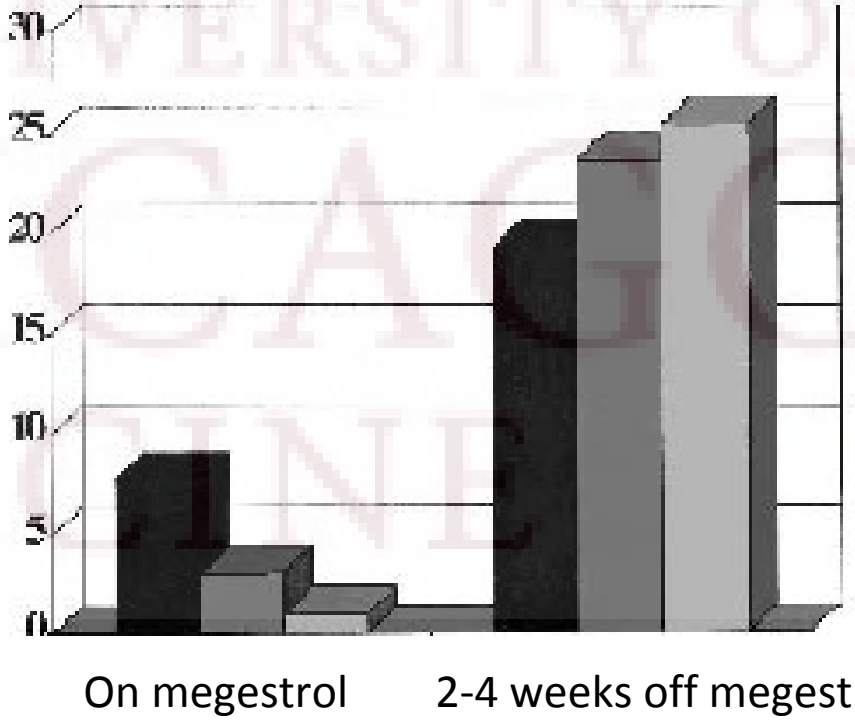
Bodenner et al 2005

Megestrol and the HPA axis

ACTH (pg/mL)



Peak Cortisol (ug/dL)



Meacham et al (2003)

Is megestrol associated with AI?

- megestrol binds to GR with 0.5x binding affinity of dexamethasone and 2x binding affinity of cortisol (Kontula et al 1983)
- cases of Cushing syndrome AND Adrenal insufficiency reported
- other studies show abnormal CRF-stim and ITT tests in megestrol treated patients

13 patients with Breast Ca on megestrol with Adrenal Insufficiency	
Mean Age (y)	67
Mean duration of megestrol (months)	17 (2-72)
% with weakness	100%
% with hypotension	62%
% with anorexia,N/V/D	23%
Mean basal cortisol ug/dL	1.5 (1-4)
Mean cort stim +30m ug/dL	8.7 (3-16)
Mean cort stim +60m ug/dL	8.3 (3-17)

Subramanian et al 1997

Is megestrol associated with AI?

- Glucocorticoid receptor agonist vs. antagonist

? binding/blocking of GR

? missed doses of megestrol

? acute stress/illness

- Clinicians advised to be aware of potential need for stress glucocorticoids for acute illness in pts on megestrol

Take Home Points

- Megesterol is a synthetic progestin used in AIDS and cancer patients with anorexia/cachexia
- Megestrol is commonly associated with significant, reversible suppression of the H-P-Adrenal axis
- Megestrol can rarely be associated with adrenal insufficiency and use of stress corticosteroids should be considered with acute illnesses

References

- Maltoni et al. High-dose progestins for the treatment of cancer anorexia-cachexia syndrome: a systematic review of randomised clinical trials. Annals of Oncology 2001 (12): 289-300.
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- Meachem L et al. Mechanism of transient adrenal insufficiency with megestrol acetate treatment of cachexia in children with cancer. J of Pediatric Hematology/Oncology 2003 (25): 414-417.