Topiramate causing elevation of urinary cortisol assay

Bryan Benjamin Grissett, D.O., Max Sosa-Pagan, M.D., Qasim Zafar Iqbal, M.D.
Ochsner Health – Department of Endocrinology

Background

- Topiramate, a common anti-convulsant drug, has multiple mechanisms of actions:
  - Reduces the frequency of action potentials
  - Increases the activity of GABA-A receptors
  - Suppresses AMPA excitatory glutamate receptors
- Topiramate is readily absorbed in the gut with a large volume of distribution
  - Not extensively metabolized (~18% metabolized hepatically)
  - ~82% is excreted unchanged renally
- Unclear how topiramate artificially elevates urine cortisol
  - Hypothesis: Topiramate metabolites may be responsible for false elevations of urinary cortisol

Case Description

- 69-year-old female presented for endocrinology follow-up
- Pertinent Past Medical History:
  - Pituitary adenoma [status-post transsphenoidal resection and gamma knife surgery 6 years prior]
  - Isolated growth hormone deficiency [taking somatropin 0.2 mg subcutaneous daily]
  - Migraines [taking topiramate 75 mg daily]
  - Left adrenal incidentaloma
  - Primary hypothyroidism [taking levothyroxine 75 mcg]
  - Secondary hyperparathyroidism from vitamin-D deficiency [taking ergocalciferol 50000 units weekly]
  - Hypertension [taking hydrochlorothiazide 25 mg daily]
- Physical Exam:
  - Afebrile, hypertensive at 163/71 mmHg, heart rate 91 beats per minute, respiratory rate 18 breath per minute, saturating 100% on room air
  - Patient appeared obese (weight: 105 kg; BMI: 40)
  - No cervicodorsal fat pads or abdominal striae
  - No other significant cushingoid features
- PTH elevated at 232 pg/mL; otherwise labs within normal limits including TSH of 1.28 mIU/L, free T4 of 1.21 ng/dL, corrected calcium of 9.7 mg/dL, vitamin-D 25 of 43 ng/dL, ACTH of pg/dL, and IGF-1 of 75 ng/mL

Assessment

- History of left adrenal incidentaloma and prior pituitary adenoma resection with obesity
  - Integrity of the hypothalamus-pituitary-adrenal axis was tested
- Dexamethasone suppression test
  - 8:00 a.m. cortisol was insufficiently suppressed at 5.2 mcg/dL after 1 mg dexamethasone
  - Raised concern for hypercortisolism either from recurrent pituitary adenoma or adrenal adenoma but possible false positive due to growth hormone therapy affecting dexamethasone metabolism and cortisol binding globulin
- Diagnostic labs:
  - Rechecked ACTH for further assessment of pituitary origin
  - Rechecked DHEA-S and 24-hour urine cortisol collection for further assessment of adrenal origin
  - 24-hour urine collection revealed an elevated cortisol level of 878 mcg/day . A surprising finding given the lack of Cushingoid features
- Hypothesis: possible assay interference

Plan

- An in-depth review of home medications
- Literature review revealed that topiramate can cause interference of urinary cortisol measurement by radio immunoassay
  - ~80% of absorbed topiramate is excreted unchanged through the kidneys
- Studies on cortisol immunoassays analyzing various experiment concentrations of solutions containing topiramate caused a corresponding increase in the measured cortisol
- Patient was asked to discontinue topiramate and repeat urine cortisol level

Discussion

- Patient's topiramate was discontinued
- Repeat 24-hour urine cortisol measured 8 weeks later resulting normal at 8.9 mcg/day
- Additionally, patients had four negative midnight salivary cortisol levels
- We concluded that the topiramate had been responsible for the observed lab discrepancy
- The cessation of topiramate followed by a normal urinary cortisol in this and prior case studies suggests that topiramate and its metabolites causes false elevation of urinary cortisol, though cause remains unknown

Teaching Points

- Be aware of the possibility of topiramate causing false elevation of cortisol in patients being worked up for hypercortisolism.
- Multiple points of evidence of hypercortisolism (serum, saliva, or urine) are required to confirm the presence of hypercortisolism.

References

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