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When Two Isn't Better Than One: A Case of Severe Hyponatremia from Combination Thiazide Diuretic and ARB Therapy

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INTRODUCTION

- Thiazide diuretics and angiotensin II receptor blockers (ARB) are common medications for hypertension and are widely used together to counteract thiazide-induced hypokalemia
- Thiazide-associated hyponatremia (TAH) is fairly common. There are also multiple case series in the literature of severe hyponatremia in elderly pts attributed to initiation of a thiazide-ARB combination, even when the thiazide dose was low. This is a unique case of hyponatremia in which ARB on thiazide therapy seems to have precipitated severe hyponatremia.

CASE REPORT

- This is a 74-year-old female with a history of essential hypertension with intolerance to several antihypertensive medications, post-operative hyponatremia after laminectomy for cervical stenosis, mild peripheral edema, and chronic intermittent cough, who was being followed in clinic for refractory hypertension

- Previously on combined HCTZ 25mg + telmisartan with improved BP but pt stopped telmisartan due to cough (also had cough with ACE inhibitor and carvedilol)
- Severe hyponatremia s/p cervical laminectomy thought due diuretics and poor PO intake leading up to surgery
 - Stopped chlorthalidone 25mg and spironolactone 25mg
 - Continued amlodipine 5mg and started low dose metoprolol
 - Chlorthalidone resumed a month later for refractory HTN, repeat BMP normal
- Above goal again → re-attempted amlodipine 10mg

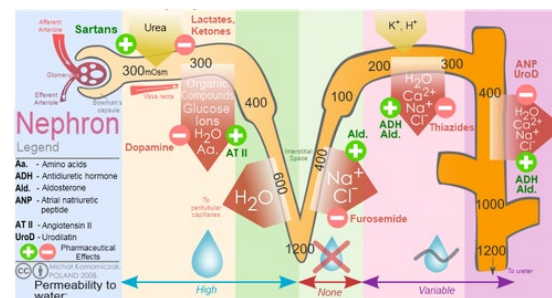
- Max amlodipine was not effective and caused increased leg swelling → **started irbesartan 75mg**, amlodipine decreased, and **chlorthalidone 25mg continued**
- Day 1 of ARB → developed lightheadedness/weakness, nausea, head fullness
- Day 3 → stopped taking irbesartan but symptoms persisted
- Day 7 → pt seen in clinic, labs showed **Na 113 mmol/L** → referred for admission

- Low serum osmolality of 238 mOsm/kg, high urine osmolality of 427 mOsm/kg, and high urine sodium of 64 mmol/L in the setting of recent diuretic therapy was consistent with hypotonic hypovolemic hyponatremia
- TSH wnl, low renin 1.5 ng/ml/hr
- **Hyponatremia resolved with holding chlorthalidone and irbesartan, cautious isotonic saline and D5W correction for 24 hrs, then no further IVF**

- Pt was hesitant to re-trial irbesartan with close monitoring
- BP controlled on aliskiren 150mg daily, amlodipine 5mg BID; Na/BMP stable

DISCUSSION

- Given the temporal correlation of initiating irbesartan therapy to her symptoms, previously normal sodium levels on chlorthalidone alone, improvement with isotonic saline, resolution of hyponatremia with discontinuation of these medications, and no evidence of other underlying etiology, her severe hyponatremia was attributed to the addition of the ARB to her thiazide diuretic.
- Thiazides reduce plasma volume and therefore blood pressure through inhibiting sodium reabsorption in the distal convoluted tubules. ARBs inhibit the vasoconstriction and aldosterone-secreting effects of angiotensin II, similarly leading to renal sodium loss by decreased sodium reabsorption in the distal tubules and collecting ducts.



- TAH has been reported in up to 30% of hospitalized pts. Proportions meta-analysis of 52 case series and 49 case reports of TAH pts showed **risk factors include:**
 - older age (mean age=75)
 - female sex (79% of pts)
 - possibly genetic susceptibility involving prostaglandin transporters (causing increased ADH activity)
- HCTZ was by far the most frequently implicated, either alone or with amiloride (~70% of cases), followed by bendroflumethiazide, indapamide, HCTZ-triamterene, chlorthalidone, and HCTZ-losartan (though there was high level of heterogeneity between studies)
- There are multiple case series in the literature of *severe* hyponatremia in elderly pts attributed to thiazide-ARB combination even though the thiazide dose was low.
- In this case, the pt had tolerated higher dose chlorthalidone well until the addition of irbesartan. Literature review did not reveal any similar cases of ARB initiation on ongoing thiazide therapy that precipitated hyponatremia
- Literature review did not reveal data stratifying risk of hyponatremia between different ARBs
- A possible mechanism includes lower renin and aldosterone activity and reduced renal response to aldosterone in the elderly compared to younger patients, on top of their susceptibility to TAH as above

CONCLUSION

- Cases of severe hyponatremia can occur with thiazides alone, but can be further promoted in combination with ARBs. Pts of advanced age and female sex seem at highest risk
- Early recognition through routine or symptom-onset lab monitoring can lead to timely drug discontinuation and medical management as needed to prevent serious complications

Hypertension Treatment History Highlights

Adding ARB to Thiazide Therapy

Admission for Severe Hyponatremia

Months Later ...