VOLUME - 10, ISSUE - 11, NOVEMBER - 2021 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Endocrinology

POSACONAZOLE INDUCED PSEUDOHYPERALDOSTERONISM WITH CONCURRENT ACUTE PRIMARY ADRENAL INSUFFICIENCY-A CASE REPORT

Priyadharshini Swaminathan	MD(General Medicine).
Bharath Kumar	DNB.
Indumathi K	DCP, MD(Path),DNB(Path).
Theranirajan	MD DCH MRCPCH(UK)FRCPCH(UK).

ABSTRACT In this covid 19 pandemic,there were increased incidence of Mucormycosis and thereby increase in usage of antifungals especially oral posaconazole which is more recently available in tablet form.There are already enough case reports of the incidence of new onset hypertension and hypokalemia with supressed renin and aldosterone which is termed as "Posaconazole induced pseudohyperaldosteronism".We describe here about a similar case that presented with hypertensive urgency as Acute pulmonary edema with an associated primary adrenal insufficiency.The potential mechanism include inhibition of 11 β HSD which degrades cortisol to cortisone,thereby increasing the levels of cortisol that stimulates Mineralocorticoid receptor.Also there is inhibition of steroidogenesis at the level of adrenal which in our patient presented with features of Acute adrenal insufficiency.

KEYWORDS : posaconazole induced pseudohyperaldosteronism, acute adrenal insufficiency

INTRODUCTION

CASE SUMMARY

49 year old female a known case of Type 2 Diabetes mellitus and Essential hypertension who has recently recovered from COVID-19 pneumonia had a FESS done for left maxillary sinusitis with growth of mucor without angio invasion in HPE presented to us with Hypertensive urgency as Acute pulmonary edema.She has been recently started on oral Posaconazole of 300mg/day.She was initially managed with iv frusemide and labetolol with non invasive ventilatory support.She had anasarca with shortness of breath and vague abdominal pain with vomiting. Investigations showed hyponatremia of 118mEq/L,Hypokalemia of 2.4mEq/L and a normal ABG.Imaging showed bilateral moderate pleural effusion and moderate ascitis.Her BP was not controlled with 12 hours of antihypertensives. We diagnosed the patient as Posaconazole induced pseudohyperaldosteronism as it was on D4 of starting Posaconazole she had onset of pedal edema and oliguria and PSA/PRA ratio was sent.Patient was started with Spironolactone of 100 mg/day in divide doses and left pleural tapping was done for symptomatic relief.On D3 of admission patient BP was under control ,but there was persistence of abdominal pain and vomiting with a sequential drop in Sr.Na to 108mEq/L.We suspected acute adrenal insufficiency and we proceeded with ACTH stimulation test and Sr.cortisol was 11g/dL.She was started with iv.hydrocortisone 100mg stat followed by 50 mg iv BD as she was having a documented Mucor in HPE.Her PSA/PRA ratio was 2.26 which indicated supression probably due to apparent mineralocorticoid excess like state. On day 7 of admission, she had an extreme diuretic phase of 10L/24hrs.We obtained an ENT opinion, since there was no active involvement or angioinvasion of mucor,Amphotericin B nasal douching was done.The final diagnosis was Posaconazole induced Pseudohyperaldosteronism with concurrent Primary acute adrenal insufficiency.She was tapered on steroids and spironolactone and was off all drugs with previous AHT and OHA at discharge.

DISCUSSION

The recent usage of Posaconazole for Mucormycosis has increased.Posaconazole induced pseudohyperaldosteronism has been a well documented entity with a similar incidence with Itraconazole.The mechanisms are at multiple sites predominantly by the inhibition of 11 b HSD2 at the level of distal renal tubules that is involved in conversion of Cortisol to Cortisone thereby increases the serum concentration of Cortisol. Cortisol stimulates Mineralocorticoid Receptor with similar efficacy as that of Aldosterone ,since it is degraded very quickly the effect is not apparent in a normal individual. Also there is decreased conversion of Deoxycortisone to Cortisone at the level of adrenal, DOC having equal stimulation on MR .This also explains the onset of primary adrenal insufficiency with high BP[2].Posaconazole induced Pseudohyperaldosteronism is diagnosed with Refractory Hypertension, Hypokalemia and a supressed Renin and Aldosterone levels.Our patient also had an associated primary adrenal insufficiency which was diagnosed on day 4 of admission since hyponatremia was initially thought of due to hypervolemic state.The drop in Sr.Na in the presence of typical symptoms of vague abdominal pain and intractable vomiting triggered us to do an ACTH stimulation test that confirmed a low adrenal reserve of Cortisol.Itraconazole and Hydroxy Itraconazole has a similar phenomenon.

A single centre retrospective observational study done by Minh-Vu H-Nguyen defined PIPH as "increase in Systolic BP of atleast 10mmHg or decrease in 0.5mEq/L after starting Posaconazole supplemented with elevated 11-Deoxycortisol and an undetectable Aldosterone levels and a low to normal Renin activity in the absence of any other condition or medications causing similar laboratoty values"[3].The study showed 23.2 % patients developed PIPH with median time of diagnosis of 49 days (range:14-96 days).The trough Sr.posaconazole levels more than 4mcg/dL marking the incidence of PIPH in 100% of patients. They had also documented that elderly and pre existing hypertension as risk factors for developing PIPH. Larger the azole scaffold size, the more potent its inhibitory activity towards 11β-HSD2 and the higher the selectivity over the closely related 11β-HSD1.Apparent mineralocrticoid excess usually presents with increase in bicarbonate levels,but there was no documented increase in Sr.bicarbonate levels. Oral spironolactone [4] (MR antagonist) has a promising role in treating these patients. Eplerenone is metabolised by CYP3A4 and combining with azole that inhibit CYP3A4 increases the side effects of Eplerenone. Beck et al. [5] recently noted that 11β-HSD2 was not included in off-target screening during drug development. They identified drugs that could potentially interact with this enzyme using a pharmacophore model and virtual screening of the FDA-approved DrugBank, human cell cultures, and mouse and rat kidney homogenates

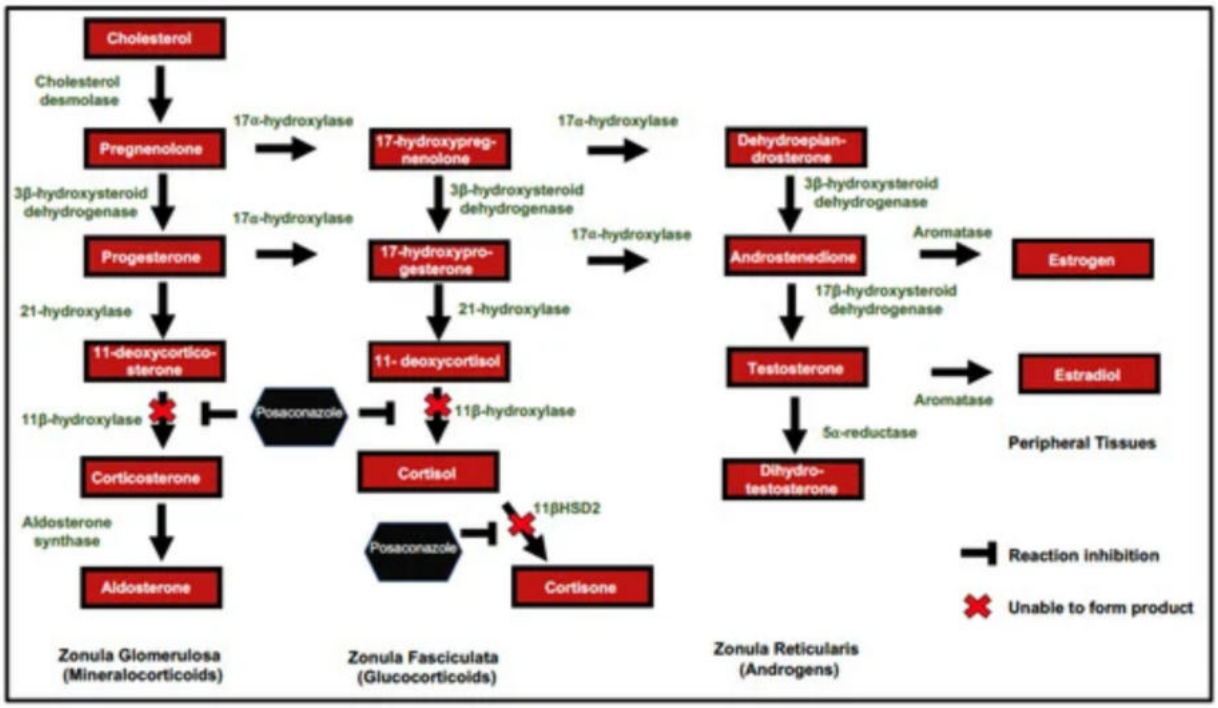

Fig.1 : MECHANISM OF PIPH AND INHIBITION OF ADRENAL STEROIDOGENESIS

CONCLUSION

Posaconazole induced Pseudohyperaldosterone is a well documented entity and with increasing usage of posaconazole in post covid Mucormycosis the incidence have further increased and patient presenting with uncontrolled hypertension and hypokalemia should raise the suspiscion.Also even though Acute primary adrenal insufficiency is rare in this setting,this should not be missed.

REFERENCES :

1. Inhibition of 11β-hydroxysteroid dehydrogenase 2 by the fungicides itraconazole and posaconazole. Beck KR, Bächler M, Vuorinen A, Wagner S, Akram M, Griesser U, Temml V, Klusonova P, Yamaguchi H, Schuster D, Odermatt A.Biochem Pharmacol. 2017Apr15;130:93-103doi:.1016/j.bcp.2017.01.010.Epub2017Jan25.PMID:28131847
2. Severe Posaconazole-Induced Glucocorticoid Deficiency with Concurrent Pseudohyperaldosteronism: An Unfortunate Two-for-One Special byAlejandro Villar-Prados1, J. Chang2,†,David A. Stevens3,4,Gary K. Schoolnik3andSamantha X. Y. Wang5,*Academic Editor: David S. Perlin*J. Fungi*2021,7(8), 620;https://doi.org/10.3390/jof70806201
3. Posaconazole Serum Drug Levels Associated With Pseudo hyper aldosteronism Minh-Vu H Nguyen,[1]Matthew R Davis,[2]Rebecca Wittenberg,[2]Ian Mchardy,[3]John W Baddley,[4]Brian Y Young,[5]Alex Odermatt,[6] and George R Thompson, III[3,7]
4. Management of posaconazole-induced pseudohyperaldosteronism Matthew R. Davis, Minh Vu H. Nguyen, Thomas J. Gintjee, Alex OdermattBrian Y. Young,George R. Thompson NephrologyInfectious Diseases
5. PMCID:PMC5923153PMID29530850 Posaconazole- Induced Pseudo hyper aldosteronism Kevin Kuriakose, [a]Whitney J. Nesbitt,[b]Matthew Greene,[a] and Bryan Harris[a]