Myoclonus, speech difficulty and AKI associated with Ranolazine

Chaugai S[1,2] MD, M Med, Sourbeer K[1,3] MD

1 Department of Neurology, Veterans Affairs Medical Center, Nashville, TN,

2 Department of Internal Medicine, Meharry Medical College, Nashville, TN

3 Department of Neurology, Vanderbilt University Medical Center, Nashville, TN

BACKGROUND

Ranolazine is a piperazine derivative sharing molecular structure with psychotropic medications. The precise molecular mechanism of anti-anginal effect of ranolazine remains incompletely understood but it is known to inhibit voltage gated late Na channels found in cardiomyocytes as well as neuronal cells, and may interact with a wide variety of CNS ion channels which could be a plausible explanation for neurological adverse effects

CASE PRESENTATION

- A 67-year-old Caucasian male presented to the emergency department with involuntary movement of limbs, facial twitching, and speech difficulty
- He was prescribed ranolazine a week prior for extensive CAD as he was not a candidate for intervention and got hypotensive with higher doses of metoprolol and ISMN. His chest pain improved but he developed episodic involuntary jerky movements in his extremities bilaterally and twitching of facial muscles 3 days later. He also developed speech difficulty described as stuttering speech and perceived difficulty finding words. He denied similar symptoms in the past. The symptoms worsened over the next 3-4 days to the extent that he was unable to drive back home and struggled to articulate words. He attributed these symptoms to his new medication ranolazine and stopped it one day prior to ED visit. He denied any focal weakness or sensory loss, gait imbalance, loss of consciousness or head trauma. He reported subjective improvement in his symptoms 12 hours after withholding ranolazine
- Complete resolution of symptoms within 72 hours of withholding ranolazine

Past Medical History :

Coronary artery disease, Hypertension, End stage renal disease on HD

Medications :

Metoprolol, Aspirin, Isosorbide mononitrate and Ranolazine

Physical Exam:

Vitals: afebrile, hypertensive to 150s/70s

Neuro: alert and fully oriented. Diffuse myoclonic twitches in face and extremities

NIH Stroke Scale score was 0

Cardiorespiratory : NAD

ED labs:

134	91	56	124
4.6	19	7.06	

10.6	10.6	317
	33.8	

Baseline :

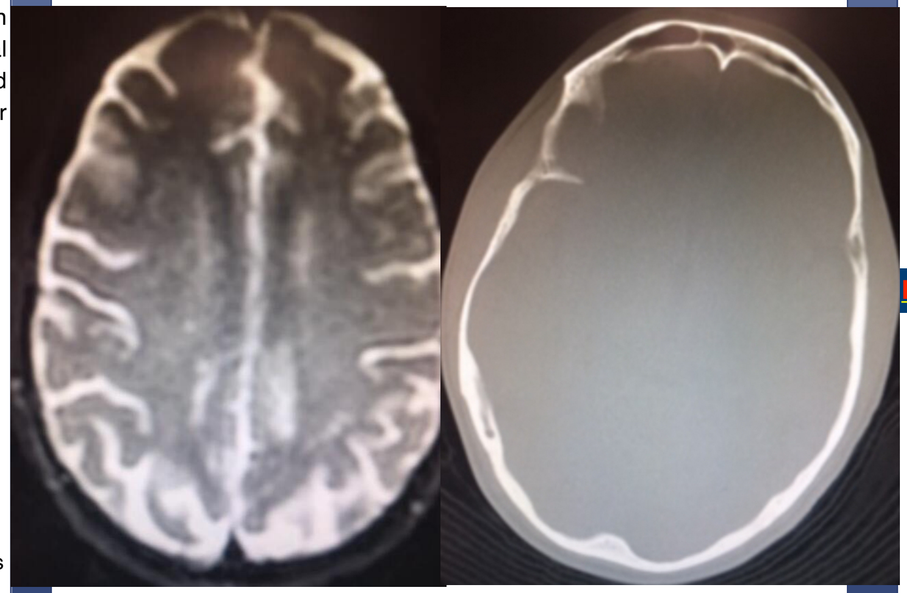
133	88	42	132
4.2	21	5.56	

10.6	11.0	312
	35.7	

- EKG: Normal sinus rhythm
- Outpatient EEG : no significant finding on the ictal or interictal spectrum

Imaging:

- CXR: No acute cardiopulmonary process
- MRI Head : Chronic microvascular ischemic disease; No acute abnormality



*Naranjo probability score = 6; probable causal relationship***

*** Drug rechallenge not done*

DISCUSSION and CONCLUSIONS

- Although extremely rare, myoclonus appears to be disruptive to the patient's daily life by interfering with their movement and speech (vocal myoclonus)
- Elderly appear to be at particularly higher risk of toxicity due to increased volume of distribution associated with decline in ranolazine clearance; estimated to be approximately 0.5-0.6% per year
- Manufacturer advises discontinuing the drug if acute kidney injury develops in patients with preexisting renal impairment
- Renal impairment has been reported to result in significantly impaired clearance of ranolazine and it's metabolites (CVT-2738, CVT-2512, CVT-2514) as well
- Significant PK variability with both 500 mg and 1000 mg BID doses of ranolazine has been reported among maintenance HD patients suggesting neither can be recommended as a starting dose

CONCLUSIONS

- Careful history taking can avoid costly and time consuming investigations and help alleviate patient anxiety
- Renal function should be monitored before and after starting ranolazine especially in patients with pre-existing renal impairment
- Ranolazine should be use cautiously in patients with end stage renal disease and the elderly

REFERENCES

Ranexa is indicated for the treatment of chronic angina . Ranexa may be used with beta, nitrates , calcium channel blockers , anti-platelet therapy , lipid-lowering therapy , ACE inhibitors , and angiotensin receptor blockers . Dosing Informatio. Published online 2006:1-15.

Undrovinas AI, Belardinelli L, Undrovinas NA, Sabbah HN. Ranolazine improves abnormal repolarization and contraction in left ventricular myocytes of dogs with heart failure by inhibiting late sodium current. In: Journal of Cardiovascular Electrophysiology. ; 2006. doi:10.1111/j.1540-8167.2006.00401

Jerling M, Abdallah H. Effect of renal impairment on multiple-dose pharmacokinetics of extended-release ranolazine. Clin Pharmacol Ther. Published online 2005. doi:10.1016/

Scoville BA, Segal JH, Salama NN, et al. Single dose oral ranolazine pharmacokinetics in patients receiving maintenance hemodialysis. Ren Fail. Published online 2019. doi:10.1080/0886022X.2019.1585371

Porhomayon J, Zadeii G, Yarahmadi A. A Rare Neurological Complication of Ranolazine. *Case Rep Neurol Med*. Published online 2013. doi:10.1155/2013/451206