Background

There is sparse but growing evidence that loperamide when taken in chronic, high dosages is associated with cardiac conduction disturbances and arrhythmias.

Hypothesis

High dose loperamide abuse is associated with significant cardiac conduction dysfunction and ventricular arrhythmias.

Methods: Case Report

• 28 year-old female with remote history of opioid dependence presents with 2 weeks of intermittent episodes of syncope.
• Initial EKG showed prolonged QRS and QTc of 795 ms
• After 5 days of hospitalization and multiple brief ventricular arrhythmias with cardiac syncope she was transferred to our institution.
• Echocardiogram and cardiac MRI were normal.
• VS upon transfer: T 98.1 F, HR 77 bpm, BP 136/69 mmHg, RR 16, O2 sat 100%
• Physical exam was unremarkable.
• WBC 12.8 x 10^3, K+ 3.2 mg/dL, Phos and Mg normal
• Urine drug screen by UPLC-TOF-MS confirmed the presence of morphine (given at prior hospital pre-transfer). Methadone, cocaine and methamphetamines were not detected.

Methods: Case Report Continued

• Soon after transfer, the patient has 2 syncopal events, the first 15 seconds and the second 58 seconds in duration, with the following corresponding EKGs, and both spontaneously resolved.
• The patient divulged she had been taking 400-600 mg of loperamide (200-300 tablets) and 2000 mg of cimetidine (20 tablets) divided throughout the day for many months to self-treat her “opiate withdrawal”, and had been continuing to do so during her hospitalization.
• She soon after had an episode of torsades de pointes as seen in Fig. 4, which self-resolved.
• Isoproterenol infusion titrated to a HR > 90 bpm successfully increased heart rate and narrowed QTc and prevented further arrhythmogenic events. Isoproterenol was required for 5 days before it could be weaned off without ventricular ectopy resulting.
• With the discontinuation of loperamide and cimetidine the the QRS and QTc intervals narrowed slowly and gradually over her hospital course.
• She was discharged on hospital day 16. QRS normalized and QTc was 516 ms, see Fig. 5

Results

• Serum concentration of loperamide was 83.2 ng/mL (therapeutic range 0.24-3.1 ng/mL and cimetidine was 6 µg /mL (therapeutic range 0.5-1.5 µg/mL).

Discussion

• Marrafa et al. Have previously described a case series of five patients detailing chronic high dose loperamide with QRS and QTc prolongation and various ventricular arrhythmogenic events.
• The widened QRS interval would suggest loperamide causes sodium channel blockade, but little evidence is available to substantiate this mechanism.
• There is some suggestion loperamide is an inhibitor of the rectifier potassium ion current (I_k) which would explain the QTc interval prolongation
• Reported half-life in chronic overdose state is 34.8 hours (Eggleston et al). The physiological effects of delayed intestinal motility may prolong absorption as well.
• Cimetidine is an inhibitor of CYP450 3A, a known metabolizer of loperamide. We propose cimetidine was taken to increase serum concentration of loperamide through inhibited metabolism.

Conclusion

• Loperamide, taken chronically and and in high doses, can cause life threatening cardiac conduction dysfunction and ventricular arrhythmias. The effects can be seen many days after discontinuation.
• Isoproterenol used to increase heart rate may be a useful medicinal modality to limit arrhythmogenic effects in the setting of loperamide overdose.