Pantoprazole (Proton Pump Inhibitor) Contributing to Torsades de Pointes Storm

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Proton pump inhibitors (PPI), commonly used medications for peptic ulcer prophylaxis, have been recently described to cause hypomagnesemia through both urinary and gastrointestinal losses. Very few reports have linked hypomagnesemia with life-threatening ventricular arrhythmias. However, these reports included patients with other complex medical problems that may have also contributed to these arrhythmias. To our knowledge, ventricular arrhythmias associated with hypomagnesemia induced by proton pump inhibitors have never been reported. We present a case of a 53-year-old chronic alcoholic male patient, who was started on a proton pump inhibitor for peptic ulcer prophylaxis, which resulted in resistant hypomagnesemia associated with a storm of life-threatening arrhythmias, namely Torsades de Pointes (TdP).

Case Report

A 53-year-old man with no previous cardiac history was brought by Emergency Medical Services with a chief complaint of palpitations and dizziness for 1 day. His only significant medical history was chronic alcohol abuse and was not taking any medications before his admission. His physical examination was normal, except for an irregularly irregular rapid pulse and a blood pressure of 157/104 mmHg. The ECG on admission showed atrial fibrillation with a QTc of 0.38 s. Patient remains well during his 1-year follow-up.

On day 16 of admission, pantoprazole was discontinued. Three days after the cessation of pantoprazole, the QTc shortened to a daily average of 0.457±0.0275 s until the day of discharge (Day 41; Figure 3). Together with the shortening of the QT interval, the daily requirements of magnesium supplementation were significantly reduced to an average of 2 g per day. There were no recurrences of pVT or TdP after the discontinuation of pantoprazole (Figure 4). Coronary angiography was also performed during this admission, and it showed no coronary artery disease. Follow-up after 1 month showed a normal ECG with a QTc of 0.38 s. Patient remains well during his 1-year follow-up.

Discussion

The question of whether hypomagnesemia results in cardiac arrhythmias remains unsolved, largely because of the absence of associated ECG and clinical electrophysiological changes. However, few ECG changes caused by hypomagnesemia succeeded cardioversions, which eventually restored sinus rhythm. Another 2 g of magnesium sulfate was administered intravenously, and the patient was intubated for airway protection. After successful cardioversion, a 12-lead ECG showed sinus rhythm at 95 beats per minute, with T wave alternans. The measured QT was 0.62 s (QTc = 0.65 s), alternating with 0.46 s (QTc = 0.51 s; Figure 2). (All QTc’s were calculated using Bazett formula on 2 separate leads.)

During his hospital stay (41 days), the patient was maintained on IV lidocaine at 2 mg/min, as well as IV magnesium for replacement (up to 6 g of magnesium sulfate per day). Despite the daily high doses of magnesium administered, the serum level fluctuated from 1.5 mg/dL to 2.7 mg/dL, and the QTc remained prolonged varying from 0.47 to 0.72 s (average of 0.538±0.062 s). Incessant sustained and nonsustained episodes of pVT and TdP continued to occur over the span of 16 days, requiring another 6 direct current cardioversions during this period. These episodes of pVT were always heralded by marked QTc prolongation, with a range of 0.55 s to 0.72 s (Figure 1B and 1C). The patient was still receiving 40 mg of pantoprazole daily. A 24-hour urine magnesium showed a urinary loss of 13.5 mg/dL.

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were described in the setting of acute myocardial infarction by Dyckner et al. These changes included widening of QRS complexes, peaking of T waves in mild magnesium losses, prolongation of the PR interval, and diminution of T waves in severe magnesium losses. Ventricular tachycardia and TdP were also reported in a few cases of magnesium deficiency. However, these cases had other contributing factors that may have caused the cardiac arrhythmia in these patients.

Intracellular magnesium and magnesium-ATP have been shown to play an important regulatory role on potassium and calcium channels in animal experiments. Experimentally, cytosolic magnesium has been described to influence the inward rectification of the potassium channels (IKr) by plugging the opened channels as well as modulating the outwardly directed potassium current (Ito), thereby allowing the potassium current to repolarize the myocardial cell. Inhibition of the IKr channel is the most common cause of prolonged QT leading to TdP. Another possible mechanism of prolonged QT caused by hypomagnesemia could be through its effect on the membrane ATP-ase, which provides the energy for transport of sodium out of the cell and potassium into the cell. Thus, magnesium deficiency, theoretically, will lead to intracellular potassium loss. With a cellular loss of potassium, repolarization of the cell will change, resulting in a prolonged QT interval. On the other hand, magnesium exerts its salutary effect on the treatment of ventricular arrhythmias associated with prolonged QT by blocking the L-type calcium current, thus shortening the QT interval. The L-type calcium channels (ICa-L) are subject to several modulatory actions of magnesium. In animal experiments, cytosolic magnesium inhibits the phosphorylated ICa-L by 63% and decreases the non-phosphorylated ICa-L by 20%. TdP is known to be caused by early after depolarizations (EADs) occurring during the prolonged plateau of repolarization or during the late repolarization phase of the prolonged action potential. ICa-L is the depolarizing current that generates the EAD upstroke and is therefore the primary mechanism for plateau-EAD formation, whereas EADs developing during the late repolarization phase is caused by modulation of the depolarizing forward-mode INaCa. Plateau EADs are generated by ICa-L if conditions for its reactivation develop during the action potential plateau. In our case, hypomagnesemia through modulation of the potassium current can prolong the action potential plateau and can set the stage for EAD generation by ICa-L. The salutary effect of cytosolic magnesium could therefore be attributed to its inhibition of ICa-L, resulting in abolition of EADs. This supports the clinical evidence that TdP responds to magnesium therapy, and hence it is considered the standard of care for pVT/TdP associated with QT prolongation.
Our patient experienced frequent episodes of fatal arrhythmias, namely TdP during his hospitalization. The only electrolyte abnormality noted was intractable hypomagnesemia. Hypomagnesemia in our patient can be attributed to 2 additive causes, namely chronic alcoholism and the use of PPI therapy. Hypomagnesemia can occur in chronic alcoholism because of renal losses as well as gastrointestinal malnutrition, which tends to resolve within 4 weeks of abstinence from alcohol. Recently, it has been shown that patients taking PPIs have a 2.5-fold increased risk of hypomagnesemia, which occurs through both renal and gastrointestinal losses. Despite the abstinence of alcohol intake, our patient continued to have persistent QT prolongation causing TdP until the discontinuation of pantoprazole on day 16 of admission. This is in concordance with the significant reduction in the daily requirement of the IV magnesium supplementation to maintain a QTc with an acceptable duration (Figure 4).

In summary, we conclude that the addition of a PPI, which is the standard of care in critically ill patients, should be used with caution in patients who have a previous tendency to hypomagnesemia, as in our patient. In these patients, PPIs can potentiate the hypomagnesemia-induced lethal arrhythmias, which can result in sudden cardiac death. PPI therapy can potentially be dangerous in critically ill patients who are prone to electrolyte and nutritional abnormalities.

Disclosures
None.

References

Key Words: arrhythmia ■ hypomagnesemia ■ pantoprazole ■ proton pump inhibitors ■ torsades de pointes
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