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Letters to the Editor

Hepatotoxicity and insomnia secondary to ranolazine

Key words: Drug-induced liver injury. Insomnia. Ranolazine.

Dear Editor,

Ranolazine is an antianginal drug indicated in the complementary symptomatic treatment of stable angina (1,2). Its mechanism of action is unknown and it appears to be due to inhibition of the delayed sodium current in cardiac cells, thereby reducing the overload of intracellular calcium (1,2). Since its commercialization, there have been no reports of elevated liver enzymes that have required suspending treatment. We present a case of elevated transaminases with insomnia associated with ranolazine treatment.

Clinical case

This was a 63-year-old female with a history of hypertension and unstable angina without signs of myocardial damage. She was on treatment with double anti-platelet medication, bisoprolol 5 mg, amlodipine 10 mg and atorvastatin 40 mg. In September of 2011, ranolazine 375 mg every 12 hours was added. At 3 months she began to experience general malaise, insomnia and alteration in liver function tests (previously normal): AST/ALT (normal value: 1-35 U/l): 97/201 U/l, GGT: 213 U/l, alkaline phosphatase (normal value: 30-120 U/l): 150 U/l. Total bilirubin: 0.55 mg/dl. The abdominal ultrasound was normal and liver disease testing with ANA, AMA, hepatitis B and C, CMV, and toxoplasmosis serologies were negative.

Ranolazine was discontinued, leaving the patient clinically asymptomatic with normalization of liver function tests (AST/ALT: 26/46 U/l; GGT: 72 U/l; alk. phos.: 75 U/l) at 2 months after discontinuing the drug.

Discussion

Ranolazine was approved in Europe in July of 2008. Its effects do not depend on changes in heart rate, blood pressure or vasodilation (1,2). It is contraindicated in cases of hypersensitivity, severe renal failure, or moderate or severe liver failure. It should be used with caution in liver or renal failure, advanced age, low body weight or moderate to severe congestive heart failure (1,2). It has several interactions and should not be administered concomitantly with powerful CYP3A4 inhibitors or class I or III antiarrhythmic drugs (1,2).

Adverse reactions are mild to moderate and are dose dependent, the most common being: dizziness, headache, constipation, vomiting/nausea, asthenia and prolongation of the QT interval (1,2). Other less common (< 1 %) adverse reactions include: Anorexia, anxiety, somnolence, syncope, blurry vision, vertigo, dry mouth, arthralgia, hyperhydrosis and insomnia (1), as in our case. They usually appear in the first 2 weeks of treatment and changes in liver enzymes are rare (> 1/10,000 to < 1/1,000).

The most common viral and autoimmune causes were ruled out, with the laboratory results pointing towards a hepatocellular toxic-medication source (3), with a temporal relationship with the start of ranolazine treatment and clinical improvement and normalization of laboratory results after discontinuing the medication. According to the CIOMS scale, a score of 8 points indicates a "probable" relationship between the drug and liver damage (5,6).

Hepatotoxicity continues to occur in the post-marketing period of new drugs, making an active approach in diagnosis and reporting by medical personnel fundamental for adjusting their safety profile.

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References

1. Reffelmann T, Kloner RA. Ranolazine: An anti-anginal drug with further therapeutic potential. Expert Rev Cardiovasc Ther 2010;8:319-29.
2. Chaitman BR, Skettino Sl, Parker JO, Hanley P, Meluzin J, Kuch J, et al. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. J Am Coll Cardiol 2004;43:1375-82.
3. Lozano-Lanagrán M, Robles M, Lucena MI, Andrade RJ. Hepatoxicity in 2011: Progressing decisively. Rev Esp Enferm Dig 2011; 103:472-9.
4. Bénichou C. Report an International Consensus Meeting. Criteria of drug-induced liver disorders. J Hepatol 1990;11:272-6.
5. Danan G, Bénichou C. Causality assessment of adverse reactions to drugs I. A novel method based on the conclusions of international consensus meetings: Application to drug-induced liver injuries. J Clin Epidemiol 1993;46:1323-30.
6. Andrade RJ, Robles M, Fernández-Castañer A, López-Ortega S, López-Vega MC, Lucena MI. Assessment of drug-induced hepatotoxicity in clinical practice: A challenge for gastroenterologists. World J Gastroenterol 2007;13:329-40.