Hepatotoxic Interaction Between Telithromycin and Amiodarone: Case Report

Telitromisin ve Amiodaron'un Hepatotoksik Etkileşimi

Gülay KOÇAK, MD,[a]
Erdem KOÇAK, MD,[b]
Murat CAN, MD[c]

[a]Department of Internal Medicine Ankara Education and Research Hospital,
[b]Department of Internal Medicine, Kızılcahamam State Hospital, Ankara
[c]Department of Biochemistry Zonguldak Karaelmas University, Faculty of Medicine, Zonguldak

Geliş Tarihi/*Received:* 15.01.2009
Kabul Tarihi/*Accepted:* 08.06.2009

Yazışma Adresi/*Correspondence:*
Erdem KOÇAK, MD
Kızılcahamam State Hospital, Department of Internal Medicine, Ankara
TÜRKİYE/TURKEY
kocak67@ hotmail.com

ABSTRACT To report a case of telithromycin-amiodarone interaction resulting in elevated liver enzymes and toxic hepatitis. A 65-year-old woman developed acute hepatitis as a result of an interaction between amiodarone 200 mg/day and telithromycin 800 mg/day. Serological tests for viral and autoimmune hepatitis were all negative. The drugs were withdrawn and laboratory findings returned to normal over the following days. Telithromycin is a new ketolide antimicrobial, specifically developed for the treatment of community-acquired respiratory tract infections. Telithromycin is a strong inhibitor of the cytochrome P450 3A4 system. Co-administration of telithromycin tablets and a drug primarily metabolized by the cytochrome P450 3A4 enzyme system may result in increased plasma concentration of the drug co-administered with telithromycin. Amiodarone is metabolized to desethylamiodarone by the cytochrome P450 enzyme group, specifically cytochrome P450 3A4 and CYP2C8. Reviewing the literature we found no case report of telithromycin-amiodarone interaction resulting toxic hepatitis. The mechanism for this interaction is inhibition of the metabolism of the amiodarone by telithromycin via inhibition of the cytochrome P450 3A4. This case report shows the necessity of hepatic monitoring of patients treated with amiodarone especially if interacting medications, such as telithromycin, are added.

Key Words: Hepatitis, toxic; telithromycin; amiodarone; drug interactions

ÖZET Telitromisin ve amiodaron etkileşimi sonucu karaciğer enzim yüksekliği ve toksik hepatit tablosu gelişen bir olgunun sunulması amaçlandı. Altmış beş yaşında bayan hastada amiodaron 200 mg/gün ve telitromisin 800 mg/gün kullanımına bağlı olarak akut hepatit tablosu gelişti.Viral seroloji ve otoimmun hepatit belirteçleri negatifti. İlaçları kesilen hastanın laboratuar bulguları takip eden günler içerisinde normal düzeylere geriledi. Telitromisin toplum kaynaklı solunum yolu enfeksiyonlarının tedavisi için geliştirilen yeni ketolid sınıfı antimikrobiyaldir. Telitromisin sitokrom p450 3A4 sisteminin güçlü bir inhibitörüdür. Sitokrom p 450 3A4 sistemi ile metabolize olan ilaçların telitromisin ile birlikte kullanılması bu ilaçların plazma düzeylerinde yükselme ile sonuçlanabilmektedir. Amiodaron sitokrom p450 3A4 sistemi, özelliklede sitokrom p450 3A4 ve CYP2C8 ile desetilamiodaron a metabolize olmaktadır. Literatürde telitromisin ve amiodaron etkileşimi sonucu ortaya çıkan toksik hepatit vakası bildirilmemiştir. Bu etkileşimin telitromisin tarafından sitokrom p450 3A4 sisteminin inhibisyonu ile amiodaron metabolizmasının azalması sonucu olduğu düşünülmektedir. Amiodarone kullanan hastalarda telitromisin benzeri ilaçlar kullanıldığında karaciğer fonksiyon testlerinin takibi gerekmektedir.

Anahtar Kelimeler: Toksik hepatit; telitromisin; amiodaron; ilaç etkleşimi

Turkiye Klinikleri J Gastroenterohepatol 2010;17(1):51-4

Telitromycin is a new ketolide antimicrobial, specifically developed for the treatment of community-acquired respiratory tract infections, is widely precribed in primary care practice. Telitromycin is highly active against beta lactam, macrolide and fluoroquinolone redu-

ced-susceptibility pathogenes.[1] Treatment-related adverse events are mainly of gastrointestinal origin and generally mild in intensity. It should be used with caution in abnormal muscle weakness, coronary heart disease, decreased kidney function, decreased liver function. There are many drug interactions associated with telithromycin, since it is a cytochrome p450 enzyme inhibitor.[2,3] Reviewing the literature, we found a few case reports of hepatitis due to telithromycin.[4-7]

Amiodarone is a widely used and effective long-term antiarrhythmic drug. The adverse effect profile of amiodarone is diverse, involving the cardiac, thyroid, pulmonary, hepatic, gastrointestinal, ocular, neurological, and dermatological systems. Interstitial pneumonitis and hepatitis are potentially fatal, but the vast majority of adverse events are less serious.[8,9]

Two main categories of drugs can produce liver disease. One group consists of intrinsic (predictable) drugs, whereas a second group consists of idiosyncratic (unpredictable) drugs.[10] Diagnosis of drug-induced hepatotoxicity requires first and foremost a careful history of drug ingestion. Liver biopsy sometimes provides an important clue to certain drug injuries, but more commonly the histologic pattern is nonspecific and/or mimics other primary liver disorders.[11] We report the first case of toxic hepatitis probably due to concomitant administiration of telithyromicin with amiodarone.

CASE REPORT

A 65 year old woman was admitted to our hospital with complaints of nausea, vomiting and abdominal pain. Three days before admission, she was admitted to the hospital because of cough and weakness. The clinicans considered acute sinusitis and atypical pneumonia and telithromycin 800 mg/day was given. At that time liver enzymes were normal. Alanine aminotransferase (ALT) 32.43 (0-42) u/l, aspartate aminotransferase (AST) 34.41 (0-37) u/l, alkaline phosphatase (ALP) 82.04 (54-110) u/l, gamma glutamyl transferase (GGT) 40.18 (5-44) u/l. Her past medical history consists of atrial fibrillation, which was diagnosed one year ago. Electrical cardioversion was performed. Thereafter sinus rhythm was restored, and amiodarone 200 mg/day was given to prevent recurrence.

During the recent hospitalization, physical examination revealed her body temperature as 37.2°C, pulse rate as 60 beats per minute, and blood pressure as 130/80 mmHg. Right sided upper abdominal tenderness was found on abdominal examination. Her respiratory, cardiac, and abdominal examinations revealed normal findings.

Labaratuary tests were ; the hemoglobine 11.8 g/dl, white-cell count 4.400/mm3, platelet count 424.000/mm3 and erythrocyte sedimentation rate 30 mm/hour. The levels of urea nitrogen, creatinine, glucose, calcium, phosphorus, magnesium, sodium, and potassium were normal. ALT 1240. 41 (0-42) u/l, AST 1480.93 (0-37) u/l, ALP 187.43 (54-110) u/l, GGT 234.04 (5-44) u/l were elavated. Amylase, lipase, total and conjugated bilirubin, prothrombine time and activated partial thromboplastin time were normal. HBsAg, anti-HBs, anti-HBcIgM, anti-HCV, anti-HAV IgM, anti-CMV IgM, EBV VCA IgM and autoantibodies (ANA, SMA, SLA, LKM) were negative. Electrocardiogram was showed sinus rhythm and no ischemic events. There were no pathological findings on abdominal ultrasonography.

She was hospitalized with the diagnosis of drug-induced hepatitis and all drugs (Telithromycin and amiodarone) were withdrawn, and laboratory findings progressively returned to normal over the following days. The patient was discharged on the fifth day of hospitalization. There after the patient was followed as outpatient and one month after discharge the labaratory tests were normal. (Table 1).

DISCUSSION

Ketolides are a new class of semi-synthetic agents derived from erythromycin. Telithromycin (HMR 3647) is the first member of this new class to be approved to treat sinusitis, acute exacerbations of chronic bronchitis, cellulitis, pneumonia. The most common adverse events of telithromycin include diarrhaea, nausea, headache, vomiting and dizzi-

TABLE 1: The liver enzymes of the patient.

	AST (u/l)	ALT (u/l)	ALP (u/l)	GGT (u/l)
1. day	1480.93	1240. 41	187.43	234.04
2. day	225.81	330.92	139.7	156.98
3. day	89.43	232.82	118.86	121.63
5. day	64.44	162.7	102.81	112.98
1. month	24.12	32.17	74.41	43.37

ness. Recently telithromycin induced toxic hepatitis have been reported.[4-7]

Telithromycin is a strong inhibitor of cytochrome P450 3A4. Co-administration of telithromycin tablets and a drug primarily metabolized by the cytochrome P450 3A4 enzyme system may result in increased plasma concentrations of the drug.

Amiodarone is metabolized to desethylamiodarone by the cytochrome P450 enzyme group, specifically cytochrome P450 3A4 and CYP2C8. Therefore, amiodarone has the potential for interactions with drugs or substances that may be substrates, inhibitors, or inducers of CYP3A4. While only a limited number of in vivo drug-drug interactions with amiodarone have been reported, the potential for other interactions should be anticipated.

Patients who receive amiodarone may develop mild increases in serum aminotransferase levels, which may normalize despite contiunation of therapy. This can be accompanied by engorgement of lysosomes with phospholipid. Hepatic toxicity of amiodarone leads to two histologic pictures: pseudo-alcoholic hepatitis and phospholipoidosis. Immune mechanisms are also possible in amiodarone-induced hepatotoxicity.[12]

In our case, she did not agree to a liver biopsy so histopathological examination was not performed. Before telithromycin administration, her liver enzymes were normal, and she had been on amiodarone therapy for one year. Three days after starting telithromycin, she developed elevated aminotransferase levels, which resolved following the drugs withdrawal.

In this case it seems that hepatitis was devoloped due to telithromycin or pharmacokinetic drug interaction between telithromycin and amiodarone. In this case report the documentation of amiodarone plasma levels before and after telithromycin co-administration was required. But we have no plasma levels before and after telithromycin administration. It is not possible to state that the abnormalities were definitively due to one drug or another, or if so, which one.

Reviewing the literature there are a few case reports about hepatotoxicity of telithromycin. Therefore we considered that in this case toxic hepatitis was devoloped because of drug-drug interactions.

The Council for International Organizations of Medical Sciences (CIOMS) developed a scale that aims to generate valid and reproducible cause-effect assessments of drug-induced adverse hepatic reactions,[13] which was found to be more accurate in attributing causality in a previous study.[14] CIOMS score revealed that this adverse drug event as a result of the telithromycin and amiodarone interaction was probable.

In summary, this case report showed the necessity of hepatic monitoring of patients treated with amiodarone, especially if interacting medications, like telithromycin, are added.

REFERENCES

1. Spiers KM, Zervos MJ. Telithromycin. Expert Rev Anti Infect Ther 2004;2(5):685-93.
2. Kolilekas L, Anagnostopoulos GK, Lampaditis I, Eleftheriadis I. Potential interaction between telithromycin and warfarin. Ann Pharmacother 2004;38(9):1424-7.
3. Reed M, Wall GC, Shah NP, Heun JM, Hicklin GA. Verapamil toxicity resulting from a probable interaction with telithromycin. Ann Pharmacother 2005;39(2):357-60.
4. Clay KD, Hanson JS, Pope SD, Rissmiller RW, Purdum PP 3rd, Banks PM. Brief communication: severe hepatotoxicity of telithromycin: three case reports and literature review. Ann Intern Med 2006;144(6):415-20.
5. Bertino JS. Severe hepatotoxicity of telithromycin. Ann Intern Med 2006;145(6): 472.
6. Onur O, Guneysel O, Denizbasi A, Celikel C. Acute hepatitis attack after exposure to telithromycin. Clin Ther 2007; 29(8):1725-9.
7. Bolesta S, Roslund BP. Elevated hepatic transaminases associated with telithromycin therapy: a case report and literature review. Am J Health Syst Pharm 2008;65(1):37-41.
8. Lewis JH, Ranard RC, Caruso A, Jackson LK, Mullick F, Ishak KG, et al. Amiodarone hepatotoxicity: prevalence and clinicopathologic correlations among 104 patients. Hepatology 1989;9(5):679-85.
9. Podstawka A, Mosiewicz J, Myśliński W. Pulmonary complications in amiodarone treatment. Ann Univ Mariae Curie Sklodowska Med 2004;59(2):172-7.
10. William ML, Frank VS. Drug-induced liver disease. In: Yamada T, Alpers HD, Kaplowitz N, Laine L, Owyang C, Powel WD, eds. Textbook of Gastroenterology. 4th ed. Philadelphia: Lippincott Williams and Wilkins; 2003.p. 2355-65.
11. Pınarbaşı B, Demir K. [Drug induced hepatitis]. Turkiye Klinikleri J Int Med Sci 2006; 2(1):62-9.
12. Drazen JM, Gill GN, Griggs RC, Kokko JP, Mandel GL, Powel DW, et al. Toxic and drug induced liver disease. In: Goldman L, Claude Bennett J, eds. Cecil. Text Book of Medicine. 21st ed. Philadelphia: WB Saunders Company; 2000. p.781-2.
13. Danan G, Benichou 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(11):1323-30.
14. Lucena MI, Camargo R, Andrade RJ, Perez-Sanchez CJ, Sanchez De La Cuesta F. Comparison of two clinical scales for causality assessment in hepatotoxicity. Hepatology 2001;33(1):123-30.