Hepatotoxic Interaction Between Telithromycin and Amiodarone: Case Report

Telitromisin ve Amiodaron'ın Hepatotoksik Etkileşimi

**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 The drugs were withdrawn and laboratory findings returned to normal over the following days.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 3A4 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


**Anotaht Kelimeler:** Toksik hepatit; telitromisin; amiodaron; ilaç etkileşimi

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Telitromycin is a new ketolide antimicrobial, specifically developed for the treatment of community-acquired respiratory tract infections, is widely prescribed in primary care practice. Telitromycin is highly active against beta lactam, macrolide and fluoroquinolone redu-
ced-susceptibility pathogenes. 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. Reviewing the literature, we found a few case reports of hepatitis due to telithromycin.

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.

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. 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. We report the first case of toxic hepatitis probably due to concomitant administration of telithromycin 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 clinicians 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.

Labaratory tests were; the hemoglobin 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, 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 elevated. Amylase, lipase, total and conjugated bilirubin, prothrombine time and activated partial thromboplastin time were normal. HBsAg, anti-HBs, anti-HBcIgM, anti-HCV, anti-CMV IgM, anti-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 diarrhoea, nausea, headache, vomiting and dizzi-
iness. Recently telithromycin induced toxic hepatitis have been reported.\textsuperscript{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 continuation 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.\textsuperscript{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 developed 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 developed 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,\textsuperscript{13} which was found to be more accurate in attributing causality in a previous study.\textsuperscript{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.

| 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        |

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REFERENCES