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Paracetamol and Simvastatin: A Potential Interaction Resulting in Hepatotoxicity

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Key words: *paracetamol; simvastatin; drug interaction; hepatotoxicity.*

Summary. *The safety profile of paracetamol and simvastatin is sufficiently well known, although no interactions between these two medicinal products have been described in the scientific literature so far.*

A 66-year-old female patient who experienced myocardial infarction and underwent coronary artery bypass grafting 9 years ago was taking simvastatin at a daily dose of 10 mg. Liver enzyme tests were carried out regularly, and their results were always normal. Later on, the patient took 6 tablets of fixed combination medicinal product Gripex™ (paracetamol, pseudoephedrine, and dextromethorphan) per day due to a fever. The daily dose of paracetamol taken by the patient totaled 1.95 g. The patient developed severe jaundice, nausea, vomiting; blood bilirubin levels increased more than 3 times; alanine transaminase, more than 10 times; and asparagine transaminase, more than 5 times. Paracetamol is metabolized by CYP enzymes (CYP2E1, 1A2, 2A6, 3A4) to a reactive metabolite, N-acetyl-p-benzoquinone-imine (NAPQI). Under conditions of excessive NAPQI formation or reduction in glutathione stores by approximately 70%, NAPQI covalently binds to the cysteinyl sulfhydryl groups of cellular proteins, forming NAPQI-protein adducts. Simvastatin is a substrate of CYP3A4 enzyme.

Clinical and pharmacological data, available in the published literature, allow the assumption that simvastatin may induce CYP3A4 and result in increased hepatoxicity of paracetamol.

Introduction

Paracetamol, also known as acetaminophen, is the most widely used pharmaceutical analgesic and antipyretic agent (1). It has been in use for more than 50 years. Various formulations of paracetamol are available: tablets, suspensions, elixirs, dissolvable tablets, chewable tablets, etc. Paracetamol is a component of many over-the-counter cold and analgesic medications and prescription combinations. Paracetamol has long been recognized as potentially hepatotoxic in association with paracetamol misuse and overdose (2).

Simvastatin is a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase enzyme inhibitor that effectively reduces total and low-density lipoprotein (LDL) cholesterol levels in blood. Although considerable clinical experience has been acquired in the use of both products, no interactions between simvastatin and paracetamol have been described in the scientific literature so far. We present a case of hepatotoxicity possibly associated with a concurrent use of paracetamol and simvastatin.

Case Report

A 66-year-old female patient weighing 70 kg was admitted to the hospital emergency department at 8 PM on December 17, 2010, due to severe jaundice, nausea, vomiting, and weakness. The patient became ill on December 15, 2010. She had a fever; therefore, she took 6 tablets of a fixed combination medicine, Gripex™ (1 tablet contains 325.0 mg of paracetamol, 30.0 mg of pseudoephedrine hydrochloride, and 10.0 mg of dextromethorphan hydrobromide). The body temperature returned to normal the next day, but the patient experienced jaundice, nausea, vomiting, and dark urine. The patient had myocardial infarction 9 years ago and underwent coronary artery bypass grafting. She had been taking simvastatin (Vasilip™) at a dose of 10 mg once daily. The patient was aware of the possible hepatotoxicity of simvastatin; therefore, she repeated the tests of hepatic enzymes in blood twice a year, and no changes were observed. Furthermore, the patient had been taking ramipril (Cardace™) at a dose of 5 mg once daily, metoprolol (Betaloc Zok™) at a dose of 50 mg once daily, isosorbide mononitrate (Imdur™) at a dose of 30 mg once daily, and aspirin at a dose of 100 mg once daily. The patient had a history of jaundice 2 times 50 years ago and hysterectomy due to an oncological disease 7 years ago. The patient neither smoked nor consumed alcohol.

Laboratory Investigation. Blood cell counts were assessed on December 17, 2010: leukocyte count was 10.9×10^9/L (reference range, $4–9\times10^9$/L); he-

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moglobin and erythrocyte counts were with the reference range. Blood chemistry tests carried out on December 17, 2010 revealed the following values: total bilirubin, 65.3 μmol/L (reference range, 3.4–20.5 μmol/L); conjugated bilirubin, 41.3 μmol/L (reference range, 0–5.1 μmol/L); nonconjugated bilirubin, 24 μmol/L; alanine transaminase (ALT), 287 U/L (reference range, 10–28 U/L); asparagine transaminase (AST), 160 U/L (reference range, 9–36 U/L); alkaline phosphatase (AP), 144 U/L (reference range, 40–141 U/L); C-reactive protein (CRP), 190 mg/L (reference range, 0–5 mg/L); potassium, glucose, creatinine, *p*-amylase levels and prothrombin index were within references ranges. The urine test performed on December 18, 2010, showed the following values: leukocytes 0/μL (reference range, 0–10/μL); erythrocytes, 200/μL (reference range, 0–5/μL); ketones, 3.9 mmol/L (reference range, 0 mmol/L); and bilirubin, 17 μmol/L (reference range, 0 μmol/L). The findings of immunological tests for hepatitis B and C performed on December 21, 2010, were as follows: HbsAg, negative; AntiB cor, positive; and antiHCV, negative. Abdominal ultrasonography performed on December 20, 2010, revealed the liver without changes, the wall of the gallbladder without thickening with sediments, a stone 0.3 cm in diameter, and not extended biliary ducts. The kidneys, pancreas, and spleen were without changes. Abdominal computed tomography revealed the increased, homogeneous liver; the changes in focal density were not observed. The gallbladder, biliary ducts, pancreas, kidneys, and adrenal glands were without changes. The lymph nodes were not enlarged.

During a surgeon's consultation, no evidence of mechanical jaundice was documented. During a consultation with an infectious disease physician, no hepatitis B or C was found. Gastroesophageal fibroscopy showed erosive gastropathy. No changes were seen on a chest x-ray.

Toxic hepatitis was diagnosed for the patient. It could be developed due to an interaction between simvastatin and paracetamol. Treatment with simvastatin and paracetamol was discontinued; the patient continued to use oral ramipril, metoprolol, isosorbide mononitrate, and aspirin. Additionally, drotaverine and silymarin tablets were administered. Moreover, fluid therapy was initiated. The patient began to feel better: nausea and vomiting disappeared, and general condition improved. The patient was discharged from the hospital on December 23, 2010. She arrived at the reappointment on January 3, 2011. The patient felt well, she was taking the recommended medications without simvastatin and paracetamol. The following findings of biochemical tests were recorded: potassium and creatinine were within the reference ranges; total bilirubin, 34.7 μmol/L; conjugated bilirubin, 12.4 μmol/L; unconjugated bilirubin, 22.3 μmol/L; ALT, 477 U/L; AST, 205 U/L; AP, 300 U/L; and CRP, 5.0 mg/L. The patient was consulted again by an infectious disease physician on January 19, 2011. In addition, tests for HBeAg and antiHBe were carried out, and their results were negative. The tests of hepatic enzymes, repeated on February 1, 2011, revealed a significant decrease in the following enzyme levels: ALT, 44 U/L; AST, 36 U/L; and AP, 151 U/L.

Discussion

The maximal recommended daily dose of paracetamol is 4 g. When dosing recommendations are followed, the risk of hepatotoxicity is extremely low, but an overdose may result in liver damage. Besides, liver damage associated with a therapeutic use of paracetamol is idiosyncratic in a small proportion of patients. The ingested amount of paracetamol at which toxicity may occur may be lower in cases of chronic ethanol use, malnourishment, or diminished nutritional status, fasting, or viral illness with dehydration, or if substances or medications known to induce the activity of cytochrome P450 (CYP450) oxidative enzymes are used (1).

Certain circumstances, particularly if paracetamol is taken at doses higher than recommended, have been associated with elevated aminotransferase levels (3). Aspartate aminotransferase and ALT levels start to elevate within 24 hours after the ingestion of paracetamol and reaches a peak at about 72 hours. The activity of serum aminotransferase depends on synthesis, degradation, and release from cells in the liver, muscles, and other tissues (4). The activity of ALT may increase due to apoptosis through increased hepatocyte membrane permeability without cell death, secondary to increased enzyme production, or from reduced enzyme degradation or clearance (5).

The mechanism of paracetamol hepatotoxicity is well defined. Damage to the liver occurs not due to paracetamol itself but due to its reactive intermediate metabolite, N-acetyl-*p*-benzoquinone imine (NAPQI), which is produced by the hepatic CYP450 system. Under normal conditions, NAPQI is rapidly conjugated with glutathione (GSH) to form mercapturic acid and other related products, which are nontoxic and excreted in urine. If, however, glutathione stores are depleted by malnutrition or if insufficient glutathione is available (as in alcoholics), or if the production of NAPQI exceeds the capacity of its detoxification (as in an overdose of paracetamol), unconjugated NAPQI accumulates, binds covalently to hepatic tissue macromolecules, and causes oxidative stress, tissue damage, or necrosis (6). Several isoenzymes of CYP450 (CYP2E1, 1A2, 2A6, and 3A4) are capable of producing NAPQI, although the production of NAPQI is caused by two isoenzymes, CYP2E1 and CYP1A2 (7). The inducers of CYP2E1 and CYP1A2 may enhance the production of NAPQI and, consequently,

increase the toxicity of paracetamol given even at the recommended doses. It has been recently suggested that CYP3A4 may participate in paracetamol metabolism to a greater extent than previously realized, and the induction of this isoform may predispose patients to paracetamol-induced hepatotoxicity (8). Furthermore, the genetic polymorphisms of CYP2D6 may contribute to significantly different rates of NAPQI production. Individuals can be classified as "extensive," "ultrarapid," and "poor" metabolizers (and also producers of NAPQI), depending on their levels of CYP2D6 expression. Although CYP2D6 metabolizes paracetamol into NAPQI to a lesser extent than other P450 enzymes, its activity may contribute to paracetamol toxicity in extensive and ultrarapid metabolizers and in cases when paracetamol is taken at very large doses (7).

Simvastatin is also metabolized by CYP450 enzymes. CYP3A4, CYP3A5, and CYP2C8 catalyze the formation of 3 metabolites of simvastatin, and CYP3A4 is most active. CYP2D6 as well as CYP2C19, CYP2C9, CYP2A6, CYP1A2, and CYP2E1 are not involved in the metabolism of simvastatin (9). Simvastatin does not induce CYP2E1 enzyme. The most important adverse effects associated with statins, including simvastatin, are asymptomatic increases in liver transaminases and myopathy. The majority of liver abnormalities occur within the first 3 months of therapy. According to the data retrieved from large clinical trials, the elevation of liver transaminases by more than 3 times the reference value in the statin-treated patients was only slightly greater compared with the placebo groups. During the initial postmarketing surveillance of statins, elevations in hepatic transaminases were reported at incidences of up to 1%, although it was not significantly different from placebo (10). The possible interaction of statins and paracetamol was described earlier, when Raje et al. reported a hepatotoxic interaction between other statin, lovastatin, and paracetamol in mice (11).

We reported the case of hepatotoxicity in the patient who had been treated with simvastatin for a long time without any toxic effect on the liver as evidenced by regular liver function tests. The signs of hepatic toxicity manifested after the patient took 6 tablets of Gripex™ because of fever. It totaled to 1.95 g of paracetamol; thus, the safe daily dose of 4 g was not exceeded. The patient had been also taking a few concomitant medications, any of which could be able to induce the CYP3A4 enzyme and thus enhance the conversion of paracetamol to its toxic metabolite NAPQI. The patient was not taking other known hepatotoxic agents or alcohol. The results of tests for hepatitis B or C were negative. We assume that hepatotoxicity could have resulted from a concomitant use of paracetamol and simvastatin, because the signs of hepatotoxicity disappeared after the discontinuation of both medicinal products, whereas other medicines were continued. Metoprolol is a substrate for CYP2D6, but it neither induces nor inhibits this enzyme. Ramipril and isosorbide mononitrate are not substrates for CYP450 isoenzymes. Of note, these agents undergo glucuronidation, and glucuronides are excreted in urine. However, the possibility that another drug or disease was the true cause of liver injury cannot be excluded.

Conclusions

The concomitant use of simvastatin and paracetamol may enhance hepatotoxicity of these products. As in the case of all drugs, the decision to use paracetamol rests on a thorough risk-benefit assessment, and the administration of acetylcysteine (paracetamol antidote) concomitantly should be considered.

Statement of Conflict of Interest

The authors state no conflict of interest.

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