Repaglinide induced Acute Hepatotoxicity

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ABSTRACT

Repaglinide is considered a safe drug; adverse events are mild to moderate which includes hypoglycemia, headache, nausea, vomiting, diarrhea and dyspepsia as similar to sulphonylureas. This case report describes a rare side effect of repaglinide. In rare cases, elevated liver enzymes have been noted. We report a case of acute hepatotoxicity in a 78 year old woman who developed acute hepatotoxicity while taking repaglinide.

Key Words: *hepatotoxicity, hypoglycemia, repaglinide,*

INTRODUCTION

Repaglinide is fast, short acting meglitinide analog antidiabetic drug approved for the treatment of type 2 diabetes mellitus. Although chemically unrelated to the sulphonylureas, repaglinid acts similarly by stimulating release of insulin from the pancreatic beta cells. Hypoglycemia is a major adverse effect of this drug.[1] In rare cases, elevated liver enzymes have been noted.[2] Repaglinide clearance is dependent on liver enzyme activity and secondarily on hepatic blood flow. It is rapidly cleared from blood stream with a half life of less than one hour.[3] It is extensively metabolized in the liver by cytochrome P450 (CYA) to inactivate metabolites. The primary route of elimination of repaglinde and its metabolites is via biliary fecal excreation.[4]

CASE REPORT

A 78 year old, white female was transferred from a nursing home facility to our hospital with a chief complaint of epigastric pain associated with nausea. Her past medical history was significant for hypertension, type 2 diabetes, hypercholesterolemia, coronary artery disease, multi-infarct dementia and depression, cerebrovascular accident, status post percutaneous endoscopic gastrostomy (PEG) and colostomy (secondary to volvulus of sigmoid colon), deep venous thrombosis of leg, status post inferior vena cava filter, and polymyalgia rheumatica. She denied any vomiting, fevers, chills, shortness of breath, headaches, dizziness, palpitations. There were no complaints with feeding tube and the colostomy site was working normally. Repaglinide was started one month prior to this admission to the hospital. On physical examination, she had apparent scleral and skin icterus. Other than minimal epigastric and right upper quadrant tenderness, rest of her examination was benign. There were no palpable lymph nodes and no organomegaly. Comprehensive metabolic panel revealed deranged liver function tests with an alkaline phosphatase of 210 U/L (36-115 U/L), AST 289 U/L (10-41 U/L), ALT 582 U/L (5-49 U/L), total bilirubin 1.6 mg/dl (0.3-1.1 mg/dl), direct bilirubin

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0.4 mg/dl (0-0.3 mg/dl), serum albumin 3.2 g/dl (3-5 g/dl), serum globulin of 4 g/dl (2.3-3.5 g/dl). PT, PTT, INR, complete blood counts, rest of the basic metabolic panel, lipase and amylase were all within normal limits. Her viral hepatitis panel and screening for autoantibodies was negative.

An ultrasound of the liver demonstrated sludge within the gallbladder with no wall thickening, or pericholecystic fluid or dilatation; nonetheless, there was positive sonographic Murphy sign. Consequently, she had a nuclear cholescintigraphy (HIDA scan) performed which showed normal liver size with normal intensity of the parenchymal uptake. However, there was persistent hepatic retention of tracer throughout the 24 hours study without excretion and without visualization of the intrahepatic biliary ducts, common bile duct, and intestinal tract, so, the gallbladder was not visualized as no tracer was being excreted. There were no demonstrable mass lesions. One consideration at that time was severe intrahepatic cholestasis secondary to diffuse hepatocellular disease; although parenchymal intensity of the liver was normal making possibility of hepatocellular disease less likely.

Thereafter, she had a Magnetic Resonance Cholangiopancreatography (MRCP) performed which was essentially normal. Again, there was no evidence of ductal dilatation or choledocolithiasis. There was probable sludge in the gallbladder without evidence of calculus disease or wall abnormality. She had a follow-up ultrasound performed 6 days later which remained unchanged.

Repaglinide was discontinued on third day of admission and she was transferred back to nursing home with a plan to follow-up liver function tests as an out-patient and to pursue a biopsy if they continued to deteriorate. Two weeks following the discharge, follow-up liver function tests showed alkaline phosphatase 114 U/L (36-115 U/L), AST 21 U/L (10-41 U/L), ALT 66 U/L (5-49 U/L), total bilirubin 0.9 mg/dl (0.3-1.1 mg/dl), direct bilirubin 0.4 mg/dl (0-0.3 mg/dl), serum albumin 3.4 g/dl (3-5 g/dl), serum globulin of 4.1 g/dl (2.3-3.5 g/dl) and remained stable thereafter.

DISCUSSION

Most drug induced hepatotoxicity is idiosyncratic, occurring in a small percentage of patients ingesting the drug. Idiosyncratic hepatic reactions are often associated with partial dose dependence and a relationship to drug metabolism.[4] Repaglinide clearance is dependent on liver enzyme activity and secondarily on hepatic blood flow. It is rapidly cleared from blood stream with a half life of less than 1 hour. It is extensively metabolized in the liver by cytochrome P450 (CYA) to inactivate metabolites. The primary route of elimination of repaglinde and its metabolites is via biliary fecal excreation.[5]

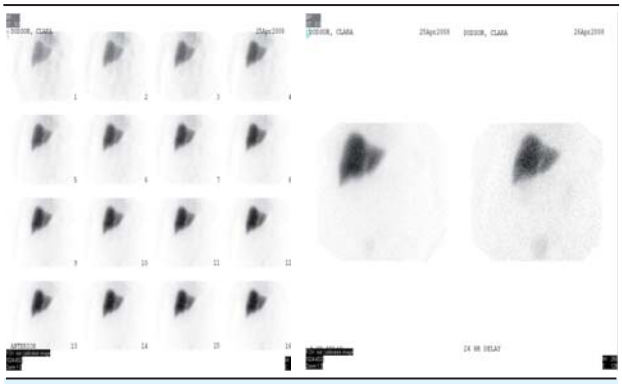

Figure 1. HIDA scan showing persistent hepatic retention of tracer throughout the 24 hours study without excretion and without visualization of the intrahepatic biliary ducts, common bile duct and intestinal tract

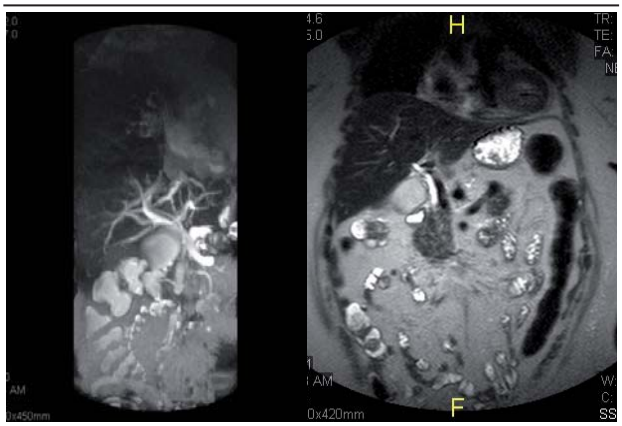

Figure 2. MRCP showing no evidence of ductal dilatation or choledocolithiasis, probable sludge in the gallbladder without evidence of calculus disease or wall abnormality

Two types of reactions have been described, hypersensitivity reactions are immune mediated: occur within first 4 to 6 weeks; and are associated with fever, rash, eosinophilia, and hepatitis like disease. Metabolic idiosyncratic reactions tend to occur at almost any time during the first year of treatment.

To our knowledge it is the first case reported in United States. There are two case reports on cholestatic hepatitis associated with repaglinide, both are from Spain.[6,7] The putative role of repaglinide in this case of acute cholestasis is strongly supported by its temporal eligibility, the careful exclusion of alternative causes and rapid improvement after drug withdrawal. Multiple comorbidities could account for the transient abnormalities but temporal association strongly implies the drug etiology.

Repaglinide induced liver toxicity can occur, and clinicians should be aware of this possibility when prescribing this drug.

REFERENCES

1. Hatorp V. Clinical pharmacokinetics and pharmacodynamics of repaglinide. Clinical Pharmacokinet. 2002;41: 471-83.
2. Jovanovic L, Dailey G III, Huang WC, Strange P, Goldstein BJ. Repaglinide in type 2 diabets: a 24-week, fixed dose efficacy and safety study. J Clinical Pharmacology. 2000;40: 49-57.
3. Culy CR, Javis B. Repaglinide: a review of its therapeutic use in type 2 diabetes mellitus. Drugs. 2001;61: 625-60.
4. Owens DR, Repaglinide: a new short acting insulinotropic agent for the treatment of type 2 diabets. Eur J Clin Invest. 1999;29 (Suppl 2): 30-7.
5. Kaplowitz N, Aw TY, Simon FR, Stolz A. Drug induced hepatoxicity. Ann Internal Medicine. 1986;104: 826-39.
6. Lopez-Garcia F, Borras J, Verdu C, Salazar V.R, Ruiz J A, Sales J. Cholestatic hepatitis associated with repaglinide. Diabetic Care. 2005;28: 752-3.
7. Nan D N, Herndndez J L, Fernandez-Ayala M, Carrascosa M. Acute hepatotoxicity caused by repaglinide. Annals of Internal medicine. 2004;141(10): 823.