A new cause of acute hepatitis : Gemifloxacin

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To the Editor,

We wish to draw attention to a largely unreported side effect of the drug Gemifloxacin, drug induced hepatotoxicity, which has been observed in our institution.

Gemifloxacin is a recently introduced fluoroquinolone antibiotic which is frequently used for its broad spectrum. In generally gemifloxacin is well tolerated with most side effects being comparable with other compounds. The most frequent side effects are abdominal pain, diarrhoea, and headaches (1).

Factors that determine individual vulnerability to liver toxicity may include age, genetic predisposition, systemic disease, nutritional status and concomitant exposure to other hepatotoxic agents. Most of the drug-induced liver injuries are idiosyncratic reactions and occur in an unpredictable manner. These reactions may occur at any time during exposure to a drug (2).

However, certain patient groups are at increased risk of drug adverse effects. Presence of HBV infection or an underlying silent chronic liver disease were found to increase the risk of drug induced hepatotoxicity (3). A case report of levofloxacin induced acute fulminant hepatic failure in a hepatitis B virus carrier patient has previously been published (4). To our knowledge, to the time of writing, there has been no other reported case of gemifloxacin-associated liver injury. Here, we report a case where a woman developed acute hepatitis after taking gemifloxacin.

A 45-year-old woman with elevated liver enzymes was referred to our department by her family physician. According to the history given by the patient, two weeks earlier she had gone to her local hospital suffering from malaise, fever, purulent nasal discharge and unilateral maxiller sinus tenderness which had occured over the last five days. At that time, she was diagnosed as having acute rhinosinusitis, and oral gemifloxacin 320 mg once daily for 10 days was prescribed empirically. Ten days later, the patient returned to the same hospital showing symptoms of jaundice and pruritus which had developed over the previous three days. Blood tests revealed elevation of liver enzymes, so she was referred to our department where she was admitted for follow up. Her past medical history revealed HBsAg positivity showing that she had been as an asymptomatic hepatitis B virus (HBV) carrier for ten years. Treatment had been carried out in her local hospital, and the results of her liver function tests were within normal limits. She said she had not consumed any alcohol, any herbal or folk remedies, or any other over-the-counter agents. Biochemical parameters performed on admission were as follows: alanine transaminase (ALT): 361 IU/mL (normal range 0-32 IU/mL), aspartate transaminase (AST): 132 IU/mL (normal range 0-32 IU/mL), alkaline phosphatase: 276 IU/mL (normal range 45-129 IU/mL), gammaglutamyltranspeptidase (GGT): 1076 IU/mL (normal range 0-73 IU/mL), total bilurubin 8.2 mg/dL (normal range 0-1.2 mg/dL), direct bilurubin 5.2 mg/dL (normal range 0-0.2 mg/dL). Other serum biochemistry results, including serum albumin level, prothrombin time and renal function tests, were within the normal ranges. Her laboratory findings for hepatitis B at that time included; HBS Ag positive, Hbe Ag negative, HBV IgM negative, HBV DNA negative. Serological markers for other acute viral hepatitis were negative for hepatitis A, herpes simplex viruses, Epstein-Barr virus, and cytomegalovirus. Anti-HCV, anti-HIV, and HCV RNA were all negative. In addition, laboratory tests for autoimmune hepatitis, hemochromatosis, thyroid diseases or Wilson's disease were also negative. Abdominal ultrasonography revealed no evidence of extrahepatic obstruction, biliary ductal disease, hepatic parenchymal abnormalities, or cholelithiasis. Gemifloxacin was stopped and liver function improved. The patient was discharged in a clinically asymptomatic condition eight days after admission. Tests showed that liver function reached normal levels within four weeks. The results of liver function tests over time are presented in Table 1.

Drug-induced hepatotoxicity is categorized as predominantly cholestatic or hepatocellular. For many drugs, however, the type of reaction is more variable, with hepatocellular, cholestatic, or mixed injury. Mixed injury is usually either predominantly hepatocellular with prominent cholestatic features or predominantly cholestatic with evident parenchymal injury (5). Our patient's elevated values of serum transaminases, alkaline phosphatase, γ-glutamyl transferase and bilirubin levels

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Table 1. — **The time course of the liver function tests**

Parameter	Admission	Week			
		1	2	3	4
AST (0-34 U/L)	132	111	67	43	22
ALT (0-49 U/L)	361	264	162	78	34
GGT (0-73 IU/mL)	1072	784	558	226	68
Total bilirubin (0-1.2 mg/dL)	8.2	5.4	2.1	1.4	0.7
Direct bilirubin (0,0-0,2 g/dL)	5,2	3.1	1.1	0.7	0,1

were consistent with mixed-type liver injury. From animal studies, gemifloxacin has been found to have a serious adverse profile with an acute overdose. They include: increases in liver weight, chronic hepatitis, acute gastritis, erosion of the articular surface of joints and histopathological changes in the Achilles tendon. Increase in white blood cell count, total bilirubin, glucose, alanine aminotransferase, and decreased total protein levels were also seen, but at the end of treatment they returned to normal levels (6). Our patient's liver function also returned to normal levels after stopping gemifloxacin.

The temporal relation between the use of gemifloxacin, and the exclusion of other causes of hepatitis was compatible with the diagnosis of gemifloxacin-associated hepatotoxicity. The Naranjo Adverse Drug Reaction Probability Scale score for this association was "probable" (score 5) and the Roussel Uclaf Causality Assessment Method Scale score was "highly probable" (score 8) (7-8).

To conclude, doctors should be aware of the possibility of gemifloxacin associated hepatic injury when prescribing this drug. It is unclear whether routine monitoring of hepatic function is needed with gemifloxacin treatment especially in patients with hepatitis B.

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