



Glacier National Park

PIC QUESTION OF THE WEEK: 1/23/12

Q: Has amoxicillin/clavulanic acid been implicated as a cause of liver disease?

A: The majority of medications requiring FDA action (new warnings, removal from the market, etc.) are a result of their propensity to cause severe liver injury. Intentional over-dosage with acetaminophen is still the leading *drug-related* cause of acute liver failure and liver transplantation; however, many compounds in a variety of therapeutic categories have been associated with this severe complication of drug therapy. The extensive list of drugs implicated in hepatotoxicity includes analgesics and anti-inflammatory agents, antimicrobials, cardiovascular agents, neuropsychiatric agents, chemotherapeutic compounds, and herbal supplements. Among the wide variety of antimicrobial drugs, the combination of amoxicillin/clavulanic acid (Augmentin) is undoubtedly the most common medication associated with severe drug-induced liver injury (DILI). Hepatic injury due to amoxicillin/clavulanic acid is related to the clavulanic acid component. The incidence of DILI from this combination is estimated to be 1-17 for every 100,000 prescriptions. The clinical presentation of amoxicillin/clavulanic acid-related liver injury is typically cholestatic (obstructive) in nature; however, occasional patients present with evidence of hepatocellular (cytotoxic) or a mixed type of liver injury. While most cases in the elderly population are cholestatic or mixed, younger patients usually develop hepatocellular injury. Symptoms typically begin weeks after the medication has been discontinued. Due to this latency period, the association is often not suspected and the diagnosis may be delayed. Patients often present with symptoms consisting of nausea, vomiting, malaise, fatigue, abdominal pain, fever, pruritus, and jaundice. Although the majority of cases produce only mild impairment, severe hepatotoxicity has resulted in the need for liver transplantation and occasional fatality. In one study, this combination was the leading cause (23 cases) of liver injury among 300 patients in a prospective study of DILI in the United States. Cases involving mild injury are generally self-limiting and resolve within 3-4 months following discontinuation of the drug. Those cases involving severe hepatotoxicity with unfavorable outcomes occur in 7% of patients with DILI. Risk factors include individuals aged sixty-five years and older as well as exposure to higher doses or for an extended period of time. As should be evident, the combination of amoxicillin-clavulanic acid is considered one of the most common causes of severe DILI.

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