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Correspondence

Severe idiosyncratic acute hepatic injury caused by paracetamol

To the Editor:

Paracetamol, an intrinsic hepatotoxic agent, is generally well tolerated at therapeutic doses. Hypersensitivity reactions, mainly cutaneous and respiratory, are rarely reported (1). We report the first incidence of paracetamol-induced idiosyncratic hepatic injury confirmed by drug rechallenge.

Because of bronchitis, a previously healthy 29-year-old woman was prescribed roxithromycin and paracetamol 500 mg t.i.d. for 7 days. During the last day of therapy, a pruriginous skin rash developed and oral prednisone was started. Seven days later, she experienced anorexia and malaise, and 3 days prior to hospital admission (11 days after stopping paracetamol), she presented with fever, abdominal pain and jaundice. She had no known allergies or toxic habits and was taking no other drugs. Exhaustive inquiry about over-the-counter medications, including herbal preparations, was negative.

Physical examination showed an alert, slightly obese woman with scleral icterus and abdominal tenderness. There was no organomegaly or lymphadenopathy. AST was 1895 U/l (normal 5–31 U/l), ALT 945 U/l (normal 5–31 U/l), alkaline phosphatase 532 U/l (normal 91–258 U/l), γ-glutamyl-transferase 347 U/l (normal 7–32 U/l), and total bilirubin 238 μmol/l (normal 3.4–17.1 μmol/l), with direct bilirubin 171 μmol/l (normal 1.7–4.2 μmol/l). Leukocyte count was 13.1×10^9/l with 7% eosinophils, prothrombin time was 29.3 s (INR 2.24), and platelet count was 90×10^9/l, total protein 64 g/l, albumin 26 g/l, gammaglobulin 29 g/l (polyclonal), C_3 2.25 g/l (normal 8–14 g/l), C_4 0.66 g/l (normal 1.5–5 g/l). Serum glucose was 66 mg/dl. Values for BUN, serum creatinine, alpha-1 antitrypsin and ceruloplasmin levels were normal.

Serology ruled out viral hepatitis A, B and C (RNA negative, Amplicor Roche), cytomegalovirus, herpes simplex, Epstein-Barr virus and *Coxiella burnetii*. A screen for autoimmune liver disorders revealed anti-smooth-muscle antibody 1:160. Abdominal ultrasound examination showed no expanded bile ducts and a small amount of ascites.

Hyperosmolar glucose infusions and vitamin K were started. During the following days the patient's clinical condition gradually improved and she was discharged on the 26th day. Laboratory findings were normal at 2 months.

Several days later, the patient had a headache and took paracetamol 500 mg in the afternoon. Because no improvement was obtained, an additional 1 g of paracetamol was administered on the following day and the clinical picture of hepatitis reappeared a few hours later. An emergency laboratory work-up revealed AST 3216 U/l and prothrombin activity 50%. She refused hospitalization. By the 8th day serum AST was 46 U/l, ALT 257 U/l, and total bilirubin 10 μmol/l. Her next appointment 3 months later revealed normal liver function (Fig. 1). She has been followed every 3 months since then for 2 years and the results of liver tests have remained normal.

In this patient severe acute hepatocellular injury developed several days after a 1-week course (1.5 g/d) of paracetamol. Readministration led to prompt reappearance of liver damage. The dramatic positive rechallenge and the presence of hypersensitivity symptoms are highly suggestive of an allergic mechanism of liver injury.

Despite the world-wide use of the drug, we have found only one other report of paracetamol-mediated hypersensitivity-like hepatic injury (2). Although this is surprising, the high frequency of paracetamol use may have camouflaged its possible etiological role in other cases of liver injury. In fact, current data suggest that drugs can be the cause of many cases of acute hepatitis and acute liver failure that remain unexplained (3). Investigation of severe hepatic injury of unknown etiology thus requires carefully designed case-control studies to establish the role of drugs commonly used in clinical practice. The mechanism underlying immunological drug reactions is poorly understood (4), one possible explanation being that covalent binding of reactive metabolites to hepatic proteins triggers the immune response (5). Aberrant paracetamol metabolism through the P-450 system may have been the initial event in sensitization of this patient.

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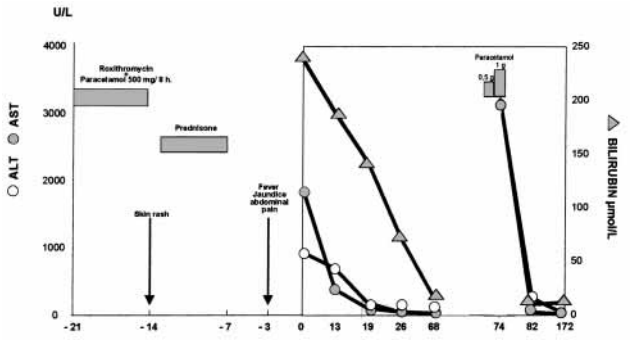

Fig. 1. Serum levels of aspartate aminotransferase (AST, ●), alanine aminotransferase (ALT, ○), total bilirubin (▲), and clinical outcome after 1 week of treatment with paracetamol 500 mg t.i.d. and inadvertent rechallenge.