OBSERVATIONS

Metformin-Induced Hepatotoxicity

Metformin is the first choice oral antidiabetic drug for type 2 diabetes and currently the most consumed. Although gastrointestinal intolerance is frequent, metformin-induced hepatotoxicity is rare. Fewer than 10 cases have been reported (1). In all of those cases, metformin was associated with concomitant intake of other potentially hepatotoxic drugs. We present what we feel may be the first documented case of hepatotoxicity due to metformin with no other drug interference.

A 61-year-old man was admitted to the hospital with a 3-day history of painless jaundice. He had no history of liver disease or toxic habits and denied previous consumption of drugs or herbal products, but had been taking metformin (1,700 mg/day for 6 weeks) after being diagnosed with type 2 diabetes.

Laboratory tests showed a mixed pattern of liver damage (total bilirubin 2.9 mg/dL, direct bilirubin 2.4 mg/dL, aspartate aminotransferase [AST] 290 units/L [≤40], alanine aminotransferase [ALT] 861 units/L [≤35], γ-glutamyltransferase [GGT] 861 units/L [≤35], and alkaline phosphatase [ALP] 622 units/L [≤120]). International normalized ratio and eosinophil counts were normal. Diagnostic work-up ruled out viral hepatitis A, B, and C, as well as autoimmune and metabolic liver disease (negative antinuclear antibodies, anti-mitochondrial antibodies, smooth muscle antibodies, anti-liver/kidney microsomal antibodies; normal ceruloplasmin, α-1 antitrypsin, copper). Abdominal ultrasound and cholangio-MRI showed no pathological findings. The patient refused a liver biopsy. After stopping metformin, the patient's clinical condition progressively improved and liver enzymes normalized in 30 days. He was discharged with only recommendations to modify his lifestyle.

Six weeks after discharge, the patient again developed malaise, nausea, and jaundice 24 h after deciding on his own to take a dose of 850 mg of metformin. Laboratory tests showed total bilirubin 4.8 mg/dL, direct bilirubin 3.8 mg/dL, AST 237 units/L, ALT 764 units/L, GGT 3,318 units/L, and ALP 622 units/L. Continued laboratory tests showed progressive improvement, reaching normal values in 4 weeks. He has since been treated with gliclazide-modified release (60 mg/day) and remains asymptomatic with good metabolic control (HbA_{1c} 6.8%).

The diagnosis of hepatotoxicity remains difficult because of the lack of reliable markers for use in general clinical practice. In our patient, the exclusion of other diagnostic alternatives, the temporal sequence with positive unintentional rechallenge, and the absence of other drugs all convincingly support the diagnosis of metformin-induced liver damage.

Clinical scales may add consistency to the diagnostic process by translating the suspicion of hepatotoxicity into a quantitative score. The CIOMS/RUCAM (Council for International Organizations of Medical Sciences/Roussel Uclaf Causality Assessment Method) instrument (2) is currently considered the best method for assessing causality in drug-induced hepatotoxicity and states the following rates: ≤1 relationship excluded, 1–2 unlikely, 3–5 possible, 6–8 probable, >8 highly probable. Our patient scored 13 points, which indicates a certain or very likely diagnosis of metformin-induced liver toxicity.

Metformin is not considered intrinsically hepatotoxic. In fact, metformin may be beneficial in patients with nonalcoholic fatty liver disease (1) and chronic hepatitis C (3). Metformin is only contraindicated in patients with advanced cirrhosis because it heightens the risk of developing lactic acidosis (4). However, given the increasing prevalence of type 2 diabetes and expanding indications for metformin (5), it is important that clinicians be alert to the occurrence of rare but potentially serious side effects of this drug, such as idiosyncratic hepatotoxicity.

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