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CASE

The patient is a 54-year-old man who works as an organic chemist, a job that could expose him to known carcinogens. He presented to his primary care provider for an annual physical examination, which showed him to be in good health. However, results of a urine dipstick analysis indicated 3+ bilirubin. All other laboratory values were within normal ranges, including serum bilirubin, urobilinogen, AST, ALT, and alkaline phosphatase. The patient was not jaundiced, he had no abdominal complaints, there was no tenderness on palpation, and his liver was not enlarged.

The patient did not have a history of bilirubinuria, but according to his medical record, he was taking several drugs for chronic conditions, including loratadine for seasonal allergies, etodolac for chronic back pain secondary to a slipped disk, and bupropion for depression. He also received weekly allergy injections.

After a repeat urine dipstick analysis produced a positive result, a spectrophotometric assay was performed. Those findings were also positive for bilirubinuria.

WHAT IS CAUSING THE BILIRUBINURIA?

- Gilbert's syndrome
- Chronic hepatitis
- Crigler-Najjar syndrome
- Medication
- Hepatocellular disease due to chemical toxins

DISCUSSION

The etodolac this patient was taking for his chronic back pain was producing the false-positive results. Metabolites of etodolac were reacting with the diazonium salt on the urine dipstick, producing the color change indicative of a positive result. This was first described in 1986 by Ferdinandi and colleagues.¹ The spectrophotometric assay also uses a diazo reagent, thereby producing the same false-positive result.² Other medications that may cause false-positive results for bilirubinuria include phenothiazines, mefenamic acid, phenazopyridine, and nabumetone. The Harrison spot test, a urine test which does not use a diazo reagent, can be used to differentiate between a true bilirubinuria and a medication-related false-positive result.

Treatment The patient had started taking etodolac several months earlier for his back pain, with excellent results. Prior to this, he had been taking rofecoxib until that drug was withdrawn from the market. Ibuprofen offered limited relief.

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TABLE 1

Causes of bilirubinuria

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|-----------------------------|--------------------------|
| • Biliary obstruction | • Hereditary causes |
| • Cirrhosis | — Dubin-Johnson syndrome |
| • Hepatic or biliary cancer | — Rotor's syndrome |
| • Hepatitis | • Pancreatic cancer |

The etodolac was discontinued and, after 10 days, the patient's urine tested negative. Since the diagnosis of bilirubinuria was proven to be based on false-positive test results and there was no liver damage, the patient elected to restart the etodolac. His urine was tested 2 weeks after resuming the etodolac, and the result once again was 3+ bilirubin.

Comment Small amounts of bilirubin, a bile pigment formed by the breakdown of RBCs, is normally present in plasma in the form of unconjugated bilirubin. The liver conjugates the bilirubin to make it soluble for excretion. Unconjugated bilirubin is not soluble and thus is never found in urine. Conjugated bilirubin, however, may spill into the urine as plasma levels increase; therefore bilirubin in the urine indicates hepatobiliary pathology. The most common causes of bilirubinuria are listed in Table 1.

Because Gilbert's syndrome, a common, benign, inherited disorder of an enzyme deficiency, causes serum elevation of unconjugated bilirubin, it would not be the cause of the patient's bilirubinuria. Gilbert's syndrome is usually asymptomatic and requires no treatment. Chronic hepatitis, defined as inflammation of the liver for 6 months or longer, is accompanied by elevations of AST and ALT values, although ALT levels may be normal. The patient's normal AST values ruled out this diagnosis. Crigler-Najjar syndrome is a rare syndrome of congenital hyperbilirubinemia caused by an enzyme deficiency in the liver, but it manifests as severe jaundice in neonates a few days after birth. This patient's work environment was a concern because it exposed him to toxic substances. However, he had no other indications of biliary pathology, leading to the suspicion that the dipstick and assay results were false-positives.

Etodolac is an NSAID with analgesic properties. Approved by the FDA for clinical use in 1991, etodolac is classified as a cyclooxygenase inhibitor with selectivity between that of rofecoxib and celecoxib and has been found to have reduced GI effects compared to other NSAIDs.³ In addition, etodolac is currently being investigated for use in the treatment of some cancers. □

REFERENCES

1. Ferdinandi ES, Sehgal SN, Demerson CA, et al. Disposition and biotransformation of 14C-etodolac in man. *Xenobiotica*. 1986;16(2):153-166.
2. Sho Y, Ishiodori T, Oketani M, et al. Effects of urinary metabolites of etodolac on diagnostic tests of bilirubin in urine. *Arzneimittelforschung*. 1999;49(7):572-576.
3. Weideman RA, Kelly KC, Kazi S, et al. Risks of clinically significant upper gastrointestinal events with etodolac and naproxen: a historical cohort analysis. *Gastroenterology*. 2004;127(5):1322-1328.