Case report

Normal in the blood, abnormal in the urine

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A 67-year-old lady with known seropositive Rheumatoid Arthritis (RA) was investigated for persistent unexplained positive urine dipstick test for bilirubin, despite normal liver function tests (LFTs).

She had originally presented, aged 45 years, with painful feet, minimally responsive to a non-steroidal anti-inflammatory (NSAID), indomethacin. She was found to be strongly rheumatoid factor positive (1:1280) and a diagnosis of RA was made. Initial treatment was with the disease modifying anti-rheumatic drug (DMARD), sulphasalazine. Over the following years, her synovitis and erosive arthropathy became refractory to sulphasalazine and she required another DMARD, weekly intramuscular methotrexate 12.5 mg (with folic acid), corticosteroid (deflazocort 3 mg daily) and (etodolac 300 mg) to control her disease. While on these DMARDs she was monitored with 6–8 weekly monitoring of her liver, renal and bone marrow function. At a routine blood and urine monitoring visit she was found to have a positive urinary dipstick for bilirubin.

Urine dipstick testing is routinely performed in patients with rheumatic disease and can give vital information about end-organ damage, indicating disease progression or complications of therapy, such as haematuria or proteinuria (renal involvement), glycosuria (diabetes secondary to corticosteroids) or bilirubinuria (hepatic involvement). Only conjugated bilirubin is able to enter the urine (bilirubinuria), as unconjugated bilirubin is tightly bound to serum albumin and is not subject to glomerular filtration. The most common causes of bilirubinuria are hepatocellular or cholestatic disease. The differential diagnosis also includes rare inherited defects of excretion, such as Rotor and Dubin–Johnson’s syndrome, or drug toxicity such as phenothiazines, mefanamic acid, phenazopyridine, nabumetone or etodolac.

This patient had normal liver function (serum bilirubin, alkaline and aspartate phosphatase, albumin), clotting tests (prothrombin time) and amylase. She also had a normal liver ultrasound, viral screen (Hepatitis A, B, C, Ebstein-barr virus, Cytomegalovirus), metabolic tests (ferritin and caeruloplasmin), serology (anti-smooth and mitochondrial antibodies) and paracetamol levels. As hepatic and cholestatic causes were excluded, bilirubinuria in this case was attributed to etodolac.

Etodolac (1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetic acid) is a potent NSAID. Two small studies, of four patients and eight patients, have separately shown that urine samples of patients treated with etodolac and normal serum bilirubin concentrations, give positive reactions for bilirubin with a diazo method. This is the conventional method for measuring bilirubin and involves a colorimetric assessment of azobilirubin, formed by reaction of bilirubin with a diazonium salt (containing a terminal group with two linked nitrogen atoms) found in the Multistix dip test. Urinary metabolites were extracted with ethyl acetate and purified using high performance liquid chromatography (HPLC). The eluate was incubated with the diazo reagent and three positive fractions were found. The retention times of the two metabolites in HPLC were equivalent to those of the 6- and 7-hydroxylated metabolites of etodolac (6- and 7-OH-etodolac). Authentic compounds of the 6- and 7-hydroxylated metabolites also gave a positive reaction in the diazo methods. These results indicate that 6- and
7-OH-etodolac are mainly responsible for the false positive reactions of the urine sample from patients treated with etodolac. The hydroxy group at the phenol ring (present in 6- and 7-OH-etodolac) is essential for the diazo reaction, since the aliphatic hydroxylated metabolite (8-OH-etodolac), gave a negative reaction. The ‘positive reaction’ persisted even when the urine was exposed to sunlight for 5 h, suggesting the metabolites are stable.1

Positive urine dipstick tests for bilirubin may be alarming in patients with rheumatoid arthritis on hepatotoxic drugs such as methotrexate, as this may indicate hepatic damage due to disease or iatrogenic effects. We have reported a patient with false positive bilirubinuria secondary to phenolic urinary metabolites of etodolac (6- and 7-OH-etodolac). In patients with normal liver function tests, false positive reactions should be considered.

Conflict of interest: None declared.

References