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CASE REPORT

Neutropenia, thrombocytopenia and hepatic injury associated with dexketoprofen trometamol therapy in a previously healthy 35-year-old woman

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SUMMARY

This case report describes a previously healthy 35-year-old woman, with an episode of fever, neutropenia, thrombocytopenia and elevation of biochemical markers of liver injury, 10 days after beginning drug therapy with dexketoprofen trometamol. Infectious and autoimmune causes of neutropenia, and viral or autoimmune hepatitis were excluded. The resolution following withdrawal of dexketoprofen trometamol confirms the possibility of an adverse drug reaction.

Keywords: **adverse drug reaction, dexketoprofen trometamol, hepatic injury, neutropenia, thrombocytopenia**

INTRODUCTION

Dexketoprofen trometamol, the active enantiomer of rac-ketoprofen, is a non-steroidal antiinflamatory drug (NSAID) of the arylpropionate family, widely used for pain relief. Several clinical trials conducted with orally administered dexketoprofen trometamol in patients affected by acute and chronic pain have confirmed its high analgesic potency and good tolerability profile (1–4). The parenteral formulation has also shown a good safety profile in acute pain conditions (5, 6). Although both neutropenia and thrombocytopenia are described as possible adverse drug reactions in the product information of dexketoprofen trometamol with an incidence <0.01%, to our knowledge (Medline search June 2007), this is the first case report of this association.

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CASE REPORT

A previously healthy 35-year-old woman was admitted because of fever over the past 5 days. She did not have a history of adverse effects to any medication and denied alcohol intake or recent ASA use. Ten days before admission, she began drug therapy with dexketoprofen trometamol 25 mg three times daily because of shoulder pain after a traffic accident. Physical examination findings did not reveal any problems except for fever of 38.4°C. Serum chemistry showed the following: AST 210 IU/L (normal 12–36 IU/L), ALT 216 IU/L (normal 7–40 IU/L), GGT 58 IU/L (normal 12–54 IU/L), alkaline phosphatase 105 IU/L (normal 89–279 IU/L), LDH 1175 IU/L (normal 230–460 IU/L), total bilirubin 0.5 mg/dl (normal 0.2–1 mg/dL) and proteins 5.9 g/dL (normal 6–8 g/dL). Prothrombin time, activated partial thromboplastin time, thrombin time and fibrinogen level were normal. Total leucocyte count was 1600/μL (normal 4000–10 000/μL), absolute neutrophil count (ANC) was 992 (ANC <1500/μL is the generally accepted definition of neutropenia), haemoglobin 12.4 g/dL (normal 12–16 g/dL) and platelet count 94 000/μL (normal 150 000–400 000/μL). Dexketoprofen was discontinued and the patient was started on ceftriaxone (2 g per day), acetaminophen (3 g per day) and granulocyte colony-stimulating factor (G-CSF) therapy (5 μg/kg/day). On the second day after admission, the patient was afebrile and acetaminophen was stopped. Abdominal ultrasonography and chest radiograph were normal. Blood and urine cultures, antinuclear antibodies and results of serologic testing for hepatitis A, B and C virus were negative. Results of serological testing for Epstein–Barr virus and cytomegalovirus were IgM-negative. On the fourth day, total leucocyte

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count was 14 400/μL, absolute neutrophil count 9072, and platelet count 143 000/μL. Biochemical markers for liver injury were as follows: ALT 345 IU/L, AST 201 IU/L, GGT 122 IU/L, alkaline phosphatase 200 IU/L, LDH 1065 IU/L. Ceftriaxone and G-CSF therapy were stopped. The patient remained without fever. Two weeks later, total leucocyte count was 5900/μL, absolute neutrophil count 2478 and platelet count 234 000/μL. Serum chemistry showed the following: ALT 51 IU/L, AST 19 IU/L, GGT 64 IU/L, alkaline phosphatase 101 IU/L, LDH 489 IU/L.

DISCUSSION

It has been estimated that from 5% to 7% of the hospital admissions are related to adverse effects of drugs, and of these hospitalizations, those that result from gastrointestinal, nervous system, renal or allergic effects of aspirin or non-aspirin NSAIDs are responsible for approximately 30% (7). Neutropenia is an infrequent complication of NSAID therapy. Strom *et al.* (8), found that the relative risk for the occurrence of neutropenia in patients treated with NSAIDs was 4.2 compared with controls (90% confidence interval, 2.0–8.7). Drug-induced neutropenia occurs as an idiosyncratic reaction with the exception of neutropenia following cytotoxic chemotherapy. The two basic mechanisms are immune-mediated destruction of circulating neutrophils by drug-dependent or drug-induced antibodies and direct toxic effects upon marrow granulocyte precursors. Immune forms may present days to weeks after beginning the drug and often with acute symptoms like fever and sore throat; in toxic forms, presentation may be delayed for months. Immune neutropenias are associated with the presence of circulating antineutrophil antibodies. This assay was not performed in our patient. Hepatic injury, most probably caused by an idiosyncratic reaction resulting from an immunologic response or altered metabolic pathways, is another sequela of NSAID use. This is usually reversible (9), because liver function test abnormalities generally settle within 4–6 weeks of stopping the causative drug, although in some patients this may lead to acute liver failure (10). There are many acquired causes of neutropenia, with infection, drugs and immune disorders being the most common. Acute clinical presentation, associated fever, hepatitis, neutropenia and thrombocytopenia, strongly suggest an idiosyncratic hypersensitivity reaction. Infectious and autoimmune causes of neutropenia, viral or autoimmune hepatitis were excluded. The time association between dexketoprofen-withdrawal and haematological and liver function tests normalization strongly suggest a cause-and-effect relationship, although G-CSF therapy could have accelerated the normalization of leucocyte count. Although safety data on dexketoprofen trometamol are mainly from short-term trials (1–6), in patients with bone cancer or osteoarthritis of the knee treated for 1–2 weeks (2, 3), as was the case in this report, adverse events most frequently described are gastrointestinal complaints such as abdominal pain, dyspepsia, nausea, vomiting and flatulence. Only two out of 57 patients with bone cancer, treated with dexketoprofen trometamol, showed liver and biliary system-related adverse events. No patient in either trial showed any abnormal haematological laboratory parameters.

CONCLUSION

Given the wide use of dexketoprofen both for acute and chronic pain relief (1–6), and its commonly regarded good tolerability profile, it is important that clinicians are made aware of potentially serious adverse events occurring with its use.

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