ADVERSE DRUG REACTION

Sulfasalazine-induced immune thrombocytopenia

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Sulfasalazine is a well established disease-modifying anti-rheumatic drug commonly used in the treatment of rheumatic disorders and inflammatory bowel disease. Sulfasalazine was generally well tolerated in clinical trials, the most frequently reported adverse effects being adverse gastrointestinal effects, headache, dizziness and rash; myelosuppression can also occur. We are now reporting the first case of autoimmune thrombocytosis following sulfasalazine treatment.

A 65-year-old man was referred to our hospital in June 2004 showing symmetrical swelling and tenderness in proximal interphalangeal joints and distal interphalangeal joints. The patient's medical history included psoriasis. Blood samples disclosed only moderate signs of inflammation, blood cell counts were normal, and the patient was HLA (human leucocyte antibody) B27 negative.

The patient was diagnosed with psoriatic arthritis, and sulfasalazine 1500 mg was taken daily, along with aceclofenac 100 mg daily. The patient did not take non-prescription drugs, such as acetaminophen or agents containing quinine. In September 2004, the symptoms of arthritis improved but laboratory investigation showed a decreased platelet count ($79 \times 10^9/l$); red blood cells and leucocytes were normal excluding a general bone marrow suppression. Coagulation studies and renal and liver function tests were normal. There was no serological evidence of recent viral infection and no evidence of spleen enlargement. Autoimmune serology revealed the presence of platelet-reactive autoantibodies (IgG) and positivity for lupus anticoagulant. There were no clinical signs of systemic lupus erythematosus (SLE). Sulfasalazine was suspected as the causative agent and was therefore discontinued while the patient continued taking aceclofenac 100 mg daily. Three months after stopping sulfasalazine, the platelet count returned to normal, and was platelet reactive. Autoantibodies as well as LAC disappeared (table 1). Beginning in January 2005, the patient started treatment with methotrexate 10 mg weekly, and continued taking aceclofenac. The platelet count remained normal during 22 months of follow-up.

DISCUSSION

Sulfasalazine is still a mainstay in the treatment of inflammatory bowel disease and rheumatoid or seronegative arthritis.

Table 1 Blood counts and platelet-reactive autoantibodies before starting sulfasalazine treatment, at the time when the drug was withdrawn, and in the following month

	June 2004	September 2004	January 2005
Red blood cells/mm ³	5310000	5130000	5040000
Leucocytes/mm ³	7140	7080	7160
Platelets/mm ³	171000	79000	129000
Platelet-reactive autoantibodies	Not done	Positive	Negative

Learning points

- Sulfasalazine is widely used in psoriatic arthritis
- Though safe, it may rarely cause immune thrombocytopenia
- Sulfasalazine-induced thrombocytopenia should be resolved when the drug is withheld

Based on considerations of safety, convenience and cost, many rheumatologists select sulfasalazine as initial treatment. The most common adverse events are gastrointestinal effects, headache, dizziness and rash; myelosuppression can also occur. Sulfasalazine has been reported to reduce the levels of tumour necrosis factor α (TNF α); some authors have described the development of SLE or SLE-like disease during sulfasalazine treatment, as well as the occurrence of anti-dsDNA antibodies and SLE-like syndrome during treatment with monoclonal antibodies to TNF α .^{1,2} Like several drugs, sulfasalazine can induce thrombocytopenia by decreasing platelet production (bone marrow toxicity).³ In our report we suggest another mechanism of sulfasalazine-induced thrombocytopenia—increased platelet immune destruction. The underlying mechanism of drug-induced immune thrombocytopenia is not completely clear, but at least three different antibodies appear to play a role: hapten-dependent antibodies, platelet-reactive autoantibodies, and drug-dependent antibodies.⁴ Thrombocytopenia is also a rare but classic complication of treatment with non-steroidal anti-inflammatory drugs (NSAIDs), but there are no data on studies for drug-dependant antiplatelet antibodies.⁵ In our case we carefully evaluated the causal relationship of sulfasalazine considering the total blood count and peripheral blood smear (to rule out pseudothrombocytopenia) and platelet serology tests. We exclude the role of an NSAID in reducing platelet count because aceclofenac was continued when sulfasalazine was withdrawn. The diagnosis of immune thrombocytopenia was established by identifying platelet-reactive autoantibodies after three months of treatment in association with a decreasing number of platelets, which ceased when the drug was withheld. This paper reports the first case of autoimmune thrombocytosis following sulfasalazine treatment.

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Abbreviations: NSAIDs, non-steroidal, anti-inflammatory drugs; SLE, systemic lupus erythematosus; TNF α , tumour necrosis factor α

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