Case Report

Sulindac-Induced Hypersensitivity Reaction

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INTRODUCTION

Sulindac is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the relief of the signs and symptoms of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute painful shoulder, and acute gouty arthritis. That sulindac is suggested to be renal sparing may make it more attractive as compared to alternative NSAIDs.[1,2] However, sulindac is not without serious adverse effects. We report a case of sulindac-induced hepatitis, acute renal failure, pneumonitis, and rash which resolved with discontinuation of therapy.

Case

A 65 year-old female was admitted with complaints of fever, headache, myalgias, upper abdominal discomfort, nausea, and a maculopapular rash on her face, neck, trunk, and extremities which first occurred one week prior. Her past medical history included a cholecystectomy, hypertension, hypothyroidism, and osteoarthritis. Her medications on admission were enalapril 5 mg po daily which she had been taking for approximately one year, levothyroxine 0.1 mg po daily for several years, and sulindac 150 mg po bid for three weeks. In the past she had developed a rash secondary to diclofenac.

On admission, her temperature was 38.6°C, heart rate was 72 beats per minute, blood pressure was 120/70 mmHg, and respiratory rate was 14 per minute. Her WBC was 8.6 x 10^9/L (N: 4.0-11.0 x 10^9/L). Liver enzymes were elevated with an aspartate aminotransferase (AST) of 72 U/L (N: 0-35 U/L), total bilirubin 20 umol/L (N: 2-18 umol/L), alanine aminotransferase (ALT) of 92 U/L (N: <35 U/L), and a gamma glutamyl transferase (GGT) of 316 U/L (N: 40-90 umol/L) with a normal blood urea nitrogen (BUN) of 7.5 umol/L (N: 1.8-8.2 umol/L). Other laboratory values were unremarkable.

The patient was admitted and calamine lotion was prescribed for her itchy rash. She continued to receive enalapril and sulindac over the next eight days. On day eight, the patient's condition deteriorated; she became more lethargic and itchy, and complained of sore ears and throat. On day nine, her temperature rose to 39°C, systolic blood pressure was less than 100 mmHg, heart rate was elevated to 90 beats pre minute, WBC count was elevated at 16.5 x 10^9/L, erythrocyte sedimentation rate (ESR) was 23 mm/hr (N: 0-20mm/hr), and the eosinophil count was 2.4 x 10^9/L (N: 0-0.5 x 10^9/L). Both enalapril and sulindac were discontinued and gentamicin 80 mg IV q12h and ceftazidime 2 g IV q8h was added to her antibiotic regimen and she was transferred to the intensive care unit. Chest X-rays showed a left pleural effusion, and in subsequent days the pleural effusion increased with a possible consolidation in the left lower lobe. Serum creatinine rose to 233 umol/L. The patient failed to respond to antibiotics and the impression was that this scenario was most compatible with a sulindac-induced hypersensitivity reaction. On day 14, all antibiotics were discontinued and the patient was ordered methylprednisolone 100 mg IV q8h for the next four days. The patient's symptoms of lethargy and itchiness began to resolve on day 15, and the rash disappeared seven days after antibiotics were discontinued with subsequent resolution of the chest X-ray and decrease in serum creatinine. Blood cultures remained negative six days after starting antibiotics.

DISCUSSION

This presentation is typical of a possible Type III (immune complex) hypersensitivity reaction. The postulated mechanism of this reaction is that the NSAID molecules are perceived as foreign antigens by the body. The antigen is normally complexed with an antibody (usually IgG or IgM) and cleared by the reticuloendothelial system. Immune complexes that are not cleared can deposit in various tissues such as the kidney, lung, joints, arteries, and skin, and trigger a variety of inflammatory processes such as complement activation, neutrophil chemotaxis, release of lysozymes, and ultimately cause

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tissue injury.[4] The resultant hypersensitivity reaction is due to the local and general effects of inflammation and can present as fever, chills, skin rash, changes in liver function, pancreatitis, pneumonitis, leukopenia, eosinophilia, anemia, renal impairment, and arthralgia.[5] The onset of symptoms associated with Type III hypersensitivity usually occurs between a few hours to three weeks after drug exposure.[5] While rare, the condition may be fatal.[3,6]

Several cases of sulindac-induced organ toxicity have been reported. In an investigation of 338 sulindac-related hepatotoxicity reports to the FDA between 1978 and 1986, 27% of the cases were considered sulindac-induced with hypersensitivity involvement in two-thirds of the cases.[6] Fein published a case of severe pneumonitis with consolidation after a 76 year-old woman reportedly received six months of sulindac.[7] Upon discontinuation of therapy and starting corticosteroid therapy, the pulmonary symptoms resolved. Several months later, the patient resumed therapy and within five days again developed symptoms which gradually improved upon dechallenge.

Russell described a case of hypersensitivity reaction involving tingling peripheral dysesthesias, anorexia and nausea in a 26 year-old patient after receiving sulindac for nine days.[8] The symptoms resolved after stopping therapy for five days. The patient restarted therapy two weeks later for arthralgia, and this time developed a blotchy erythema in addition to nausea and dysesthesia. One week later, after taking one dose of sulindac, the patient developed pruritus over the entire body, peripheral dysestheia, severe headaches, back pain, chest pain, colicky abdominal pain, nausea, and vomiting. The symptoms resolved with diphenhydramine, fluids, and corticosteroids.

Sulindac may be toxic either to a single organ system, most commonly pulmonary[7,9] or hepatic,[6,10] or show multisystem involvement[11] as in our case. The temporal sequence of events with a hypersensitivity reaction within weeks of therapy, suggests a possible adverse drug reaction due to sulindac. This reaction could not be explained by an exacerbation of her arthritic condition since osteoarthritis is not associated with systemic reactions such as those seen in patients with rheumatoid arthritis and her symptoms resolved upon discontinuation of an agent often used to treat this exacerbation. Rechallenge to confirm the reaction was not performed as it was deemed inappropriate.

It is possible that the hypersensitivity reaction could be attributed to the patient's enalapril therapy or a combination of both, since both sulindac and enalapril were discontinued at the same time. However, the patient had received and tolerated enalapril therapy for approximately one year making this agent less likely to be causative.

In conclusion, although the incidence of reaction is rare, the occurrence of sulindac hypersensitivity is often severe and even potentially fatal and pharmacists should be aware that such reactions may occur.

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