Nimesulide-induced hepatitis and toxic epidermal necrolysis

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Nimesulide, a selective cyclo-oxygenase (COX-2) inhibitor was first launched in Italy in 1985 and subsequently marketed in more than 50 countries including India.[1,2] In 2003, following worldwide reports of fatal adverse events in children, some countries banned it while others have issued restrictions in pediatric usage. In India, however, it is available for usage in adults though some pharmaceutical companies have voluntarily withdrawn the pediatric formulation. Its adverse effects commonly involve the hepato-biliary, renal, cutaneous and gastrointestinal systems.[1,3] Acute hepatitis, fulminant hepatic failure, cholestatic liver injury, multiple enterocolic perforations and end stage renal failure with nimesulide intake have been reported.[3-5] Dermatological reactions include urticaria, angioedema, maculopapular rash, pityriasis rosea-like lesions, necrotizing fasciitis, fixed drug eruption and acute exanthematous pustulosis.[1,2,6]

We report a case of suspected nimesulide-induced toxic epidermal necrolysis (TEN) and hepatitis in a young female patient.

Case History

A 21-year-old lady presented at the emergency of this hospital with a history of severe exfoliating skin rash affecting nearly 70% body surface area along with ocular and oral mucosal involvement of 2 days duration. Drug history revealed intake of only nimesulide 100 mg daily orally for last 5 days for myalgia/feverishness as an over-the-counter preparation prior to development of the rash. There was past history of single episode of drug rash with cotrimoxazole more than 5 years back, however, there was no history suggestive of atopic state. There was no history of any addictions or past history of significant medical/surgical disorders like jaundice. However, documentary evidence to substantiate normal baseline liver function was not available. She was evaluated by a team of clinicians and admitted in the emergency medical unit. The skin rashes were associated with blistering, ulceration and peeling of sheets of skin and she also had fever, arthralgia, mild icterus and respiratory distress.

Initial laboratory investigations after admission are enlisted in Table 1. Diagnostic tests for viral hepatitis, HIV infection and autoimmunity hepatitis (rheumatoid factor, ANF) were negative. Ultrasonography showed no specific hepatobiliary pathology. Skin biopsy revealed total thickness epidermal necrosis with mononuclear cell infiltration suggestive of TEN. Repeat investigations 7 days after drug discontinuation: WBC TC: 10,800/cmm; DC: Neutrophil: 81%; Eosinophil: 2%; Basophil: 0%; Lymphocyte: 16%; M onocyte: 1%; serum total bilirubin 3.4 mg/dl; AST: 316 U/l; ALT: 340 U/l; Alkaline phosphatase 696 U/l; total protein 5.5 gm/l; serum albumin 2.2 gm/l; random plasma sugar 121 mg/dl, urea 20 mg/dl and creatinine 0.4 mg/dl. Although liver biopsy was advised the patient refused to give consent. She was treated with parenteral fluids and electrolytes, short duration of systemic steroid along with specialized skin and mucosal care. Serial hematological and biochemical tests showed gradual normalization by about 4 weeks. She was discharged after 32 days and has attended two follow-up visits without any significant ailments.

The case was diagnosed to be a suspected case of drug-induced TEN with hepatitis on the basis of drug history, clinical presentation, improvement with dechallenge and exclusion of other likely causes of TEN and hepatitis. Using Naranjo’s Adverse Drug Reactions (ADR) probability scale we made a causality assessment by which this reaction categorized as a probable case of nimesulide-induced TEN with hepatitis.[7]

Table 1: Baseline investigation reports

<table>
<thead>
<tr>
<th>Hematological</th>
<th>Hemoglobin: 13.0 gm/dl; Total Count WBC: 19,800/cmm; Differential Count: Neutrophil: 88%; Eosinophil: 4% Basophil: 0%; Lymphocyte: 7%; Monocyte: 1%</th>
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<tr>
<td>Biochemical</td>
<td>Serum total bilirubin - 7.5 mg/dl; Aspartate aminotransferase (AST) - 1275 U/l; Alanine aminotransferase (ALT) - 2340 U/l; Alkaline phosphatase - 846 U/l; total protein - 6 gm/l; serum albumin - 3.2 gm/l; fasting plasma sugar - 104 mg/dl; serum urea - 59 mg/dl; serum creatinine - 0.9 mg/dl; Serum sodium - 132 mEq/l; serum potassium 3.4 mEq/l</td>
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Discussion

Drug-induced hepatotoxicity has been a matter of great concern with the bandwidth of such adverse reactions ranging from asymptomatic elevation of liver enzymes, acute hepatitis, acute cholestasis, chronic hepatic fibrosis to fulminant hepatic failure. Acute idiosyncratic hepatitis is one of the commonest forms of drug-induced hepatotoxicity culminating into the withdrawal of several drugs from the market despite proven clinical efficacy. The incidence of nimesulide-induced hepatotoxicity is however low, about 0.1 case per 100,000 treated patients and is usually unpredictable and possibly idiosyncratic in nature.

Nimesulide is metabolized in the liver and in subjects with hepatic insufficiency the rate of elimination of the drug and its metabolites are remarkably reduced, therefore a dose reduction may be required. In this case although clinically there was no evidence of preexisting chronic liver disease documentary evidence of normal liver function at baseline was not available.

Toxic epidermal necrolysis is a rare, life-threatening cutaneous adverse drug reaction which is characterized by widespread necrosis and exfoliation of the epidermis, usually involving >30% of the body surface area. In over 80-90% of cases drugs implicated in the causation. NSAIDS, namely celecoxib, valdecoxib, meloxicam, diclofenac have reported to cause TEN and SJS.

Although TEN may be associated with mild elevation of liver enzymes the occurrence of jaundice with very high levels of serum transaminase is rarely encountered, therefore we presume that these two drug-induced reactions are separate entities. However, on the flip side it could be that they represent diverse presentations of the same immunological phenomenon. Past history of cutaneous drug reaction with sulphonamides and occurrence of TEN within a short duration of drug exposure (5 days) made us speculate whether cross-reactivity to sulphonamides was possible. However, due to conflicting information in the literature, such association till date stands inadequately substantiated.

This case is being reported taking into consideration the rarity of dual association of nimesulide-induced TEN with hepatitis. The WHO ADR database (Vigibase), has several reports of nimesulide-induced hepatotoxicity and skin reactions but till date there are no reports of hepatitis with TEN. A MEDLINE search (up to October 2006) showed no published report of nimesulide-induced hepatitis with TEN.

Conclusion

Although selective COX-2 inhibitors have a better ADR profile than nonselective agents with regard to GIT, the safety and tolerability of these agents warrant cautious and judicious use, especially in subjects with history of drug allergy. This case report intends to draw the attention of clinicians and patients to the importance of recognizing any possible signs of cutaneous adverse reactions during nimesulide therapy, although only extensive epidemiological data can define the real impact of such toxicity.

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References