Case Report

Severe Systemic Hypersensitivity Reaction to Ibuprofen: a Presentation of Systemic Lupus Erythematosus

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ABSTRACT. We describe the first severe systemic hypersensitivity reaction to ibuprofen in a pediatric patient with previously undiagnosed systemic lupus erythematosus (SLE). An 11-year-old Thai male presented with fever, rash, altered mental status, and hypotension after oral administration of ibuprofen leading to the diagnosis of SLE. Re-dosing with ibuprofen resulted in recurrence of presenting symptoms. Severe hypersensitivity with hypotension can be a rare consequence of the use of ibuprofen in children with collagen vascular disease. When encountered in an otherwise healthy child, a high index of suspicion must be maintained for the diagnosis of SLE. (J Rheumatol 2006; 33:171-2; First Release: Nov 15, 2005)

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IBUPROFEN SYSTEMIC LUPUS ERYTHEMATOSUS PEDIATRICS
COLLAGEN VASCULAR DISEASE SEVERE HYPERSENSITIVITY REACTION

A distinctive systemic hypersensitivity reaction to ibuprofen has been described in patients with known collagen vascular disease[1-8]. The syndrome primarily consists of fever, gastrointestinal symptoms, myalgia, aseptic meningitis, and in some, profound hypotension[3,7]. We report the novel observation of such an adverse reaction to oral administration of ibuprofen as the initial clinical manifestation of systemic lupus erythematosus (SLE) in a child.

CASE REPORT

An 11-year-old Thai male presented to his family physician complaining of dizziness at school. He was diagnosed with a cold, given 400 mg of ibuprofen, and instructed to rest. After this visit, he became diaphoretic, nauseated, and lost consciousness.

His initial examination in a local emergency department revealed a diffuse erythematous rash, low-grade fever, tachycardia, poor perfusion, and hypotension. He received subcutaneous epinephrine for possible anaphylaxis, volume resuscitation, and required the initiation of inotropic agents. Despite these interventions the patient's clinical condition deteriorated and he required intubation.

The referral facility obtained a computed tomography (CT) scan of his head, which was unremarkable. A lumbar puncture revealed no organisms and normal chemistries and cellularity. Urine toxicology screening revealed only ibuprofen. Prior to transfer to our facility, he was given one dose of methylprednisolone and ceftriaxone.

Upon evaluation in our intensive care unit (ICU), the patient's vital signs were temperature of 37.6°C; pulse 165; respiration rate 26; blood pressure 110/33, and O_2 saturation, 100% on 35% FiO_2. Physical examination revealed bilateral conjunctivitis, a cast on his right arm from a recent fracture, and a diffuse blanching erythematous rash that covered his body, sparing his forearms and lower legs. He was cool and poorly perfused. Laboratory investigation revealed metabolic acidosis: pH 7.30; pCO_2 34 mmHg; paO_2 126 mmHg; HCO_3 16 meq/l, with lactate 4.9 mmol/l. Complete blood count revealed a white blood cell count of 12,500/mm^3 with 15% bands, and a platelet count of 102,000/mm^3. There was no evidence of disseminated intravascular coagulation. Additional abnormal blood laboratories included erythrocyte sedimentation rate (ESR) of 45 and C-reactive protein (CRP) of 6.7; amylase 256 U/l; lipase 586 U/l; gamma glutanyl transferase (GGT) 85 U/l; aspartate aminotransferase (AST) 71 U/l, and alanine aminotransferase (ALT) 50 U/l.

The patient was treated with antibiotics and supportive care for presumed sepsis. Blood, urine, tracheal aspirate, and cerebrospinal fluid cultures obtained at the referral center and those repeated at our institution were negative. The patient completed a full course of antibiotics.

He developed atrial fibrillation during the first week of his ICU hospitalization, which was treated with digoxin. Cardiac echocardiography revealed only a small pericardial effusion that resolved without intervention. The patient's rash persisted but was much less erythematous. His parents stated that he appeared flushed much of the time.

The elevated ESR and CRP and constellation of signs and symptoms prompted investigation for a collagen vascular disorder. The evaluation revealed antinuclear antibody (ANA) of 1:1800 with speckled pattern; elevated anti-DNA antibody at 74 units; C3 21 mg/dl and C4 < 10 units. A diagnosis of SLE with evidence of an active flare was made. The patient

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was placed on pulse steroids and ultimately transferred to the medical ward in good condition.

While on the ward he received a dose of ibuprofen for discomfort associated with his fractured arm. Two hours after this dose he developed fever, tachycardia, increased flushing, hypotension, bilateral conjunctivitis, confusion, and combativeness. The patient was returned to the pediatric ICU with the following vital signs: temperature 37.7ºC; pulse 157; respiration rate 42; blood pressure 96/31, and SO_2 saturation 97% on room air. The patient responded to volume resuscitation and dopamine, with improvement in his hemodynamics and a clearing of his sensorium. Steroid pulse therapy was reinitiated. After 24 hours in the pediatric ICU the patient returned to his preadmission condition and was able to be discharged once again to the ward.

DISCUSSION

In 1976 the first description of an adverse reaction to ibuprofen in a patient with SLE occurred in a 36-year-old woman who presented with fevers and chills after taking ibuprofen for joint pain[2]. This association was confirmed after recurrence of these symptoms upon reexposure to ibuprofen. Not until 1979, was hypotension described as a part of this constellation[3].

In 1990, Agus, *et al* identified 31 published cases of ibuprofen hypersensitivity in 33 patients. Fifty-two percent of these patients had SLE, 12% mixed connective tissue disease, 6% undifferentiated connective tissue disease, 3% juvenile rheumatoid arthritis, and 27% no autoimmune rheumatic disease[8].

These reports provide clear evidence for the existence of a distinctive systemic hypersensitivity to ibuprofen in sensitive persons[1-8]. The syndrome primarily consists of fever, gastrointestinal symptoms, myalgia, and aseptic meningitis. Less frequent features include conjunctivitis, rash, parotitis, pleural infiltrates, edema, and increase in liver and pancreatic enzymes. Severe reactions characterized by profound hypotension, such as those observed in our patient, have only been reported in 7 cases[3,7].

The mechanism of this reaction is not known. All reported cases occurred after prior exposure to the drug[1-8]. Our patient had been taking ibuprofen for approximately one week prior to his admission, and only after redosing in his family practitioner's office did he first experience the described reaction. Although reported cases suggest prior sensitization to ibuprofen appears to be necessary, Schoenfeld, *et al* reported an *in vitro* study in which they described specific cell-mediated immunity to ibuprofen in SLE, suggesting that even without prior exposure to ibuprofen, patients with SLE may exhibit sensitization to this drug[9]. Indeed, most patients who have developed ibuprofen hypersensitivity have tolerated other nonsteroidal antiinflammatory drugs (NSAID) without difficulty. Many of the symptoms that have been described can be explained by a histamine mediated anaphylactoid reaction as proposed by Finch and Strottman[3]. Patients with collagen vascular disease, particularly SLE, appear to have increased susceptibility to this type of reaction.

In conclusion, this is the first report of a severe hypersensitivity reaction to ibuprofen as the presenting sign of SLE in a pediatric patient. This conclusion is supported by a recrudescence of the patient's presenting symptoms after re-exposure to ibuprofen in the hospital. Although uncommon, when encountering adverse reactions such as those described above in an otherwise healthy child, a high index of suspicion needs to be maintained for the diagnosis of SLE.

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