Ibuprofen-Induced Aseptic Meningitis in a Previously Healthy Patient

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THE INDUCTION of aseptic meningitis by a nonsteroidal anti-inflammatory drug is a well-documented, though rare, occurrence. Until recently,[1] all previously reported cases have occurred in patients with systemic lupus erythematosus,[2-7] mixed connective tissue disease[8] or other autoimmune disorders.[8] The following case represents the first reported occurrence of this syndrome related to ibuprofen use in a previously healthy young man.

Report of a Case

The patient, a 20-year-old man, was in good health until September 1983, when he was diagnosed as having epididymitis. Tetracycline and ibuprofen were prescribed. His epididymitic symptoms resolved shortly afterwards; however, in the ensuing five weeks he had recurring episodes of fever, headache, myalgias and rash. These episodes lasted from one to four days and resolved spontaneously. The patient had taken ibuprofen periodically during that time for tension headaches but the timing and frequency of administration were uncertain.

In October, the patient was admitted for evaluation following such an episode. Cerebrospinal fluid (CSF) analysis then showed a normal opening pressure, glucose and protein; no cells were noted. Blood, cerebrospinal fluid, urine and sputum cultures were negative for bacteria and fungus. His peripheral leukocyte count was 6,200 per μl. In addition, he had negative results on VDRL, antinuclear antibody, rheumatoid factor, heterophile antigen and febrile agglutinins. He remained asymptomatic and was discharged for outpatient follow-up.

Shortly afterward the patient was admitted to hospital. Within an hour of ingesting a single 400-mg ibuprofen tablet, he had the abrupt onset of fever, headache, photophobia and a diffuse nonpruritic erythematous rash. On physical examination on presentation he had a temperature of 40°C (104°F), conjunctival injection, meningismus, a positive Brudzinski's sign and an erythematous maculopapular rash distributed to the torso and neck. Laboratory studies elicited the following values: electrolytes, creatinine and analysis of urine normal; peripheral leukocyte count, 26,000 per μl; erythrocyte sedimentation rate, 10. CSF analysis showed a cloudy fluid with a glucose of 63 mg per dl, protein of 120 mg per dl and leukocyte count of 1,069 per μl, of which 98% were polymorphonuclear forms. No organisms were noted on Gram's stain, india ink or acid-fast stains.

The patient was treated empirically with antibiotics. All symptoms resolved and the peripheral leukocyte count was 7,000 per μl within 12 hours. All cultures of CSF, blood, urine and throat specimens were subsequently negative. The patient declined repeat lumbar puncture. Once again, the following tests were either within normal range or negative: antinuclear antibody, rheumatoid factor, erythrocyte sedimentation rate and VDRL.

The patient was discharged with the presumptive diagnosis of aseptic meningitis due to ibuprofen use and advised to avoid nonsteroidal anti-inflammatory drugs. He has had no recurrence of symptoms.

Discussion

This case is notable in several aspects. All previously reported cases but one have occurred in women and have always been associated with some underlying medical illness, especially collagen vascular disease. Our patient was a previously healthy young man who had several episodes of hypersensitivity-like illness that seemed to worsen with each subsequent administration of ibuprofen. Follow-up evaluations have consistently failed to show any systemic illness.

Aseptic meningitis has been reported with ibuprofen, sulindac and tolmetin.[1-9] The close association in the vast majority of these cases with systemic lupus erythematosus or mixed connective tissue disease has led to the suggestion in some reports of an increased susceptibility to drug reactions in these patients. Perera, however, described the only other patient with this clinical syndrome who did not have associated collagen vascular disease or autoimmune illness.[1]

The clinical scenario is quite similar in most of the reported cases. The patients usually have facial flushing, striking conjunctivitis, meningismus and fevers as high as 40°C; some have abdominal pain.[5,7-9] Laboratory studies frequently fail to show a significant leukocytosis or eosinophilia.[8] The cerebrospinal fluid specimen can show a pleocytosis ranging from several hundred to several thousand cells.[9] Unlike the aseptic meningitis seen due to systemic lupus erythematosus or mixed connective tissue disease alone,[4,7,10-12] these patients show a polymorphonuclear predominance in their cerebrospinal fluid. The protein levels are frequently elevated and the cerebrospinal fluid glucose values low. Therefore, the clinical picture is indistinguishable from that of bacterial meningitis.

The cause of this clinical syndrome is unknown. Prostaglandin synthesis inhibition probably does not play a role in the pathogenesis of this illness. The use of other prostaglandin inhibitors in these patients has generally not been associated with the illness, as indicated in previous reports. The data suggest immune-mediated hypersensitivity as the mechanism of injury. This may be related more to the specific characteristics of the involved compound than to its general properties.

Although aseptic meningitis due to the use of a nonsteroidal anti-inflammatory agent is a diagnosis of exclusion, we feel that a careful drug history is important in the evaluation of meningismus. This is especially so in patients with an associated collagen vascular disease. Our present report documents the second case of ibuprofen-induced meningitis in a

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healthy patient. This entity may be more commonly seen now that ibuprofen is approved for over-the-counter use. In addition, the report also documents the second case of this clinical syndrome in a male patient. The syndrome of aseptic meningitis due to nonsteroidal anti-inflammatory agents is indeed a clinical entity that should be considered in the appropriate clinical setting.

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Human Insulin in the Treatment of Insulin Allergy

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TREATMENT OF DIABETIC PATIENTS with conventional insulins (rather impure preparations containing beef and pork insulin) has led to local allergic manifestations in 5% to 50% of patients and to systemic reactions in 0.2% to 1%.[1,2] The highly purified single-species pork preparations have reduced the incidence of allergic reactions and have been successful in treating up to 70% of patients with established insulin allergy.[1] A likely explanation for this phenomenon is that anti-insulin IgE (the antibodies responsible for immediate-type local allergy and systemic allergy[2]) have a lower avidity for porcine as compared with bovine insulin.[3,4] The same in vitro studies have failed, however, to detect any difference between porcine and human insulin either with respect to binding to preformed IgE[3,4] or in inducing lymphocyte transformation.[4] In addition, human insulin has been reported to be ineffective in five cases of persistent local allergy to porcine insulin[2,5] and to induce de novo production of IgE antibodies, albeit transient and not accompanied by allergic manifestations.[6] It has thus been argued that human insulin would not afford significant improvement over porcine insulin in the treatment of insulin allergy.[4]

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Report of Three Cases

We wish to report on three patients whose insulin allergy responded promptly and long-lastingly to institution of therapy with biosynthetic human insulin. The clinical characteristics and history of these patients are summarized in Table 1. It can be seen that in one of the patients local allergic symptoms developed despite the fact that purified pork insulin was the first exogenous insulin he can recall having received. The other two patients had probably been sensitized by the past exposure to the beef insulin and proinsulin molecules contained in the conventional preparations, and in these patients allergic manifestations developed at resumption of treatment despite the fact that the insulin administered was now a purified pork preparation.

Human insulin was started at small incremental doses (1 U every four hours) in patient 2, who had the most severe generalized symptoms; in the other two patients it was simply substituted for the previous treatment. Within 24 hours all patients had complete clearing of symptoms and no recurrence during almost a year of observation. The success of human insulin was particularly welcome in the pregnant patient in whom the protracted use of antihistamines was a source of concern.

It is certainly possible that the two patients with systemic allergy would have responded to desensitization and that the local allergic reactions would have spontaneously subsided or eventually responded to desensitization. However, the rate of success of the desensitization procedure is 95% for systemic allergy and only 50% for local allergy,[2] thus leaving a number of patients in a potentially troublesome situation.

TABLE 1.—*Clinical Characteristics of Insulin-Allergic Patients Who Responded to Human Insulin*

Patient	Sex & Ethnicity	Age	History of Diabetes	Known Allergies	Previous Insulin History	Insulin History at Onset of Allergy	Allergic Manifestations
1	♀, Filipino	35	GDM×2	None	B-P for GDM in first pregnancy	2 weeks B-P 3 weeks PP	Local induration and urticaria
2	♀, White	60	20 yr	Penicillin	B-P during 2 hospital admissions	1 month PP	Generalized itching and urticaria
3	♂, Mexican	60	18 yr	None	None	2 months PP	Local induration

GDM = gestational diabetes mellitus, B-P = beef-pork insulin, PP = purified pork insulin