

# Ibuprofen-Induced Fever in Sjögren's Syndrome

MA Gonzalo-Garijo, P Bobadilla

Allergology Department. Infanta Cristina University Hospital. Badajoz, Spain

**Abstract.** A 68-year-old-woman with a medical history significant for Sjögren syndrome and leukocytoclastic vasculitis of small vessels presented to the emergency department with chills, malaise, a temperature of 39°C, nausea, vomiting, and hypotension. Fifteen minutes earlier she had taken ibuprofen for flu-like symptoms. She was treated with a perfusion of intravenous saline, paracetamol, and ciprofloxacin with improvement 24 hours later. Three months later, she had a similar episode, without hypotension. An oral challenge test with ibuprofen in the hospital produced the same symptoms 3 hours after the last dose. She was treated with metamizole and paracetamol and was asymptomatic the next day. This is the first report of a febrile reaction to ibuprofen in a patient with Sjögren's syndrome.

**Key words:** Adverse effects. Aseptic meningitis. Fever. Ibuprofen. Sjögren Syndrome.

**Resumen.** Una mujer de 68 años de edad, diagnosticada previamente de síndrome de Sjögren y vasculitis leucociclástica de pequeño vaso, acudió a urgencias de nuestro hospital por presentar escalofríos, malestar general, fiebre de 39 °C, náuseas, vómitos e hipotensión. Quince minutos antes había tomado ibuprofeno para tratar sus síntomas gripales. Fue tratada con suero salino intravenoso, paracetamol y ciprofloxacino, con mejoría en 24 horas. Tres meses después tuvo un episodio similar, sin hipotensión, pocos minutos después de tomar ibuprofeno. Realizamos administración controlada de ibuprofeno en el hospital. Tres horas después de la última dosis, la paciente presentó los síntomas referidos previamente. Fue tratada con metamizol y paracetamol, encontrándose asintomática al día siguiente. Comunicamos el primer caso descrito de reacción febril por ibuprofeno en un paciente con síndrome de Sjögren.

**Palabras clave:** Efectos adversos. Fiebre. Ibuprofeno. Meningitis aséptica. Síndrome de Sjögren.

We discuss the case of a patient who developed fever after the administration of ibuprofen.

## Case Description

A 68-year-old-woman with a medical history significant for Sjögren's syndrome and leukocytoclastic vasculitis of small vessels presented to the emergency department with chills, malaise, temperature of 39°C, and hypotension. Fifteen minutes earlier she had taken ibuprofen (400 mg) for flu-like symptoms. The patient was taking no other medication at the time of admission. She was treated with a rapid intravenous infusion of saline. On examination, she was sleepy, and cardiovascular and neurologic evaluations were unremarkable. The patient did not present with nuchal rigidity, cephalea, or photophobia. During the first hours she had nausea and vomiting. Laboratory data revealed 18 800 leukocytes/mm<sup>3</sup> (92% neutrophils), and 10-20 leukocytes/field in the

urinary sediment. The electrocardiogram, chest radiograph and abdominal ultrasound were normal. She was treated empirically with paracetamol and ciprofloxacin and had improved 24 hours later. Three months later, she had a similar episode without hypotension and was treated at home with paracetamol and metamizole and recovered within 48 hours. Symptoms in that episode had begun a few minutes after intake of ibuprofen (600 mg) for cystitis. After that, the patient avoided ibuprofen but tolerated acetylsalicylic acid. No virologic or bacteriologic studies were performed.

Because the cause of the patient's diagnosis was unclear, and symptoms could have been related to ibuprofen or to the underlying disease (flu or cystitis) we performed an oral challenge test with ibuprofen in the hospital after obtaining written informed consent. Blood tests and biochemistry were performed before and after the study. Blood pressure and heart rate were also checked. The starting dose of 50 mg was followed by 3 more doses

of 100, 200, and 200 mg at intervals of 30 minutes. Three hours after the last dose, the patient had chills, malaise, cephalea and a temperature of 39°C. Physical examination and blood pressure were normal. A complete blood count revealed 14 500 leukocytes (88% neutrophils, 7% lymphocytes); other laboratory findings were normal. She was treated with intramuscular metamizole and the fever improved within an hour. However, she was somnolent and nauseous. The patient refused other studies proposed (computed tomography of the head and lumbar puncture). She followed treatment with paracetamol (500 mg/6 h) and the next day had completely recovered.

## Discussion

The adverse-effect profile of ibuprofen has been extensively reviewed, but the literature includes no report of fever as an isolated symptom caused by this drug. Drug-induced aseptic meningitis is rare, but there are reports implicating ibuprofen as a cause [1, 2]. A diagnosis of aseptic meningitis is made by ruling out other possible causes of the clinical signs (fever, headache, photophobia, and nuchal rigidity). Cerebrospinal fluid findings vary greatly and usually include pleocytosis (mainly neutrophilic), an elevated protein levels, and a normal glucose level with negative cultures [1-5]. Nonsteroidal anti-inflammatory drugs (especially ibuprofen), antimicrobials, vaccines, intravenous immunoglobulins, and monoclonal antibodies are among the most commonly implicated agents [3]. This reaction is most often seen in patients with systemic lupus erythematosus or such other underlying diseases as osteoarthritis, connective tissue disease, ankylosing spondylitis or rheumatoid arthritis, but it has also been reported in healthy patients [1-5]. Sjögren's syndrome is an autoimmune disease characterized by inflammatory infiltration and secondary chronic dysfunction of exocrine glands. Aseptic meningitis has been described as a neurological manifestation of this disease, sometimes related to the administration of drugs (never with ibuprofen) [6].

The mechanism by which drugs cause this reaction is unknown, but some evidence suggests an immunologic phenomenon, given the rapid development of symptoms after re-exposure, the lack of a relationship to dose, or the association with autoimmune diseases. Prostaglandin inhibition is unlikely to play a role, since most patients tolerate other nonsteroidal anti-inflammatory drugs [1-3]. The time to onset of symptoms after the initial administration ranges from immediate to 4 weeks (several hours in most cases), and upon re-exposure symptoms develop more rapidly [1-5]. In our case, the chronology was different: 15 minutes to onset in the clinical history, and 3 hours after drug provocation. A possible explanation

for this unusual presentation would be the pharmacokinetics of ibuprofen. When ibuprofen is taken with food, the absorption rate is slower and plasma concentrations lower. Additionally, the time until peak plasma concentrations varies following administration of conventional tablets, chewable tablets, or a suspension (about 120, 62, or 47 minutes for each form, respectively) [7]. The patient had always taken ibuprofen as a suspension without food, but in the hospital we administered conventional tablets and the patient ate between the doses. Both circumstances could explain the delayed reaction we observed. Furthermore the information reported by the patient was not corroborated by anyone else because she was alone at home when both reactions happened.

Although the clinical presentation of our patient suggests the possibility of a diagnosis of aseptic meningitis, we were unable to confirm or rule it out. In any case, the possibility of this adverse effect should also be taken into account when ibuprofen is administered to patients with autoimmune diseases. Finally, to our knowledge, this is the first case of a febrile reaction induced by ibuprofen in a patient with Sjögren's syndrome.

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Dr M Ángeles Gonzalo-Garijo

Hospital Universitario Infanta Cristina  
Sección de Alergología  
Carretera de Portugal s/n. 06080 Badajoz, Spain  
E-mail: magonzalog@telefonica.net