

# Severe Immediate Reaction to Nabumetone

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## ■ Abstract

Nabumetone is a nonsteroidal antiinflammatory (NSAID) prodrug that inhibits cyclooxygenase-2. It has been recommended as a safe alternative in most patients with hypersensitivity reactions to NSAIDs. Systemic reactions caused by nabumetone are not frequent. We report 2 cases of immediate systemic reactions due to nabumetone.

The first case involved a 68-year-old woman who developed immediate generalized pruritus, erythema, morbilliform eruption, swollen tongue sensation, diarrhea, and hypotension after the ingestion of a single dose of nabumetone. In the second case, a 77-year-old woman developed generalized pruritus, palm erythema, colic abdominal pain, diarrhea, dizziness, tightness of the chest, dyspnea, and hypotension immediately after oral intake of nabumetone. Both patients had previously tolerated this drug. Since these episodes, they have avoided nabumetone. Skin prick tests with nabumetone (10 and 100 mg/mL) were negative. Oral challenge tests with other NSAIDs, even of the same group as nabumetone, were negative in both patients. The mechanisms responsible for the reaction were not established.

**Key words:** Drug allergy. Hypersensitivity. Immediate reaction. Nabumetone. Nonsteroidal antiinflammatory drugs. Systemic reaction.

## ■ Resumen

La nabumetona es un antiinflamatorio no esteroideo (AINE) inhibidor de la ciclooxigenasa-2. Ha sido recomendado como una alternativa segura en los pacientes con hipersensibilidad a AINE. Las reacciones sistémicas debidas a este fármaco son infrecuentes. Comunicamos 2 casos de reacciones sistémicas inmediatas producidas por nabumetona. Caso 1: Mujer de 68 años que presentó a los pocos minutos de tomar una dosis de nabumetona prurito, eritema y erupción morbiliforme generalizada, hinchazón de la lengua, diarrea e hipotensión. Caso 2: Mujer de 77 años, que tras tomar nabumetona presentó prurito generalizado, eritema palmar, dolor abdominal cólico, diarrea, disnea, opresión torácica, sibilancias e hipotensión. Ambas pacientes habían tolerado el fármaco previamente; después de la reacción lo han evitado. Las pruebas cutáneas en prick con nabumetona (10 y 100 mg/ml) fueron negativas. La administración oral controlada con otros AINE, incluso del mismo grupo que la nabumetona fueron negativas en las dos pacientes. Los posibles mecanismos responsables de las reacciones no han sido establecidos.

**Palabras clave:** Alergia a medicamentos. Antiinflamatorios no esteroideos. Hipersensibilidad. Nabumetona. Reacción inmediata. Reacciones sistémicas.

## Introduction

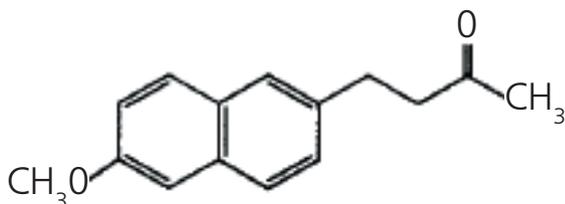
Nabumetone is a nonsteroidal antiinflammatory drug (NSAID) with antiinflammatory, analgesic, and antipyretic properties. It is a naphthylalkanone designated chemically as 4-(6-methoxy-2-naphthalenyl)-2-butanone and exerts its pharmacological effects via the metabolite 6-methoxy-2-naphthylacetic acid. This active metabolite is structurally similar to naproxen (see figure) and preferentially inhibits cyclooxygenase (COX)-2, although, as with other NSAID agents, its mode of action is not known [1]. Nabumetone has been recommended as a safe alternative in most patients with

hypersensitivity reactions to NSAIDs [2]. We report 2 patients who suffered immediate systemic reactions after oral intake of nabumetone, an uncommon adverse reaction rarely reported with this drug.

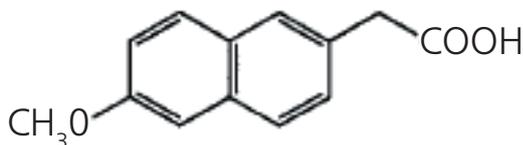
## Case Description

### Case 1

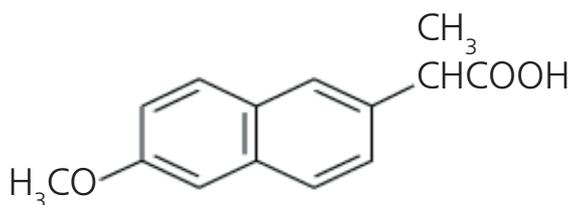
A 68-year-old woman suffering from osteoporosis developed immediate generalized pruritus, erythema, a



Nabumetone: 4-(6-methoxy-2-naphthalenyl)-2-butanone



Nabumetone metabolite: 6-methoxy-2-naphthylacetic acid



Naproxen. (S)-6-Methoxy-methyl-2-naphthalene acetic acid

Chemical structure of nabumetone, its metabolite, and naproxen

morbilliform eruption, and a swollen tongue sensation after ingestion of a single dose of nabumetone (1 g). She attended the hospital emergency department with diarrhea and hypotension and was treated with unspecified intravenous drugs with improvement 8 hours later. The patient had taken nabumetone previously (3 to 4 weeks before) with no reactions. Following this reaction, she has avoided nabumetone but she has tolerated acetylsalicylic acid, paracetamol, and ibuprofen. The patient had no previous history of atopy or drug allergy.

### Case 2

A 77-year-old woman with a history of hypertension, myelodysplasia, mesenchymal tumor, and depression developed generalized pruritus, palm erythema, colic abdominal pain, diarrhea, dizziness, tightness of the chest, and dyspnea immediately after oral administration of a single dose of nabumetone (1 g). She was treated with methylprednisolone, dexchlorpheniramine, and oxygen, and she was moved to hospital, where hypotension and tachycardia were observed. Her condition improved within 2 to 3 hours. Some days before this event, she had experienced dizziness, without other symptoms, after ingestion of a single dose of nabumetone. One month before, she had tolerated the drug without problems. The patient was receiving chronic treatment with several drugs (lornoxicam, fentanyl, sertraline, and losartan). After

this episode, she continued with the same chronic treatment and has taken paracetamol and metamizole.

Three months later, an allergy study was performed in both patients in the hospital after written informed consent had been obtained. Skin prick tests were performed using commercially available nabumetone tablets (Meda Pharma, Madrid, Spain), as the pure drug could not be obtained. Tablets were crushed in a mortar and diluted with 0.9% NaCl to achieve concentrations of 100 mg/mL and 10 mg/mL. Skin prick tests were performed on the volar surface of the arm with those dilutions. Histamine phosphate (10 mg/mL) was used as a positive control and saline as a negative control. The tests were read after 15 minutes and proved negative in both patients (reactions were considered positive when the wheal had a largest diameter of at least 3 mm greater than the negative control) [3].

In order to identify safe alternative drugs to nabumetone, we performed oral challenge tests with indomethacin, diclofenac, and piroxicam. They were negative in both patients. In patient 1, we also performed oral challenge with metamizole, and in patient 2 with ibuprofen; both tests were negative.

Tolerance of additives included in nabumetone preparations (croscarmellose sodium, povidone, sodium lauryl sulfate, vanilla essence, peppermint essence, magnesium stearate, microcrystalline cellulose, and sodium saccharin) was assessed and all of them had been tolerated after the initial reaction as ingredients of other drugs or foods. We did not perform provocation tests with nabumetone and naproxen due to the severity of the reactions experienced by our patients [4].

## Discussion

Nabumetone is generally accepted to be well tolerated, while the most commonly reported adverse effects are attributable to COX inhibition, including gastrointestinal symptoms or headache [1]. Dermatological reactions, such as pseudoporphyria and Stevens-Johnson syndrome, have also been associated with nabumetone [5,6]. However, systemic hypersensitivity reactions are not common. We have found 1 report of erythroderma with high fever induced by nabumetone demonstrated by oral challenge test; however, cutaneous or immunologic tests were not performed [7]. Recently, Wyplosz et al [8] published the case of a patient who experienced generalized urticaria with oral edema 4 days after beginning treatment with nabumetone. However, those authors did not perform tests to confirm the reaction. We report 2 cases of immediate systemic reactions associated with nabumetone. Both had a similar clinical presentation, with notably severe reactions. Clinically, it is clear that nabumetone was responsible for the syndrome suffered by our patients. According to the Naranjo probability scale [9], nabumetone was considered the probable cause of the reaction. However, it is more difficult to establish the mechanisms underlying the reaction. The clinical history made it possible to rule out drug overdose, drug side effect, and drug interaction. However, other conditions, such as drug intolerance, idiosyncratic reaction, drug allergy, or pseudoallergic reaction, can occur in certain patients and should be taken into account. To confirm a drug allergy, a relevant immunologic reaction to the drug or its

metabolites must be demonstrated [10]. Since nabumetone has a low molecular weight (228.3 daltons), it is not immunogenic and must be complexed with a carrier protein in order to elicit an immunologic response. Often, the organic radicals formed by these complexes do not cross-react antigenically with the parent compound and testing with the drug itself does not utilize the antigen responsible for the symptoms [3,4,10]. For those reasons, we cannot reach definitive conclusions regarding the negative results obtained in skin prick tests with nabumetone. Thus, while it is clear that our patients suffered a severe immediate reaction due to this drug, we cannot establish the definitive mechanism. Although some evidence suggests an immunologic phenomenon due to the rapid development of symptoms after reexposure, neither an IgE-mediated reaction nor other possible mechanisms for an immediate reaction (such as direct mediator release, anaphylotoxins of the complement cascade, or immunocomplex aggregation) could be demonstrated. In vitro tests could not be performed due to the lack of availability of pure nabumetone. Prostaglandin inhibition is unlikely to have played a role in the illness, since both patients had tolerated other NSAIDs, including drugs belonging to the same group as nabumetone. Nevertheless, we recommended that the patients avoided naproxen due to the similarity of its chemical structure to nabumetone.

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