

**Fixed exanthema after the ingestion of naproxen with tolerance to ibuprofen and dextetoprofen**

Reguero Capilla M, De Aramburu Mera T, Ochando Díez-Canseco M, Prados Castaño M

*Department of Allergology, University Hospital Virgen del Rocío, Seville, Spain*

Corresponding:

Marta Reguero Capilla

Department of Allergology, University Hospital “Virgen del Rocío”

Manuel Siurot, Str. 41013, Sevilla, Spain

[MartaregueroCapilla1993@gmail.com](mailto:MartaregueroCapilla1993@gmail.com)

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0518

**Key words:** Fixed drug exanthema, Naproxen, Arylpropionics, NSAIDs

**Palabras clave:** Exantema fijo medicamentoso, Naproxeno, Arilpropiónicos, AINE

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used worldwide because of their analgesic, anti-inflammatory, and antipyretic effects. NSAID are one of the most frequent causes of drug-induced hypersensitivity reactions, being urticaria and angioedema the most common clinical forms of presentation [1]. Patients who present symptoms after the intake of an NSAID do not usually tolerate others from the same chemical group due to a high cross-reactivity between NSAIDs which are structurally similar [2,3]. Controlled oral challenge test with the guilty NSAID is actually the gold standard diagnosis method to confirm a case of NSAID hypersensitivity [1-3].

Naproxen is a nonsteroidal anti-inflammatory drug, which belongs to the aryl-propionic acid family, and a nonselective COX inhibitor, used to treat menstrual cramps, inflammatory diseases such as rheumatoid arthritis, and fever. Fixed drug exanthema describes the appearance of a well-circumscribed erythematous patch, as a consequence of the systemic exposure to a drug. It is an allergic reaction to a medicine that characteristically recurs in the same site or sites each time a particular drug is taken. The number of drugs responsible of fixed drug eruptions is large, but it is frequently related with NSAID as ibuprofen and antibiotics [1,2,4]. In this paper we describe a case of fixed exanthema in one patient induced after several hours of taking naproxen, with tolerance to another aryl-propionic acid derivatives (ibuprofen and dexketoprofen), confirmed after performing a controlled oral challenge for each drug.

Our patient was a 25-year-old woman, with no other background than polycystic ovary syndrome, who was referred to our allergy unit because she presented, ten years ago, approximately 4 hours after naproxen intake, an itchy erythematoviolaceous patch in the right lateral side of her neck. No urticaria/angioedema occurred, nor another type of systemic symptoms.

The exanthema was resolved in 48 hours with no treatment. She did not consume naproxen again since that day, but she subsequently tolerated ibuprofen and dexketoprofen after the episode. She also occasionally consumes paracetamol and metamizol without problems.

The following diagnosis test was performed, with an interval of at least one week between the administrations of each drug:

- Patch test (epicutaneous test) with naproxen, ibuprofen and dexketoprofen, read after 48 and 96 hours (preparations were made using petrolatum as a vehicle and at similar concentrations to those suggested in other studies [6]; naproxen 30%, ibuprofen 5-10% and ketoprofen 1-10%): NEGATIVE
- Patch-test (epicutaneous test) with naproxen in the patient's neck, with a control with vaseline-patch, read after 48 and 96 hours: NEGATIVE
- Day 1: a single-blind placebo-controlled oral challenge (SBPCOC) with ibuprofen at doses of 50, 100 and 250 mg with intervals of 30, 60 and 120 minutes, and a observational period of 4:30 hours: NEGATIVE
- Day 2: a SBPCOC with the intake of a single dose of 600mg of ibuprofen (higher dose than the day before because the patient referred an intake of 600mg at home) and a observational period of 4:30 hours: NEGATIVE

- A SBPCOC with dexketoprofen; giving 6, 6 and 12mg with 30, 30 and 120 minutes of interval respectively, until reaching therapeutic dose and an observational period of 4 hours: NEGATIVE
- A SBPCOC with naproxen; 50, 150, 300mg every 30 minutes with 240 minutes of observation: the result was POSITIVE as the patient developed an itchy erythematous eruption in the lateral side of her neck, with no urticaria, angioedema or systemic symptoms associated (**Figure 1**).

We established time intervals between each DPT of 30 to 60 minutes because, once sensitised, the reaction appeared between 30 minutes and 8 hours after the intake, although this interval may be shorter with recurrent contacts with the drug [4]

The final diagnosis was fixed drug exanthema induced by naproxen.

Recent data shows that NSAIDs are the most frequent cause related with drugs hypersensitivity reactions [5]. The second most frequently described cause of these reactions, after pyrazolones [1], are the aryl-propionic acid derived, specifically ibuprofen. Fixed drug eruption is also related with ibuprofen in the first place, among NSAIDs.

Our patient could be included in the single NSAID-induced hypersensitivity reactions because she tolerates NSAID from different chemical groups. Patients with immediate reactions to 2 or more NSAIDs not structurally related, with ASA tolerance can occur and this phenotype must be taken into account [7]. She also tolerates another NSAID structurally similar to naproxen, her drug problem. There had been described cases of urticaria and/or angioedema related with one drug, but with tolerance to others from the same family [2], but in this paper we describe a case of fixed drug exanthema after the administration of one aryl-propionic acid derivative (naproxen) with tolerance to other

drugs of this family (ibuprofen and dexketoprofen). The time interval between the intake of the NSAID and the appearance of the erythema in our patient's neck was about 4 hours.

The usefulness of skin testing has been documented for pyrazolones [8] but its utility with aryl-propionics is scarce due to poor reliability.

Oral challenge remains the gold standard for diagnosing allergy to NSAID; it is not indicated in patients with a history of generalized exanthema or when the exanthema involves mucous tissues. In patients without generalized reaction or extended mucous involvement, oral challenge is considered relatively safe and remains the gold standard, confirming the affected area and the culprit agent [4]. Fixed drug eruptions characteristically reappear in the same location and with similar extension [9]. In this case, with a small skin area affected, a negative result in epicutaneous test and tolerance in oral challenge to ibuprofen and dexketoprofen, and due to the remarkable cross-reactivity between the aryl-propionic family, we decided to perform a diagnosis test with naproxen in order to prove the reproducibility of the clinic and we found a positive result when it appeared a erythematoviolaceous oval in the lateral side of the woman's neck.

We have described a case of fixed drug erythematous eruption induced after taking naproxen, with no urticaria/angioedema associated and with no cross-reactivity between the same structural groups, diagnosed by a single-blinded placebo oral challenge.

Finally, we conclude that aryl-propionic may induce fixed drug eruption as a hypersensitivity reaction in patients with good tolerance to others from the same chemical group. More studies are needed, but we would like to emphasize the importance of carrying out tolerance tests with another NSAID within the same group because of the probability of tolerance, choosing the cases individually.

### **Conflict of interest**

The authors declare that they have no conflicts of interest.

### **Funding**

The authors declare that no financial support was received for this study.

### **References**

1. Blanca-Lopez N, Perez-Alzate D, Andreu I, Doña I, Agundez JA, Garcia-Martin E, et al. Immediate hypersensitivity reactions to ibuprofen and other arylpropionic acid derivatives. *Allergy*. 2016;71:1048–56.
2. Ortega N, Doña I, Moreno E, Audicana MT, Barasona MJ, Berges- Gimeno MP, et al. Practical guidelines for diagnosing hypersensitivity reactions to nonsteroidal anti-inflammatory drugs. *J Investig Allergol Clin Immunol*. 2014;24:308-23.
3. Doña I, Barrionuevo E, Blanca-López N, Torres MJ, Fernández TD, Canto G, et al. Trends in hypersensitivity drugs reactions: more drugs, more response patterns, more heterogeneity. *J Investig Allergol Clin Immunol*. 2014;24:143-53.
4. Fernández Sánchez FJ, Blanca Gómez M, Jerez Domínguez J, Rodríguez Fernández F, Martín Casañez E. Reacciones cutáneas graves producidas por fármacos: eritema exudativo multiforme, síndrome de Lyell, síndrome de hipersensibilidad a fármacos. In: Peláez Hernández A, Dávila González IJ Editors. *Tratado de Alergología II*. Majadahonda (Madrid). Ergon, 2007; 1515-24.

5. Doña I, Blanca-Lopez N, Torres MJ, Garcia-Campos J, Garcia-Nunez I, Gomez F, et al. Drug hypersensitivity reactions: response patterns, drug involved, and temporal variations in a large series of patients. *J Investig Allergol Clin Immunol*. 2012;22:363–71.
6. Lobera Labairu T, Padial Vilchez MA, Guerrero García MA, Audicana Berasategui MT, García Abujeta JL. Concentraciones de principios activos y excipientes empleados para la realización de pruebas cutáneas y epicutáneas. In: Dávila González IJ, Jáuregui Presa I, Olaguibel Rivera JM, Zubeldía Ortuño JM Editors. *Tratado de Alergología IV*. Majadahonda (Madrid). Ergon, 2016; 1679-86.
7. Pérez-Alzate D, Cornejo-García JA, Pérez-Sánchez N, Andreu I, García-Moral A, Agúndez JA, et al. Immediate Reactions to More Than 1 NSAID Must Not Be Considered Cross-Hypersensitivity Unless Tolerance to ASA Is Verified *J Invest Allergol Clin Immunol*. 2017; 27(1):32-39
8. Himly M, Jahn-Schmid B, Pittertschatscher K, Bohle B, Grubmayr K, Ferreira F, et al. IgE-mediated immediate-type hypersensitivity to the pyrazolone drug propyphenazone. *J Allergy Clin Immunol*. 2003;111:882-8.
9. Mahboob A, Haroon TS. Drugs causing fixed eruptions: a study of 450 cases. *Int J Dermatol*. 1998;37:833-8.

Figure 1. Fixed drug eruption in patient's neck after oral challenge test with naproxen.

