

# Systemic Dermatitis due to Tetrazepam

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## ■ Abstract

Cutaneous adverse reactions to benzodiazepines seem to be rare.

We report a 61-year-old man with adverse reactions after ingestion of metamizole, diclofenac, and tetrazepam. Skin prick tests with metamizole, diclofenac, and tetrazepam were negative. Patch tests with metamizole, diclofenac, and tetrazepam (all at 5% in aqueous solution) were performed, and were positive for tetrazepam. Oral challenge was performed with metamizole, acetylsalicylic acid, diclofenac, and tetrazepam with a positive result for diclofenac and tetrazepam. The patient tolerated other benzodiazepines.

We present a patient who can tolerate diazepam but who had a type IV hypersensitivity reaction to tetrazepam confirmed by patch testing and oral challenge. The patient also presented an immediate hypersensitivity reaction after taking diclofenac.

**Key words:** Benzodiazepines. Contact dermatitis. Patch test. Tetrazepam.

## ■ Resumen

Las reacciones adversas con benzodiazepinas son poco frecuentes.

Presentamos el caso de un varón de 61 años con reacciones adversas tras la toma de metamizol, diclofenaco y tetracepam. Realizamos pruebas cutáneas en prick con metamizol, diclofenaco y tetracepam con resultado negativo. Además realizamos pruebas epicutáneas todas al 5% en SSF con los 3 fármacos siendo positiva con tetracepam. Prueba de tolerancia oral controlada con metamizol, ácido acetilsalicílico, fueron negativas; positivas con diclofenaco y tetracepam. El paciente finalmente toleró otras benzodiazepinas.

Presentamos el caso de un paciente con una reacción de hipersensibilidad tipo IV con tetracepam confirmado por una prueba epicutánea y una provocación oral controlada; el paciente toleró diazepam. Además presentó una reacción de hipersensibilidad inmediata tras la toma de diclofenaco.

**Palabras clave:** Benzodiazepinas. Dermatitis de contacto. Pruebas epicutáneas. Tetrazepam.

## Introduction

Tetrazepam is a frequently used muscle relaxant of the benzodiazepine group [1]. Neurologic disorders (sedative or paradoxical effects) and digestive disorders are the most frequent side effects classically attributed to the benzodiazepines [2].

Fixed drug eruption [3], generalized reactions [4], contact dermatitis [5], leukocytoclastic vasculitis [6], photodermatitis [7], Stevens-Johnson syndrome [5,8], and occupational airborne contact dermatitis [9] have occasionally been reported with tetrazepam and confirmed by positive patch test.

## Case Description

A 61-year-old man with no history of atopy or allergy was treated with tetrazepam (Sanofi-Synthélabo, Barcelona, Spain), diclofenac (Novartis Farmacéutica SA, Barcelona, Spain) and paracetamol (Novartis Farmacéutica SA, Barcelona, Spain) for a muscular contracture. Forty-eight hours after taking the drugs, he developed pruritus with generalized micropapular rash. Medication was discontinued, and the skin lesions resolved completely in 2 days with systemic corticosteroids and antihistamines.

Six months later, he was treated with oral diclofenac and

complained of generalized urticaria a few minutes after the first dose. The symptoms disappeared without treatment.

One year later, he presented a generalized micropapular eruption 48 hours after receiving metamizole (Boehringer Ingelheim SA, Sant Cugat del Valles, Barcelona, Spain) and tetrazepam. Since then, the patient has taken paracetamol without experiencing side effects.

We performed a skin prick test with diclofenac (50 mg/mL), metamizole (400 mg/mL), and tetrazepam (50 mg/mL), all in saline solution, and the results were negative. Histamine (10 mg/mL solution) and buffered saline were used as positive and negative controls, respectively.

Subsequently, the patient was patch-tested with the standard series (by True Test, Mekos Laboratories ApS, Hillerod, Denmark) and with tetrazepam (5% in aq), diclofenac (5% in aq) and metamizole (40% in aq). Patch tests were read at 48 and 96 hours and were applied to the skin on his upper back. Patch testing with tetrazepam 5% (+++) was positive (Figure), showing a negative result to all the standard series and to the rest of the drugs tested. Ten control subjects (5 atopic and 5 nonatopic) underwent patch testing and all proved negative.

After obtaining informed consent, we performed a single-blind oral challenge with diclofenac and the result was positive. One hour after receiving 12.5 mg of diclofenac, the patient developed generalized urticaria. Oral challenge with metamizole and acetylsalicylic acid were both negative.



Figure. Positive patch test to tetrazepam

Due to the positive oral challenge result with diclofenac and, despite a positive patch test result with tetrazepam, we performed an oral challenge with tetrazepam (87 mg), which evoked an immediate negative response. The patient was prescribed 50 mg of tetrazepam to be taken daily at home, for 3 days. On the second day (48 hours later), the patient developed generalized pruritus and micropapular eruption. To investigate possible cross-reactivity between benzodiazepines, we carried out a patch test and an oral challenge with diazepam, although no reaction was observed. Therefore, we recommended the use of diazepam for future treatments that require a benzodiazepine.

## Discussion

Cutaneous adverse reactions to benzodiazepines seem to be rare [1]. Blanco et al [2] reported 3 patients with delayed hypersensitivity to tetrazepam. Patch tests at 1% and 5% pet were positive and their patients tolerated an oral challenge with bromazepam and diazepam. Del Pozo et al [5] described 4 patients with contact dermatitis and 1 patient with Stevens-Johnson syndrome with tetrazepam. All of them tolerated oral diazepam.

The use of patch testing to detect allergy to tetrazepam has not yet been sufficiently standardized. The patch test concentrations used for tetrazepam ranged from 1% to 100% in pet or aq [1]. In our case, we performed a patch test at 5% in aq with a positive result. In some cases, patch testing on residual lesional skin may be useful [10].

As our patient's symptoms were mild, we also performed an oral challenge. The positive oral challenge result confirms that patch testing can demonstrate allergy to tetrazepam.

The clinical features of our patient and the positive patch test and oral challenge results suggest a type IV hypersensitivity reaction to tetrazepam.

In our case, patch tests with other benzodiazepines were negative, and the patient tolerated oral administration of diazepam, a benzodiazepine that shares a structural homology with tetrazepam. Therefore, we did not observe cross-reactivity with this benzodiazepine.

In summary, we report a patient with a double sensitization. First, a type IV hypersensitivity reaction to tetrazepam confirmed by a positive patch test and oral challenge, and, second, we presume an immediate hypersensitivity reaction to diclofenac, demonstrated by challenge test in spite of a negative skin test, with tolerance to other anti-inflammatory drugs.

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