

Tetrazepam drug sensitivity – usefulness of the patch test

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The muscle relaxant tetrazepam may cause severe cutaneous adverse effects. We report 4 cases of varying intensity: Stevens–Johnson syndrome, erythema–multiforme-like exanthema, maculopapular and maculo-urticarial exanthema. Patch testing with tetrazepam (10% in petrolatum) was strongly positive in the 2 patients with severe skin eruptions and weakly positive in the other 2. Oral rechallenge with tetrazepam was positive in 3 patients (1 not done). Diazepam, with a similar chemical structure to tetrazepam, was negative on patch testing and on oral challenge testing in 2 patients. Although the optimal patch test concentration of tetrazepam has still to be determined, it is a useful diagnostic tool to confirm sensitization, particularly in patients with severe bullous eruptions.

Key words: challenge test; cutaneous adverse drug reaction; diazepam; patch testing; tetrazepam.
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Tetrazepam is a frequently used muscle relaxant of the benzodiazepine group and may cause cutaneous adverse effects of various types: primarily maculopapular exanthemas but also severe forms like erythema multiforme and Stevens–Johnson syndrome (Table 1).

We describe 4 patients with moderate to severe skin reactions after oral intake of tetrazepam. Results of patch testing and oral rechallenge support a Type IV allergy.

Materials and Methods

Prick test

Tetrazepam tablets (Musaril® Sanofi-Synthelabo, Berlin, Germany) were crushed and diluted with normal saline to 50%. Readings were made at 20 min in comparison to controls (normal saline and histamine 10 mg/mL).

Patch test

The crushed tablets were diluted with white petrolatum (pet.) to 1% and 10%. The materials were

applied to the skin of the upper back for 2 days (D) using Finn Chambers on Scanpor tape (Hermal, Reinbek, Germany). Readings were made according to published guidelines (1).

Case No. 1

A 67-year-old woman with a history of lumbago developed a moderate erythema-multiforme-like exanthema 7 D after starting treatment with calcium tablets, acetaminophen and tetrazepam $2 \times 50 \text{ mg day}^{-1}$. The mucosa was not involved. After the lesions had disappeared, skin tests and oral challenge tests with paracetamol and tetrazepam were performed. Prick test, patch test and oral re-exposure with acetaminophen were negative. Patch tests with tetrazepam showed a strong positive reaction at 10% and a doubtful one at 1% (Table 2). Oral rechallenge with 12.5 mg tetrazepam caused a mild flare-up of the exanthema (redness and itch in previously affected skin) 1 D after intake.

Case No. 2

A 32-year-old patient was hospitalized because of severe lumbar pain. As treatment he received acetylsalicylic acid, bupivacaine hydrochloride injections, acetaminophen and tetrazepam $3 \times 50 \text{ mg}$

In memoriam Professor José G. Camarasa (1933–2001)
– dedicated clinician, tireless researcher, valued friend.

Table 1. Review of tetrazepam allergy reports in the literature

Author (ref.)	Clinical symptoms	Patch test results to tetrazepam	Oral challenge with tetrazepam	Patch test results to diazepam	Oral challenge with diazepam
(2)	Itchy rash (<i>n</i> = 1)	D2/4 ++ (pure powder, 1 % aq.)	n.d.	n.d.	n.d.
	Itchy rash (<i>n</i> = 1)	D2/4 ++ (pure powder, 1 % aq.)	n.d.	n.d.	n.d.
(3)	Maculopapular (<i>n</i> = 1)	D3/4 ++ (crushed tablets in pet.)	n.d.	D3 +	n.d.
	Itchy rash (<i>n</i> = 1)	D2/3 ++ (crushed tablets in pet.)	n.d.	negative	n.d.
(4)	Maculopapular (<i>n</i> = 1)	D2/D4 ++ pure powder, 1% aq.)	positive	negative	negative
(5)	Itchy rash (<i>n</i> = 4)	1 patient negative 3 patients: 1% pet. ++ 5% pet. ++	positive	n.d.	n.d.
			1 patient positive 2 patients. n.d.		
(6)	Photodermatitis (<i>n</i> = 1)	D4 ++ (10% pet., photopatch)	positive	negative	negative
(11)	Maculopapular (<i>n</i> = 1)	++ <i>in loco</i> (30%, 10%, 1% pet.)	n.d.	n.d.	n.d.
(12)	Erythema multiforme (<i>n</i> = 1)	positive (crushed tablets)	n.d.	n.d.	n.d.

Table 2. Results of patch testing and oral rechallenge with tetrazepam in 4 patients with drug allergy to tetrazepam

Patient No	Symptoms of drug allergy to tetrazepam	Prick test	Patch test with tetrazepam				Oral challenge	
			1% pet.		10% pet.		Tetrazepam	Diazepam
			D2	D3	D2	D3		
1	EEM	–	–	? +	+	++	+	n.d.*
2	SJS	–	+	+++	+	+++	n.d.	–
3	UE	–	–	–	–	? +	+	n.d.
4	ME	–	–	–	? +	? +	+	–

*Not done; UE, urticaria-like exanthema; EEM, Erythema-multiforme-like exanthema; SJS, Stevens–Johnson syndrome; ME, exanthema (maculopapular).

day⁻¹ for 5 D. His hyperuricaemia was treated with allopurinol. 7 D after the medication was discontinued he developed a severe generalized drug eruption with bullous target lesions on the trunk and extremities. In the mouth he had large haemorrhagic necrotic plaques, the conjunctivae were red and showed hypersecretion. The patient was admitted with the diagnosis of a drug-induced Stevens–Johnson syndrome. He was treated with oral prednisolone for 14 D. Topical corticosteroids and antibacterial mouth swabs were also applied. There were no laboratory signs of acute bacterial or viral infections. 3 months later, the patient still showed marked hyperpigmentation at previously affected sites, particularly on the legs. On patch testing tetrazepam showed +++ reactions at both 1% and 10% (Table 2). All other drugs taken beforehand were negative. Challenge tests with bupivacaine hydrochloride (subcutaneous injection of 8 mL), acetylsalicylic acid, acetaminophen and allopurinol did not show any reactions. Tetrazepam was not reexposed because of the strong patch test reaction and the severity of the cutaneous adverse effect. As patch testing with diazepam was negative, an oral challenge test with 10 mg diazepam was done. No skin reaction was observed.

Case No. 3

A 48-year-old woman was treated with diclofenac, acetaminophen, tetrazepam 3 × 25 mg day⁻¹ and omeprazol because of lumbago. 2 D after starting this drug regime she developed an urticaria-like exanthema on the neck and trunk. Skin tests and oral reexposure with diclofenac, acetaminophen and omeprazol were negative. Patch testing with tetrazepam showed a mild erythema at the highest concentration after 3 D (Table 2). Rechallenge with tetrazepam 12.5 mg provoked a flare-up of the exanthema within 1 D morphologically similar to the previous one.

Case No. 4

A 35-year-old woman developed a moderate macular exanthema on the neck and chest 2 D after intake of diclofenac, famotidin, tramadol, metoclopramide and tetrazepam 2 × 50 mg day⁻¹. After disappearance of the exanthema she took diclofenac again without developing any symptoms. Skin tests and oral challenge tests with famotidin, tramadol, metoclopramide were negative. Patch testing with tetrazepam showed a weak erythematous re-

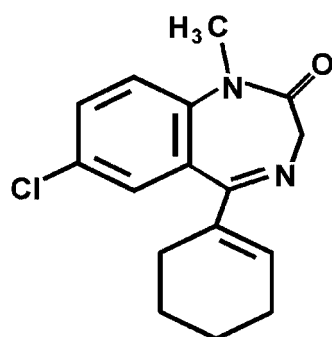
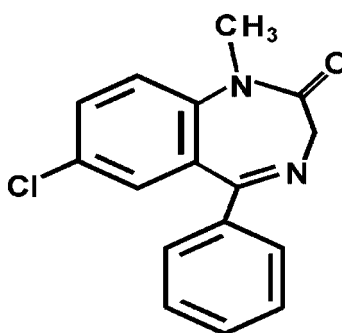
**Tetrazepam****Diazepam**

Fig. 1. Chemical structures of tetrazepam and diazepam.

action only to the 10% concentration (Table 2). 7 h after oral rechallenge with 25 mg tetrazepam, a flare-up of the exanthema was observed. Diazepam was negative on skin testing. An oral provocation test with 10 mg diazepam was well tolerated.

Discussion

Cutaneous adverse reactions to benzodiazepines seem to be rare, though exact figures on incidence are lacking. In our literature search (Medline) we found reports of 9 individual cases and 1 publication on a group of 4 patients with tetrazepam allergy (Table 1). Most authors have observed maculopapular rashes with pruritus (2–5). Quinones et al. described photosensitivity with a positive photopatch test (6). Stevens–Johnson syndrome due to tetrazepam was described by Sanchez et al. in a woman who was treated for lumbar arthralgia with tetrazepam very similarly to our case No. 2 (7). Patch testing to tetrazepam 20% pet. showed a ++ reaction at D2 and D4. To our knowledge, patient No. 2 represents the 2nd case report of Stevens–Johnson syndrome provoked by tetrazepam. He also showed strong positive patch test reactions to 1% and 10% tetrazepam in pet. Patient, nos. 3 and 4 in our series had milder skin symptoms than patient Nos. 1 and 2. Apparently, they were less sensitive to tetrazepam and developed only weak (erythematous) reactions to 10% tetrazepam. The optimal test concentration for tetrazepam drug allergy has still to be determined. 10% may be sufficient for highly sensitive patients, while 20% or higher may be needed for a lower grade of sensitivity. Furthermore, it is still unclear what the proportion of false-negative patch test reactions would be if a larger series of patients with cutaneous adverse effects due to tetrazepam were tested.

Cross-reactions between diazepam and tetrazepam have been demonstrated. Kaempgen et al.

reported a patient with maculopapular exanthema from tetrazepam who showed not only positive patch test reactions to tetrazepam but also to diazepam (3). An oral challenge test to confirm the clinical relevance of cross-reactivity was not performed. As Ortega and Quinones have demonstrated, there are also patients with Type IV hypersensitivity to tetrazepam where oral challenge with diazepam is well tolerated (4, 6). Corresponding to these results, 2 of our patients tolerated diazepam well despite its great structural similarity with tetrazepam (Fig. 1). If quantitative structure–activity relationships (QSAR) for contact allergy are considered, the tetrazepam molecule has a higher potential for sensitization than diazepam. Diazepam contains an aromatic ring whereas tetrazepam contains a cyclohexene ring. The aromatic structure would be expected to be more stable toward skin metabolism. Following hydrolysis of the imino function >N-tetrazepam gives an α - β unsaturated ketone, which is a good electrophile, while diazepam produces a less-reactive benzophenone derivative (8).

The use of patch testing for detection of allergy is well documented for drugs like amoxycillin, ampicillin, carbamazepine and also benzodiazepines (9, 10). The patch test concentrations used for tetrazepam ranged from 1% to 100% (pure powder) in pet. or aq. (Table 1). As there are no convincing data yet, we recommend a dilution series of 1%, 10% and 50% pet. when tetrazepam allergy is suspected. In some cases, patch testing on residual lesional skin may be useful, as Barbaud et al. described in a patient with a maculopapular rash from tetrazepam (11). In 3 of our 4 patients, the positive patch test to tetrazepam was supported by a positive rechallenge test with tetrazepam. These results indicate that patch testing is a useful tool to confirm tetrazepam allergy, particularly in cases with a high degree of sensitization and severe bullous skin reactions.

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