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SHORT COMMUNICATION

# Tetrazepam Allergy: A Case Series of Cutaneous Adverse Events

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Tetrazepam has been widely used in clinical praxis in many countries for over 50 years (1). As an agent belonging to the class of benzodiazepines, it has an immediate sedative, muscle relaxing, anxiolytic and anticonvulsant effect. According to the German drug prescription report for 2012, tetrazepam was the most commonly prescribed muscle relaxant after botulinum toxin (2). Common adverse reactions following systemic intake are of neurological and gastrointestinal nature, while cutaneous reactions to tetrazepam are very rare, with only a few cases reported in the literature. It has nevertheless to be assumed that only a minority of cases is reported. The accumulation of these adverse reactions in comparison with other muscle relaxing drugs led the European Commission to suspend marketing authorizations of tetrazepam-containing medicines across the European Union (EU) in 2013. As shown in Fig. S1[1], diazepam has great structural homology with tetrazepam, deviating only at R4 substitution (aromatic ring (T) and cyclohexene ring (D)). Although the chemical structure of these 2 muscle relaxants is very similar, with the exception of one report, all other reports failed to demonstrate cross-reactivity (3–5).

A summary of skin reactions previously reported in the literature is shown in Table SI[1], including (6) and (7). We retrospectively assessed patient charts in our allergy clinic and identified 8 patients with tetrazepam allergy over a period of 10 years (2003–2013). Patch-testing had been performed as follows: the crushed tablets were diluted with white petrolatum to 10% and applied to the skin of the upper back for 48 h using Finn Chambers. Readings were made according to published guidelines (8). The results of skin testing are summarized in Table I. A summary of the clinical data is available in Table SII[1].

The patients in this case series are presented, in most cases, as mild cutaneous reactions. Only one case presented as an erythema multiforme-like exanthema. In all patients skin reactions subsided without sequelae after removal of the drug. Type IV sensitization to tetrazepam could be detected in all patients. Tests (prick and patch) related to concomitant medication used at the same time as tetrazepam showed no positive reactions, suggesting that the observed skin reactions were very likely caused by tetrazepam. In addition, in one patient patch-testing of diazepam and in one patient oral challenge to lorazepam were negative.

Table I. *Overview of patch- and prick-testing with tetrazepam and diazepam in 8 patients with drug allergy to tetrazepam*

| Pat. No. | Sex/age, years | Symptoms | Prick-test | Patch-test (tetrazepam) | Patch-test (diazepam) |
|---|---|---|---|---|---|
| 1 | F/66 | EME | – | Pos. at D2 | Not done |
| 2 | F/45 | Exanthema[a] | – | Pos. at D2 | Not done |
| 3 | F/47 | Exanthema[a] | – | Pos. at D3 | Not done |
| 4 | F/65 | Exanthema[a] | – | Pos. at D2 | Not done |
| 5 | M/75 | ME (see Fig. S2[1]) | – | Pos. at D4 | Not done |
| 6 | M/48 | Exanthema[a] | – | Pos. at D3 | Not done |
| 7 | M/42 | ME | – | Pos. at D2 | Not done |
| 8 | F/49 | Exanthema | – | Pos. at D2 | Negative |

[a]Not further specified exanthema.

EME: erythema-multiforme-like exanthema; ME: maculopapular exanthema; Pos.: positive; D2, D3, D4: days after test-application; –: negative. For further detailed information relating to each patient see Tables SI[1] and SII[1].

To our knowledge, since 2002 16 cases of cutaneous adverse effects due to tetrazepam have been published. In most cases, patch-testing to tetrazepam was a sensitive tool to detect hypersensitivity. Because there are no standardized testing protocols for tetrazepam, the patch-test concentrations ranged from 1% to 10% in pet. or aqua. In several patients skin testing was followed by oral challenge testing, 5 out 7 re-challenges were positive. These results indicate that patch-testing is a good tool to identify sensitization to tetrazepam. Cross-reaction between tetrazepam and diazepam was demonstrated only in one case report (9). Most patients tolerated diazepam despite its great structural similarity to tetrazepam. The limited number of data in this regard has to be considered. Recently in healthcare workers, e.g. via crushing of drug tablets to improve drug swallowing, airborne contact dermatitis and cross-reaction between tetrazepam and benzodiazepines has been observed repeatedly (10, 11).

Due to the withdrawal of tetrazepam, and only one case of documented cross-reactivity to diazepam, physicians could take other benzodiazepine-derivates into therapeutic consideration. It remains to be seen whether skin testing and oral challenge test to other benzodiazepines derivates should be conducted prior to applying these alternative treatment options.

*The authors declare no conflicts of interest.*

## REFERENCES

1. Behles C, Rotthauwe J. Nutzen-Risiko-Verhältnis von Tetrazepam, Bulletin zur Arzneimittelsicherheit 3. Available

[1]https://doi.org/10.2340/00015555-2147

from http://www.bfarm.de/SharedDocs/1_Downloads/DE/BfArM/publ/bulletin/2013/2- 2013.pdf.
2. Schwabe U, Paffrath D. Arzneiverordnungs-Report 2012. Heidelberg: Springer, 2012.
3. Pirker C, Misic A, Brinkmeier T, Frosch P. Tetrazepam drug sensitivity – usefullness of the patch test. Contact Dermatitis 2002; 47: 135–138.
4. Barbaud A, Girault P-Y, Schmutz J, Weber-Muller F, Trechot P. No cross-reactions between tetrazepam and other benzodiazepines: a possible chemical explanation. Contact Dermatitis 2009; 61: 53–56.
5. Martinez-Tadeo J, Perez-Rodriguez E, Hernandez-Santana, G, de la Torre-Morin F. Anaphylaxis caused by tetrazepam without cross-reactivity with other benzodiazepines. Ann Allergy Asthma Immunol 2012; 108: 284–285.
6. Cabrerizo Ballesteros S, Mendez Alcalde J, Sanchez Alonso A. Erythema multiforme to Tetrazepam. J Investig Allergol Clin Immunol 2007; 17: 202–206.
7. Sanchez-Morillas L, Laguna-Martinez J, Reano-Martos M, Rojo-Andres E, Gomez-Tembleque Ubeda P. Systemic dermatitis due to tetrazepam. J Investig Allergol Clin Immunol 2008; 18: 404–406.
8. Bourke J, Coulson I, English J. Guidelines for the management of contact dermatitis:an update. Br J Dermatol 2009; 160: 946–954.
9. Kämpgen E, Bürger T, Bröcker E-B, Klein E. Cross-reactive type IV hypersensitivity reactions to benzodiazepines revealed by patch testing. Contact Dermatitis 1995; 33: 356–357.
10. Landeck L, Skudlik C, John SM. Airborne contact dermatitis to tetrazepam in geriatric nurses – a report of 10 cases. Eur J Dermatol 2012; 26: 680–684.
11. Swinnen I, Ghys K, Kerre S, Constandt L, Goossens A. Occupational airborne contact dermatitis from benzodiazepines and other drugs. Contact Dermatitis 2013; 70: 227–232.