

ORIGINAL ARTICLE

Airborne contact dermatitis to tetrazepam in geriatric nurses – a report of 10 cases

L. Landeck,* C. Skudlik, S.M. John

Department of Dermatology, Environmental Medicine and Health Theory, University of Osnabrueck, Osnabrueck, Germany

*Correspondence: L. Landeck. E-mail: llandeck@uos.de

Abstract

Background Tetrazepam, a benzodiazepine, is a frequently used muscle relaxant. The most common adverse reactions are neurological and gastrointestinal. Cutaneous reactions to tetrazepam are rare and occur predominantly after systemic administration.

Objective To present 10 health care professionals who developed airborne contact dermatitis to tetrazepam due to occupational exposure to tetrazepam dusts.

Materials and methods We report a series of 10 cases observed in our department between January 2006 and March 2011 where tetrazepam was identified to cause allergic airborne contact dermatitis. Affected individuals were employed as (geriatric) nursing staff, exposed to tetrazepam on a regular occupational basis when crushing tablets for their patients. Upon investigation, patients were patch tested with commercial and customized allergens. This included tetrazepam and in five cases diazepam. Tetrazepam revealed strong positive reactions in all patients. Additional diazepam sensitization was observed in three subjects. Following local treatment and occupational preventive action, patients recovered from their skin symptoms.

Conclusions Allergic contact sensitization to tetrazepam and cross-sensitization to diazepam seems to be underestimated and not appropriately diagnosed in patch test clinics, as it is so far insufficiently patch tested. They should be considered when allergic contact dermatitis is suspected, particularly in professionally exposed staff, and tested as supplemental allergens.

Received: 5 April 2011; Accepted: 31 May 2011

Conflicts of interest

The authors have no funding sources or conflicts of interest to declare.

Background

Benzodiazepines are one of the most frequently used medications. According to the National Health Statistics Report for 2006, benzodiazepines accounted for 3.1% of all drugs prescribed in ambulatory care visits in the United States.¹ Similar numbers of prescriptions can be assumed for Europe. Among the group of benzodiazepines, tetrazepam is one of the most popular ones, because of its outstanding muscle relaxant effect. It has also anti-convulsant, anxiolytic and hypnotic properties. Common adverse reactions after systemic intake are neurological and gastrointestinal, while cutaneous reactions to tetrazepam are rare and comprise in the majority maculopapular exanthems.^{2–8} Recently Vander Hulst *et al.* reported an occupational airborne dermatitis to tetrazepam in 10 nurses who were referred for evaluation of facial and/or hand dermatitis.⁹

Material and methods

We report a case series observed in our department between January 2006 and March 2011 where 10 health care professionals were referred for diagnostic evaluation of chronic recurrent dermatitis. Patients had a long-standing history of eczematous lesions between 2 and 10 years. The skin changes affected predominantly the periorbital and facial area but in some instances also the décolleté, neck, forearms and hands. Patients were employed as geriatric nurses/care assistants ($n = 9$) and a registered nurse ($n = 1$) and described worsening of skin lesions in the working environment (Figs 1 and 2) where they had to crush tetrazepam with a mortar and pestle for their (geriatric) patients who were unable to swallow pills. None of our patients had a past or ongoing history of atopic dermatitis, allergic rhinitis or allergic asthma. Their past medical history did not reveal evidence for systemic intake of tetrazepam or other benzodiazepines. Patients were patch tested to an extended range of allergens, including standardized and customized substances. The testing for workplace allergens comprised also

Reprints are not available from the authors.



Figure 1 Work related skin changes after crushing tetrazepam affecting the face.

drugs, and among others crushed tetrazepam (ratiopharm, Ulm, Germany) and in some cases diazepam (ratiopharm), both tested in 30% petrolatum (pet.) and/or 30% in aqua (aq.). Tests were conducted and read according to international guidelines¹⁰ applying Haye's test chambers (HAL, Düsseldorf, Germany) affixed with Fixomull stretch tape (Beiersdorf, Hamburg, Germany) to the upper back. Commercial allergens were purchased from



Figure 2 Work related skin changes after crushing tetrazepam affecting the face and neck.

Almirall Hermal (Reinbek, Germany). Patches remained in place for 24 h and were evaluated after 24, 48, 72, 96 and in some cases after 120 h. In this report only 72 h readings were incorporated. Relevance of positive results was determined by assessment of past history of contact with the allergen and if expressed symptoms were consistent with the clinical picture and history.

For scientific interest, in six patients a skin prick test was performed. In one nurse we conducted a double blind placebo controlled oral challenge to diazepam with increment dosage (1.25 mg, 2.5 mg and 5 mg) over 2 days, using P-tablets-Lichtenstein (Winthrop, Fürstentfeldbruck, Germany) as a placebo. In addition, the total IgE was quantified in five patients. Eighteen female health care professionals from the same occupations were patch tested with tetrazepam as controls.

Results

Patch test results for tetrazepam revealed in seven patients +++ and in three subjects ++ reactions after 72 h (Fig 3). Among five patients who were also tested for diazepam, three showed type-IV allergic reaction (Fig 4). Overall, reactions to diazepam were weaker than those to tetrazepam. Six patients experienced skin flares when patch tested (Figs 5 and 6). Four patients showed additional type-IV-sensitization to allergens from the standard and supplemental trays, but clinical relevance to those could not be established. Further complementary tests (skin prick test, total IgE, oral challenge) yielded negative results as shown in Table 1. Among the controls, patch test results to tetrazepam were all negative.

Subsequent to diagnostic testing, local therapy was initiated and occupational preventive action taken. This included primarily the avoidance of positive tested allergens where possible, or otherwise minimal exposure technique to avoid volatile dusts due to exhaust systems, use of gloves, protective masks and long-sleeved work clothes. Apart from one geriatric nurse who had to start an occupational re-training, all other patients recovered from skin symptoms.



Figure 3 Patch test reaction to tetrazepam after 72 h.



Figure 4 Patch test reaction to diazepam after 72 h.



Figure 6 Skin flares at the neck when patch tested to tetrazepam.



Figure 5 Facial skin flares of a patient when patch tested to tetrazepam.

Discussion

After systemic administration of tetrazepam, primarily maculopapular exanthems have been reported in the literature.^{2–8} Less frequently, Stevens Johnson syndrome,^{6–8,11} toxic epidermal necrolysis,^{12,13} erythema multiforme^{7,14} and photodermatitis/phototoxicity^{15,16} were linked to tetrazepam intake. In addition, there are individual case reports of acute generalized exanthematous pustulosis (AGEP),¹⁷ fixed drug eruption⁸ and drug rash with eosinophilia (DRESS)¹⁸ described. In contrast, airborne contact eczema^{19–22} was observed after occupational exposure to tetrazepam, without previous intake of tetrazepam. Affected individuals were employed as geriatric nurses^{19,20} and as factory staff in pharmaceutical companies^{21,22} being exposed to tetrazepam dusts

on a regularly basis. To date, there is only one case series describing 10 geriatric nurses in Belgium with airborne contact dermatitis to tetrazepam.⁹ Contact allergy to tetrazepam was confirmed by patch testing and reactions were in the majority mild to moderate. One third of the individuals were also suffering from atopic dermatitis or hay fever. Cross-reactions to diazepam were not observed upon testing.

Our patients had a substantial similarity to the before mentioned report in view of the occupational background and the clinical picture. However, there are certain specifics, we would like to highlight. As in our series none of the patients had an ongoing atopic disease, atopy does not seem to play an important role. Moreover, among our patients who were also patch tested to diazepam, 60% yielded positive results to this benzodiazepine as well. The question whether hypersensitivity to tetrazepam shares true cross-reactivity with other benzodiazepines is still debatable. Cross- and concomitant sensitization to diazepam is conceivable as both chemicals have considerable analogy in their chemical structures and are often used in the same medical environment. Besides, benzodiazepines share a common active metabolite (desmethyldiazepam) which seems to be antigenic and may account for cross-sensitivity.³

The literature, however, documents only two instances of positive patch test reactions to both, tetrazepam and diazepam.^{4,23} The reaction to diazepam was weaker than to tetrazepam. This may be related to the structure of the two chemicals. While tetrazepam contains a cyclohexene ring, diazepam has an aromatic ring⁷ that would be expected to be more stable toward skin metabolism. Hydrolysis of the imino function of >N-Tetrazepam releases an α - β unsaturated ketone, an effective electrophile while diazepam produces a less reactive benzophenone derivative and this phenomenon may account for a weaker patch test reaction.⁷

Table 1 General epidemiologic data and test results in our patients

Patient No.	1	2	3	4	5	6	7	8	9	10
Age of patients at hospitalization in years	45	27	59	61	21	52	57	58	52	47
Working experience as a geriatric nurse in years	16	7	31	11	5	11	12	18	11	9
Duration of skin rash in the periorbital/facial area in years	5	4	5	2	3	2	10	2	2	2
Sites of skin changes in addition to the periorbital/facial area	None	Neck, forearms, hands	Forearms, décolleté	Ears, neck, hands, forearms	Neck, forearm, décolleté, hands	Décolleté, arms	Hands, forearms	None	Décolleté, forearms	Neck
Ongoing atopic disease (atopic dermatitis, allergic rhinoconjunctivitis, allergic asthma)	None	None	None	None	None	None	None	None	None	None
Patch test reaction to tetrazepam at 72 h	+++pet.	+++aq., +++pet.	+++aq.	+++aq., +++pet.	+++aq.	+++pet. +++aq.	++++aq.	+++aq., +++pet.	+++aq., +++pet.	++++aq.
Patch test reaction to diazepam at 72 h	++pet.	+++aq., +++pet.	NT	NT	NT	None	NT	+aq., +pet.	None	NT
Flare up of skin lesions under testing	↗	↗	↗	None	↗	None	None	↗	↗	None
Skin prick test	Negative	NT	NT	Negative	Negative	Negative	NT	Negative	Negative	NT
Total IgE in kU/L	NT	31	NT	65	208	18	28	NT	NT	NT
Placebo controlled oral challenge test	NT	NT	NT	NT	NT	NT	NT	NT	Diazepam: none	NT
Other type-IV-sensitizations (clinical relevance was ruled out)	Nickel sulphate+, potassium dichromate+, thiuram mix++	None	Fragrance mix II+, lyral+	Potassium dichromate+, 1,3-diphenylguanidine+	Nickel sulphate+, potassium dichromate+	None	None	None	None	None

Test chemical 30% tetrazepam and/or diazepam ad aqua (aq.) and/or petrolatum (pet.).

Readings of patch test results according to ICDRG recommendations as:

?+ faint erythema.

+ erythema, infiltration, possibly papules.

++ erythema, infiltration, papules, vesicles.

+++ intense erythema, infiltration, coalescing vesicles.

NT = not tested.

Conclusions

Allergic contact sensitization to tetrazepam and cross-sensitization to diazepam seems to be underestimated and not appropriately diagnosed in patch test clinics, as it is so far insufficiently tested. These benzodiazepines should be considered, when allergic contact dermatitis is suspected, particularly in professionally exposed staff, and tested as supplemental allergens.

Author contributions

All authors substantially contributed to the conception, design, acquisition, analysis and interpretation of data. They also drafted the article and critically revised it for important intellectual content and approved the final version.

References

- Schappert SM, Rechtsteiner EA Ambulatory medical care utilization estimates for 2006. *National Health Statistics Reports* 2008; **8**: 26. <http://www.cdc.gov/nchs/data/nhsr/nhsr008.pdf> (last accessed: 14 February 2011).
- Blanco R, Díez-Gómez ML, Gala G, Quirce S. Delayed hypersensitivity to tetrazepam. *Allergy* 1997; **52**: 1146–1147.
- Ortega NR, Barranco P, López Serrano C, Romualdo L, Mora C. Delayed cell-mediated hypersensitivity to tetrazepam. *Contact Dermatitis* 1996; **34**: 139.
- Kämpgen E, Bürger T, Bröcker EB, Klein CE. Cross-reactive type IV hypersensitivity reactions to benzodiazepines revealed by patch testing. *Contact Dermatitis* 1995; **33**: 356–357.
- Sánchez-Morillas L, Laguna-Martínez JJ, Reaño-Martos M, Rojo-Andrés E, Ubeda PG. Systemic dermatitis due to tetrazepam. *J Investig Allergol Clin Immunol* 2008; **18**: 404–406.
- Del Pozo MD, Blasco A, Lobera T. Tetrazepam allergy. *Allergy* 1999; **54**: 1226–1227.
- Pirker C, Misis A, Brinkmeier T, Frosch PJ. Tetrazepam drug sensitivity – usefulness of the patch test. *Contact Dermatitis* 2002; **47**: 135–138.
- Barbaud A, Girault PY, Schmutz JL, Weber-Muller F, Trechot P. No cross-reactions between tetrazepam and other benzodiazepines: a possible chemical explanation. *Contact Dermatitis* 2009; **61**: 53–56.
- Vander Hulst K, Kerre S, Goossens A. Occupational allergic contact dermatitis from tetrazepam in nurses. *Contact Dermatitis* 2010; **62**: 303–308.
- Lindberg M, Matura M. Patch testing. In Johansen JD, Frosch PJ, Leppoittevin JP eds. *Textbook of contact dermatitis*. Springer, Berlin, 2011: 439–464.
- Sánchez I, García-Abujeta JL, Fernández L *et al.* Stevens-Johnson syndrome from tetrazepam. *Allergol Immunopathol (Madr)* 1998; **26**: 55–57.
- Delesalle F, Carpentier O, Guatier S, Delaporte E. Toxic epidermal necrolysis caused by tetrazepam. *Int J Dermatol* 2006; **45**: 480.
- Lagnaoui R, Ramanampamonjy R, Julliac B, Haramburu F, Ticolat R. Fatal toxic epidermal necrolysis associated with tetrazepam. *Therapie* 2001; **56**: 187–188.
- Cabrerizo Ballesteros S, Méndez Alcalde JD, Sánchez Alonso A. Erythema multiforme to tetrazepam. *J Investig Allergol Clin Immunol* 2007; **17**: 205–206.
- Quiñones D, Sanchez I, Alonso S *et al.* Photodermatitis from tetrazepam. *Contact Dermatitis* 1998; **39**: 84.
- Schwedler S, Mempel M, Schmidt T, Abeck D, Ring J. Phototoxicity to tetrazepam – a new adverse reaction. *Dermatology* 1998; **197**: 193–194.
- Thomas E, Bellón T, Barranco P *et al.* Acute generalized exanthematous pustulosis due to tetrazepam. *J Investig Allergol Clin Immunol* 2008; **18**: 119–122.
- Bachmeyer C, Assier H, Roujeau JC, Blum L. Probable drug rash with eosinophilia and systemic symptoms syndrome related to tetrazepam. *J Eur Acad Dermatol Venereol* 2008; **22**: 887–889.
- Breuer K, Worm M, Skudlik C, Schröder C, John SM. Occupational airborne contact allergy to tetrazepam in a geriatric nurse. *J Dtsch Dermatol Ges* 2009; **7**: 896–898.
- Lepp U, Zabel P, Greinert U. Occupational airborne contact allergy to tetrazepam. *Contact Dermatitis* 2003; **49**: 260–261.
- Choquet-Kastylevsky G, Testud F, Chalmet P, Lecuyer-Kudela S, Descotes J. Occupational contact allergy to tetrazepam. *Contact Dermatitis* 2001; **44**: 372.
- Ferran M, Giménez-Arnau A, Luque S, Berenguer N, Iglesias M, Pujol RM. Occupational airborne contact dermatitis from sporadic exposure to tetrazepam during machine maintenance. *Contact Dermatitis* 2005; **52**: 173–174.
- García-Bravo B, Rodríguez-Pichardo A, Camacho F. Contact dermatitis from diazepoxides. *Contact Dermatitis* 1994; **30**: 40.