

Occupational allergic contact dermatitis from tetrazepam in nurses

KIM VANDER HULST¹, STEFAN KERRE^{2,3} AND AN GOOSSENS¹

¹Department of Dermatology, University Hospital, K.U.Leuven, B-3000 Leuven, ²3200 Aarschot, and ³Department of Dermatology, AZ Imelda, 2820 Bonheiden, Belgium

Background: Tetrazepam is a muscle relaxant belonging to the benzodiazepine group. Drug eruptions following ingestion of tetrazepam tablets are well known.

Objective: To draw the attention to occupational airborne dermatitis and/or hand dermatitis in nurses resulting from crushing of tablets for elderly or disabled people.

Methods: Since 2003, 16 nurses with facial (eyelid) and/or hand dermatitis, suspected to be of occupational origin, were patch tested with the medication they handled during work.

Results: Ten nurses presented with a positive patch test reaction to tablets containing tetrazepam, 14 controls remaining negative. Some of them also reacted to other drugs.

Conclusion: Occupational airborne and/or hand contact dermatitis from tetrazepam might be much more common than suspected by dermatologists, particularly in view of the short period in which all cases have been observed.

Key words: airborne; allergic contact dermatitis; benzodiazepine; disabled; elderly; nurses; occupational; tetrazepam. © John Wiley & Sons A/S, 2010.

Conflict of interests: The authors have declared no conflicts.

Accepted for publication 18 December 2009

Tetrazepam is a frequently used muscle relaxant belonging to the benzodiazepine group containing a cyclohexene ring. Belgian commercial names are Myolastan[®] (Aktuapharma, Heverlee, Belgium; Pharmapartner, Hoegaarden, Belgium; Sanofi-Aventis, Diegem, Belgium), Epsipam[®] (Will-Pharma, 1301 Wavre, Belgium), and Tetrazepam EG[®] (Eurogenerics, 1020 Brussels, Belgium). Drug eruptions are well known, but occupational contact dermatitis from this compound has been occasionally reported only.

Patients, Methods and Results

From September 2003 to August 2009, 16 nurses with facial (mainly eyelid) (Fig. 1) and/or hand dermatitis, suspected to be of occupational origin, were patch tested in our Contact Allergy Unit with the baseline series (Trolab[®] Hermal,

Reinbek, Germany), antiseptics used, and medications that were handled during work, using van der Bend chambers[®] (van der Bend, Brielle, the Netherlands) mounted on Micropore[®] (3M Health Care, Borken, Germany), and fixed with Mefix[®] (Mölnlycke Health Care, Göteborg, Sweden). This particularly included tablets, which they sometimes had to crush for elderly or disabled people, and which were tested crushed and diluted 30% in white petrolatum (pet.).

Ten out of the 16 patients investigated, i.e. 9 geriatric nurses (or aids) and one nurse who worked in a clinic for multiple sclerosis patients, presented with a positive reaction to the tablets containing tetrazepam (Fig. 2).

Among them (Table 1), five suffered from airborne facial dermatitis, two from hand dermatitis, and three from both airborne and hand dermatitis. One patient also had widespread eczema lesions on



Fig. 1. Case no. 6, eczema peri-orbital, nose, and cheeks: suggestive for airborne dermatitis.



Fig. 2. Case no. 4, positive patch test to tetrazepam (D2 reading).

the feet, elbows, and legs. They all reported a clear relationship with their work, with improvement of the lesions during holidays.

All patients were simultaneously or subsequently tested with other benzodiazepine-containing tablets (Table 1), and cases 6, 8, 9, and 10 were also tested with oxazepam and diazepam, and bromazepam as pure substances diluted 10% in pet. Lorazepam (Temesta®; Aktuapharma, Heverlee, Belgium; Wyeth, Louvain-La-Neuve, Belgium) was positive in cases nos. 6 and 7, who also handled this medication during work. Some patients also reacted positively to other medications (Table 1), among which the non-chemically related drug zolpidem (Stilnoct®; Aktuapharma, Heverlee, Belgium; Sanofi-Aventis, Diegem, Belgium), which cases 6 and 8 needed to crush as well; however, case no. 10 did not have contact with this medication.

Patch tests with crushed Myolastan® tablets diluted in white pet. at 30% dilution were negative

in 14 control patients, which included six nurses who also contacted this drug at work.

After 1–66 months, nine subjects were contacted by telephone for a follow-up interview (Table 1). All, but one, had improvement in their dermatitis by avoiding contact with tetrazepam, by avoiding handling medication or by using protective measures (gloves, masks, goggles) when in contact. Subject no. 2, who only suffered from hand dermatitis, had no improvement, despite the use of gloves. This could be explained by an insufficient avoidance, as tetrazepam was still used in her department, or by other contributing factors (irritant dermatitis, other – undetected – contact allergies).

The Belgian Centre for Pharmacovigilance was informed about these cases.

Discussion

Both allergic contact dermatitis and drug eruptions following ingestion of tetrazepam have been described in the literature. In our search (PubMed) we found seven cases of occupational allergic contact dermatitis from tetrazepam: one occurred in a mother crushing Myolastan® tablets for her daughter (1), three in nurses (2–4), and three in pharmaceutical manufacturing workers (5, 6). All patients suffered from airborne contact dermatitis with lesions on the face and neck, and three of them also had erythema or eczema on the fingers and dorsum of the hands. One technician had developed a widespread eczematous dermatitis every time he repaired a machine manufacturing Myolastan® (6).

Patch tests have proven to be of great value to investigate the role of tetrazepam, both in allergic contact dermatitis and in drug eruptions (7–9).

The patch test concentrations for patch testing medication, proposed by the European Society of Contact Dermatitis, are 30% pet. or aq. for the commercialized drug and 10% pet. or aq. when testing with the pure substance (10), as we did. The preparations used in the literature vary from crushed tablets containing tetrazepam (mainly Myolastan®) and tetrazepam pure powder as is, in dilutions 1–30% aq or 0.1–30% pet. However, tetrazepam has poor water solubility.

In our series, 14 control patients tested negatively with crushed Myolastan® tablets diluted with white pet. at 30%. In the literature, patch tests with one or more of the tests, tetrazepam pure powder, 0.1–30% pet., or 1% aq. or Myolastan® crushed tablet as is, 1% aq. and ≥10% pet., were negative in 155 control patients (3, 6–8, 11–16).

Case nos. 6 and 7 of our series presented with a positive patch test to another benzodiazepine which they handled during work, namely lorazepam (Temesta®). In the literature, 12 tetrazepam-allergic

Table 1. Occupational allergic contact dermatitis from tetrazepam in nurses

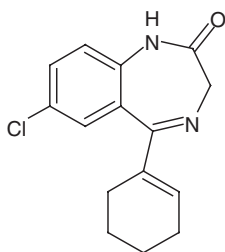
Case	Sex	Age (years)	Atopy	Location and duration of dermatitis	Previous positive patch tests	Tetrazepam patch tests		Other benzo-diazepines tested ^a , D4	Other positive tests, D4	Follow-up
						D2	D4			
1 WL 09-2003	M	40	–	Arms, hands, peri-orbital; 1 year	ND	+	+	Alprazolam –	–	66 months; free of lesions; crushing tablets in plastic bags
2 SS 04-2005	F	52	–	Hands; 1 year	Negative, 5 months earlier	+	+	Bromazepam – lorazepam – clotiazepam – diazepam – lorazepam – flunitrazepam – Alprazolam –	–	48 months; still hand eczema, uses gloves when handling drugs; oral ingestion lorazepam, without any problem
3 SS 09-2007	F	28	+	(eczema) Face; 2 months	Potassium–dichromate, thiomersal, 1 m earlier	+	++	Alprazolam –	Sodium valproate + atorvastatine +	18 months; free of lesions; avoiding Myolastan, handling medication without protective measures
4 DB 08-2008	F	44	+	(eczema) Peri-orbital; 3 months	ND	++	++	Loprazolam – clotiazepam – alprazolam – lorazepam – flunitrazepam – oxazepam – lorazepam –	p-phenylenediamine + disperse mix + p-toluenediamine + at 72 hr	8 months; less lesions, avoids crushing of medication
5 DM 09-2008	F	45	+	(hay fever) Relapsing erythema of the face; several years	Potassium–dichromate, cobalt, nickel, thiuram-mix; 4 years earlier	+	+	Alprazolam – oxazepam – lorazepam – flunitrazepam – diazepam – lorazepam – lorazepam –	–	7 months; no contact with medication; still swelling of eyelids during demolition work in house
6 FP 10-2008	M	39	–	Retro-auricular, peri-orbital, paranasal, neck, hands; 1 year	Potassium–dichromate and thiomersal	++	++	Lorazepam + alprazolam – lorazepam – lorazepam – oxazepam ^b – diazepam ^b – bromazepam ^b – clotiazepam –	Zolpidem +++	6 months; no lesions since change of work (no more crushing of medication)

Table 1. Continued

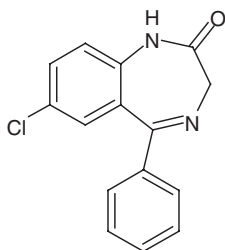
Case	Sex	Age (years)	Atopy	Location and duration of dermatitis	Previous positive patch tests	Tetrazepam patch tests		Other benzo-diazepines tested ^a , D4	Other positive tests, D4	Follow-up
						D2	D4			
7 SC 01-2009	F	51	–	Face, hands, arms	HICC, 3 months earlier	+	++	Flunitrazepam – lorazepam + lormetazepam – oxazepam – diazepam –	Nickel + cobalt + fragrance mix 1 + fragrance mix 2 ++ dichlorobenzylalcohol +	3 months; less lesions with protection measures (gloves, mask, goggles)
8 BM 06-2009	F	59	–	Eczema hands, feet, arms, legs, ears; 1.5 years	Thiuram-mix, methyl-(chloro)-isothiazolinone, carbamix, ranitidine, handsoap	++	++	Bromazepam ^b – clotiazepam – oxazepam ^b – lorazepam – diazepam ^b – lormetazepam – loprazolam – flunitrazepam –	Zolpidem + ranitidine ++ cyclohexylthiophthalimide +	2 months; less lesions, avoids crushing of medication
9 MG 08-2009	F	58	–	Eyelids, face, neck; 8 months	Fragrance mix 1	+	++	Diazepam ^b – alprazolam – lorazepam – lormetazepam – bromazepam ^b – oxazepam ^b – clotiazepam –	Cinnamic alcohol +	ND
10 PI 08-2009	F	33	–	Eyelids, lips, neck; 4 months	ND	++	++	Diazepam ^b – alprazolam – lorazepam – lormetazepam – bromazepam ^b – oxazepam ^b –	Zolpidem ++ risperdon +	1 month; no more lesions; no contact with medication

F, female; M, male; ND, not done; h, hours; HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde.

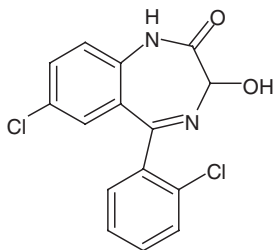
^aFor each compound the respective tablet was crushed and diluted 30% in pet.^bPure substance diluted 10% in pet.



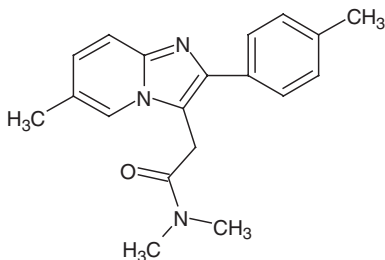
Tetrazepam with cyclohexene substituent



Diazepam with phenyl substituent



Lorazepam with chlorophenyl structure



Zolpidem

Fig. 3. Chemical structures of tetrazepam, diazepam, lorazepam, and zolpidem.

patients tested negative to this compound (2, 15–18).

Skin reactions to benzodiazepines other than tetrazepam have been less frequently described. Although tetrazepam and diazepam (Valium®) have similar chemical structures, cross-reactions are rarely seen (Fig. 3). In the literature, we found only two case reports regarding a positive patch test to diazepam in patients with cutaneous reaction to tetrazepam (1, 8): the first patient was suffering from an occupational contact dermatitis and also

had to crush tablets containing diazepam; the second case reported a maculopapular eruption after ingestion of tetrazepam tablets and denied previous intake of diazepam. In several other reports (2, 4, 11, 12, 14–20), patch tests (and oral provocation tests) with diazepam remained negative, which was also the case in our patients, as diazepam (Valium® crushed tablet 30% pet. or diazepam pure substance 10% pet.) tested negatively in the seven cases tested (Table 1).

Recently, Barbaud et al. suggested that differences in chemical structures between tetrazepam and other benzodiazepines could explain the absence of cross-reactions observed in patients with a cutaneous adverse reaction from tetrazepam. They hypothesize that the non-aromatic cyclohexene substituent of tetrazepam versus the aromatic substituent of the other benzodiazepines could either induce a selectivity at the T-cell receptor level or account for a higher reactivity towards proteins (18).

Some subjects of our series also showed positive patch tests to drugs other than benzodiazepines (Table 1), among which zolpidem that has been reported only once in the literature as a cause of occupational airborne contact dermatitis (21).

Most nurses handled several medications at work and thus could suffer from multiple contact allergies, being the expression of concomitant sensitization. However, the metabolism of drugs being complex, a cross-reaction cannot always be ruled out completely (J-P Lepoittevin, personal communication).

Conclusion

We describe here 10 cases of occupational allergic contact dermatitis from tetrazepam in nurses who had to crush tetrazepam containing tablets for geriatric or disabled people who were unable to swallow. In nurses with airborne dermatitis and/or hand eczema, one should indeed consider the possibility of drug-induced contact dermatitis and not just consider contact with antiseptics and other allergenic or irritant compounds.

In order to prevent sensitization and elicitation of allergic contact dermatitis from drugs, nurses should use crushing devices and take protective measures (gloves and masks) when handling medication.

References

1. Garcia-Bravo B, Rodriguez-Pichardo A, Camacho F. Contact dermatitis from diazepam. *Contact Dermatitis* 1994; 30: 40–58.
2. Lepp U, Zabel P, Greinert U. Occupational airborne contact allergy to tetrazepam. *Contact Dermatitis* 2003; 49: 260–261.
3. Ortiz-Frutos F J, Alonso J, Hergueta J P, Quintana I, Iglesias L. Tetrazepam: an allergen with several clinical expressions. *Contact Dermatitis* 1995; 33: 63–65.

4. Breuer K, Worm M, Skudlik C, Schröder C, John S M. Occupational airborne contact allergy to tetrazepam in a geriatric nurse. *J Deutsch Dermatol Ges* 2009; 7: 896–898.
5. Choquet-Kastylevsky G, Testud F, Chalmet P, Lecuyer-Kudela S, Descotes J. Occupational contact allergy to tetrazepam. *Contact Dermatitis* 2001; 44: 372.
6. Ferran M, Giménez-Arnau A, Luque S, Berenguer N, Iglesias M, Pujol R M. Occupational airborne contact dermatitis from sporadic exposure to tetrazepam during machine maintenance. *Contact Dermatitis* 2005; 52: 173–174.
7. Camasara JG, Serra-Baldrich E. Tetrazepam allergy detected by patch test. *Contact Dermatitis* 1990; 22: 246.
8. Kämpgen E, Bürger T, Bröcker E B, Eberhard Klein C. Cross-reactive Type IV hypersensitivity reactions to benzodiazepines revealed by patch testing. *Contact Dermatitis* 1995; 33: 356–357.
9. Pirker C, Misic A, Brinkmeier T, Frosch P J. Tetrazepam drug sensitivity-usefulness of the patch test. *Contact Dermatitis* 2002; 47: 135–138.
10. Barbaud A, Gonçalves M, Bruynzeel D, Bircher A. Guidelines for performing skin tests with drugs in the investigation of cutaneous adverse drug reactions. *Contact Dermatitis* 2001; 45: 321–328.
11. Ortega N R, Barranco P, Serrano C L, Romualdo L, Mora C. Delayed cell-mediated hypersensitivity to tetrazepam. *Contact Dermatitis* 1996; 34: 139.
12. Blanco R, Díez-Gómez M L, Gala G, Quirce S. Delayed hypersensitivity to tetrazepam. *Allergy* 1997; 52: 1146–1147.
13. Ghislain P D, Roussel S, Bouffieux B, Delescluse J. Exanthème induit par le tétrazepam (Myolastan®), avec tests épicutanés positifs: deux cas. *Ann Dermatol Veneréol* 2000; 127: 1094–1096.
14. Barbaud A, Trechot P, Reichert- Penetrat S, Granel F, Schmutz J L. The usefulness of patch testing on the previously most severely affected site in a cutaneous adverse drug reaction to tetrazepam. *Contact Dermatitis* 2001; 44: 259–260.
15. Sánchez I, García-Abujeta J L, Fernández L, Rodríguez F, Quiñones D, Duque S et al. Stevens-Johnson syndrome from tetrazepam. *Allergol Immunopathol* 1998; 26: 55–57.
16. Thomas E, Bellón T, Barranco P, Padial A, Tapia B, Morel E et al. Acute generalized exanthematous pustulosis due to tetrazepam. *J Invest Allergol Clin Immunol*. 2008; 18: 119–122.
17. Del Pozo M D, Blasco A, Lobera T. Tetrazepam allergy. *Allergy* 1999; 54: 1226–1227.
18. Barbaud A, Girault P Y, Schmutz J L, Weber-Muller F, Trechot P. No cross-reactions between tetrazepam and other benzodiazepines: a possible chemical explanation. *Contact Dermatitis* 2009; 61: 53–56.
19. Quiñones D, Sanchez I, Alonso S, Garcia-Abujeta L, Fernandez L, Rodriguez F et al. Photodermatitis from tetrazepam. *Contact Dermatitis* 1998; 39: 84.
20. Sánchez-Morillas L, Laguna-Martinez J J, Reaño-Martos M, Rojo-Andrés E, Gómez-Tembleque Úbeda P. Systemic dermatitis due to Tetrazepam. *J Invest Allergol Clin Immunol* 2008; 18: 404–406.
21. Neumark M, Moshe S, Ingber A, Slodownik D. Occupational airborne contact dermatitis to simvastatin, carvedilol and zolpidem. *Contact Dermatitis* 2009; 61: 51–52.

Address:
 An Goossens
 Department of Dermatology
 University Hospital
 K.U. Leuven
 B-3000 Leuven, Belgium
 Tel: +00 32 16 33 78 60
 Fax: +00 32 16 33 70 12
 e-mail: an.goossens@uz.kuleuven.ac.be