

Occupational airborne contact dermatitis from benzodiazepines and other drugs

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Summary

Background. Healthcare workers (or relatives) crushing drug tablets for patients with difficulties in swallowing are at risk of developing sensitization via airborne exposure. Tetrazepam, in particular, is increasingly being described as an important occupational allergen in this regard, although other drugs are also involved.

Objectives. To identify the allergenic culprits in 4 patients, namely 2 nurses, 1 pharmacy assistant, and 1 spouse, who all regularly crushed tablets of systemic drugs and presented with severe airborne dermatitis.

Methods. The patients were patch tested with all of the drugs that they handled, as well as with potential cross-sensitizing molecules.

Results. All 4 patients reacted to tetrazepam and other benzodiazepines, some of which they had not previously come into contact with, which favours cross-reactivity rather than concomitant sensitization. These patients also had positive reactions to several other non-structurally related drugs for which, in some cases, there was no history of exposure.

Conclusions. Subjects having to crush drugs, in either an occupational or a non-occupational context, and who present with dermatitis suspected of being airborne-induced, should be patch tested with all contacted medicaments, as well as with possible cross-reacting molecules. Prevention by the use of crushing devices and protective measures (gloves and masks) when medications are handled should be advised.

Key words: ACE inhibitors; airborne; allergic contact dermatitis; benzodiazepines; β -blocking agents; cross-reactions; drugs; healthcare; occupational; tetrazepam.

Healthcare workers (or relatives) crushing drug tablets for patients with difficulties in swallowing are at risk of developing sensitization via airborne exposure. Tetrazepam, in particular, has increasingly been described as an important occupational allergen in this regard, although other drugs are also implicated.

Patients

Case 1

A 30-year-old atopic woman presented in November 2010 with a 2-month history of an itchy, scaly skin reaction on the face, which was most pronounced on the eyelids. She reported a clear relationship with her work as a geriatric nurse, during which she was required to crush tablets for the elderly on a daily basis, mostly benzodiazepine drugs, including tetrazepam. When crushing tablets she wore vinyl gloves, but no protective goggles or mask. She clearly noticed improvement of the eczema during holidays.

Owing to pregnancy, patch testing was not performed until October 2011.

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Fig. 1. A patient who crushed tablets for her husband and presented with facial dermatitis that she had suffered from for 3 years, with a classical airborne distribution that later became generalized (case 2).



Fig. 2. Positive patch test reactions to the benzodiazepines tetrazepam, bromazepam (not contacted by this patient), diazepam, alprazolam, and lorazepam, and also to trazodone (Trazolan[®]), zolpidem, and captopril (case 1).

Case 2

A 66-year-old woman presented in July 2012 with a 3-year history of itchy and burning areas on the face. The eczema had first appeared on the eyelids. Later, extension to the forehead, lips and perioral region, neck, ears and even the fingers occurred (Fig. 1). Patch tests performed in 2006 and 2009 gave negative results.

As the patient's husband suffered from Parkinson's disease, she had to crush tablets for him up to five times a

day, namely tetrazepam, lorazepam, diazepam, levodopa, omeprazole, clozapine, selozok, and ropinirol. She had already experienced improvement of her skin when her husband was in a short-stay assessment centre. Because she had started to suspect the drugs, in order to protect her face, she had begun to put a plastic bag over her head (!) while handling them.

Case 3

A 44-year-old nurse presented in June 2012 with a 9-month history of eczema on the hands and face, which had started 3 months after she was required to crush tablets daily during her work as a nurse in a clinic for disabled people.

Case 4

A 24-year-old woman presented in August 2012 with eyelid dermatitis, which had started with localized oedema 4 months previously. Later, the area had become itchier, with redness and scaling. The patient did use cosmetic products, but she suspected a relationship with her work as a pharmacy assistant, which involved breaking and crushing different types of tablet.

Materials and Methods

Patch tests were performed with the European baseline series (Trolab, Hermal, Reinbek, Germany and, for case 3, from Chemotechnique, Vellinge, Sweden), a medicament series (Chemotechnique, Sweden) in case 1, a cosmetic series in cases 3 and 4, and hairdressers' series (both from Chemotechnique) in case 2. All patients were also tested with the contacted drug tablets, crushed and diluted at 30% pet., except for case 4, where they were diluted at 10% pet.; moreover, in cases 1 and 2, some drugs to which tetrazepam-sensitized subjects had previously reacted (1) were added. Several commercial drugs were tested in the different centres; hence, the vehicle components were not taken into account, which is a weakness in our results.

The materials used were IQ Ultra[®] patch test chambers (Chemotechnique), fixed with Mefix[®] (Mölnlycke Health Care, Göteborg, Sweden), except for case 3, where van der Bend[®] patch test chambers were used (Van der Bend BV, Brielle, The Netherlands), fixed with Hypafix[®] (BSN Medical, Hamburg, Germany).

We also conducted a review of the patch test results obtained with other drugs in tetrazepam-sensitized nurses or other individuals involved in crushing tablets, using a similar methodology as in the present cases.

Table 1. Positive patch test reactions in all 4 cases

	Case 1		Case 2		Case 3		Case 4		Negative controls
	D2	D4	D2	D4	D2	D4	D2	D4	
Benzodiazepines									
Alprazolam	+	+	–	–	NT	NT	+	+	21
Bromazepam	+	+	+	++	NT	NT	NT	NT	5
Clotiazepam	–	–	+	+	NT	NT	NT	NT	3
Diazepam	+	+	–	–	+++	+++	NT	NT	16
Lorazepam	+	++	+	++	+++	+++	NT	NT	20
Lormetazepam	–	–	–	–	NT	NT	+	+	11
Tetrazepam	+	++	++	+++	+++	+++	+	+	31
Antidepressant									
Trazodone hydrochloride	+	+	+	+	NT	NT	NT	NT	12
Imidazopyridine sedative hypnotic									
Zolpidem	+	+	–	–	NT	NT	NT	NT	19
β -Blockers									
Metoprolol	NT	NT	NT	NT	NT	NT	++	++	7
Bisoprolol	NT	NT	NT	NT	NT	NT	++	++	6
Propanolol	NT	NT	NT	NT	NT	NT	++	++	9
Sotalol hydrochloride	NT	NT	NT	NT	NT	NT	++	++	3
ACE inhibitors									
Enalapril	NT	NT	NT	NT	NT	NT	+	+	3
Lisinopril	NT	NT	NT	NT	NT	NT	+	+	3
Perindopril	NT	NT	NT	NT	NT	NT	+	+	3
Captopril	+	++	NT	NT	NT	NT	–	–	18
Spasmolytic									
Baclofen	NT	NT	NT	NT	+++	+++	NT	NT	0
Analgesic									
Paracetamol	–	–	NT	NT	+++	+++	NT	NT	126
Proton pump inhibitor									
Esomeprazol	NT	NT	NT	NT	++	+	NT	NT	0
Anticholinergic									
Oxybutinin	NT	NT	NT	NT	++	+	NT	NT	0
Antipsychotic									
Aripiprazol	NT	NT	NT	NT	++	+++	NT	NT	0

ACE, angiotensin-converting enzyme; NT, not tested.

Vehicle: petrolatum, 30%, except for diazepam and bromazepam, 10%. In case 4, all drugs had been diluted 10% in pet. Captopril, 5% pet. (Chemotechnique).

Results

Patient 1 reacted positively to tetrazepam, but also to the other benzodiazepines, namely alprazolam, bromazepam (not contacted during work), diazepam, and lorazepam, as well as to three unrelated allergens, namely trazodone hydrochloride, zolpidem (Table 1; Fig. 2), and captopril (5% pet.; Chemotechnique), that she came into contact with. As captopril 5% pet. may sometimes give rise to weak irritant reactions, patch testing with this compound was repeated, but an even stronger reaction was observed, at day 4 in particular.

Patient 2 reacted positively to tetrazepam and lorazepam, which were drugs that she came into contact with, but also to bromazepam, clotiazepam, and trazodone

hydrochloride (Table 1; Fig. 3), which she had not come into contact with.

Patient 3 reacted positively to nickel, cobalt, and multiple drugs, namely tetrazepam, diazepam, lorazepam, baclofen, paracetamol, esomeprazol, oxybutinin, and aripiprazol (Table 1), all of which she had come into contact with at work.

Patient 4 reacted positively to the benzodiazepines tetrazepam, alprazolam, and lormetazepam, the β -blocking agents bisoprolol metoprolol, propranolol, and sotalol, and the angiotensin-converting enzyme (ACE) inhibitors enalapril, lisinopril, and perindopril (captopril being negative), all of which she had come into contact with at work. The reaction to clonidine hydrochloride was considered to be irritant (reaction not shown) (Fig. 4).

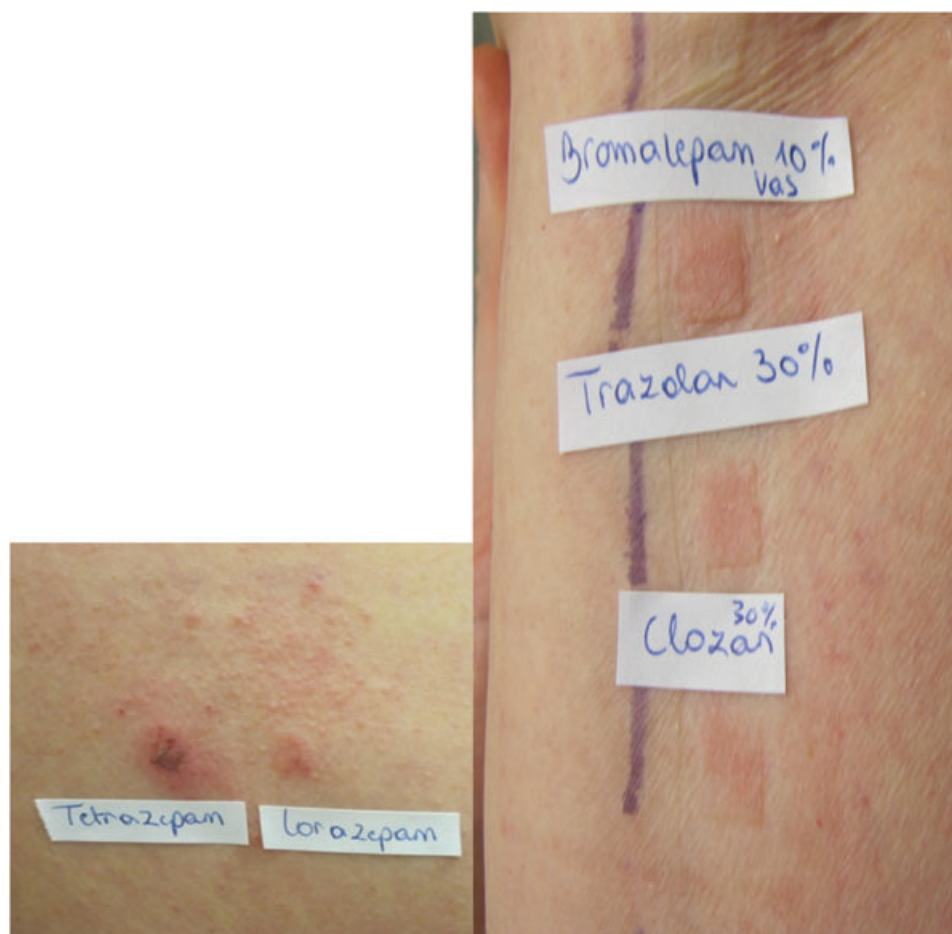


Fig. 3. Positive reactions to tetrazepam, lorazepam, bromazepam, and clotiazepam (Clozan[®]), and also to trazodone (Trazolan[®]); the patient had not come into contact with the last three of these (case 2).

Table 1 shows the positive patch test reactions to the drugs tested in all 4 cases, as well as the number of negative patch test reactions obtained in different control subjects. Table 2 shows the associated positive patch test reactions observed in tetrazepam-sensitized subjects tested with other benzodiazepines and some other drugs [results from a previously published article (1), from the current cases, and from data in the KULeuven file].

Discussion

Benzodiazepines are frequently used medicaments, especially in the elderly. Drug eruptions following ingestion are rare (e.g. 2), except for tetrazepam, a muscle relaxant. Recently, occupational allergic contact dermatitis caused by this molecule in nurses having to crush tablets for geriatric people or patients with difficulties in swallowing has been increasingly reported (1, 3–7). Cases have also been described in the pharmaceutical industry, owing

to exposure during the production process or machine maintenance (8, 9). In both occupations, the eczematous lesions are most often observed on the hands and/or in an airborne distribution (face and neck).

Cross-reactions between tetrazepam and other benzodiazepines, and with diazepam in particular, have only rarely been reported (2). Barbaud et al. (10), when discussing systemically induced drug eruptions, suggested that differences in the chemical structure of tetrazepam, which contains a cyclohexene ring, unlike the other benzodiazepines, could explain the absence of cross-reactivity. They hypothesized that the non-aromatic cyclohexene substituent of tetrazepam versus the aromatic substituent of the other benzodiazepines could either induce selectivity at the T cell receptor level or account for higher reactivity toward proteins.

However, several of our previously described patients (1), as well as the present cases (Tables 1 and 2),



Fig. 4. Positive test reactions at day 2 to tetrazepam, alprazolam, lormetazepam, propranolol, metoprolol, lisinopril, sotalol, enalapril, and bisoprolol (case 4).

Table 2. Associated positive patch test reactions in tetrazepam-sensitized subjects, some of whom also reacted to other benzodiazepines and some other drugs

	+ Tests/number of subjects tested
Alprazolam*	3/10
Bromazepam*	2/7
Clotiazepam*	2/4
Diazepam*	2/11
Lorazepam*	5/13
Lormetazepam*	1/6
Trazodone hydrochloride	3/8 [†]
Zolpidem	5/9 [‡]

*Benzodiazepines.

[†]One subject (case 2) denied contact with trazodone.

[‡]One subject sensitized to tetrazepam who suffered from a drug eruption denied previous administration of zolpidem (data on file).

presented with multiple positive patch test reactions to other benzodiazepines as well, some of which they had not come into contact with at all (except for patients 3 and 4, who had come into contact with all of the tested medicaments). In our opinion, the multiple reactions to benzodiazepines observed can thus not be explained by concomitant sensitization; hence, cross-sensitivity seems

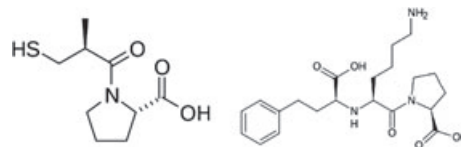


Fig. 5. Angiotensin-converting enzyme inhibitors can be divided into two groups on the basis of their molecular structure. Both captopril (left) and zofenopril contain a sulfhydryl (-SH) group, whereas enalapril, lisinopril (right) and perindopril are carboxylated compounds.

to be more likely, the pattern of which might differ from that of systemically induced reactions to tetrazepam.

Moreover, we also observed positive reactions to non-related drugs (Table 2): in 3 cases to trazodone hydrochloride, an antidepressant, and in 5 cases to zolpidem, an imidazopyridine sedative hypnotic used for the treatment of insomnia and described as an occupational allergen in the pharmaceutical industry (11). As zolpidem and trazodone are often used in association with tetrazepam in the same patient population, concomitant or subsequent sensitization in healthcare workers cannot always be ruled out completely, even when contact with them is sometimes denied. However, a patient with a systemic drug reaction to tetrazepam had a positive reaction to zolpidem without ever having used this drug (data on file), and patient 2 had definitely never had contact with trazodone. We cannot offer an explanation for this phenomenon.

Patient 4 also had reactions to β -blocking agents, which have been reported as occupational allergens in the pharmaceutical industry, in particular propranolol and carvedilol (12–14). Allergic contact dermatitis caused by β -blockers in eyedrops used for the treatment of glaucoma is a known entity, and, in several cases, different patterns of concomitant/subsequent contact dermatitis have been observed (15). However, three reports concerned reactions to β -blockers that had never been used by the patient, indicating true cross-reactivity (14, 16, 17). The patient reported here had come into contact with all of the tested β -blockers; hence, no statement can be made in this regard.

Patient 1 also reacted to captopril (contacted at work), and patient 4 showed cutaneous reactions to lisinopril, enalapril, and perindopril. ACE inhibitors are known to cause cutaneous drug reactions (18, 19), but have only rarely been reported as causes of allergic contact dermatitis. Captopril was the allergenic culprit in a case reported by Balieva and Steinkjer (20) in a non-occupational setting, and in another case reported by Dziuk et al. (21) that was occupation-related. The ACE inhibitors to which patient 4 reacted had carboxylated

molecules, whereas captopril, to which she reacted negatively, contains a sulfhydryl group (Fig. 5). The difference in chemical structure might perhaps be an explanation for the difference in reactivity.

Conclusion

Crushing drug tablets causes a significant risk of sensitization via airborne exposure. Tetrazepam, in

particular, has increasingly been described as an important occupational allergen in this regard; in contrast to systemic drug reactions, other benzodiazepines may cross-react following skin exposure. As many patients present with multiple positive reactions, patch testing with all contacted medicaments and possible cross-reacting molecules are indicated. Prevention by the use of crushing devices and protective measures (gloves and masks) should be advised.

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