

**No cross-reactions
between tetrazepam and
other benzodiazepines:
a possible chemical
explanation**

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To determine whether there is any cross-reactivity between tetrazepam and other benzodiazepines in patients with a cutaneous adverse drug reaction with a positive patch test or oral provocation test with tetrazepam, we performed skin tests and oral provocation test with other benzodiazepines (Table 1).

Methods

All patients had patch tests with tetrazepam diluted at 10% in pet. In five patients (cases 1, 2, 4, 8, and 9), we used a commercial form (Chemotechnique Diagnostics, Malmö, Sweden). In the remaining cases, we used tetrazepam obtained by SANOFI (Paris, France), diluted to 10% pet. by our pharmacy. All patients but one had patch tests with diazepam diluted at

10% pet. using a commercial form (Chemotechnique Diagnostics) in four cases. Patch tests were also undertaken with other tablets containing benzodiazepines, diluted at 30% in water and pet. according to the recommendations of the European Society of Contact dermatitis (ESCD) (1).

Prick tests were performed on the volar forearm skin with the commercial form of tetrazepam and other benzodiazepines. At 20 min, prick test reactions were considered to be positive if the weal of the reaction had a diameter at least 3 mm greater than that obtained with negative control. The positive prick test control was histamine (10 mg/ml). A delayed reading was made at D1. Intradermal tests were carried out using a sterile solution of diazepam, diluted sequentially in physiological saline (0.9% NaCl) up to 5 mg/ml. In accordance with the ESCD guidelines, 0.03–0.04 ml of solution was injected on the extensor surface of the arm (1). Intradermal tests were considered positive on immediate readings if the diameter of the reaction was equal or more than twice that of the injection weal.

Delayed reactions occurring >1 day after challenge were considered positive if an infiltrated erythematous reaction was observed.

Oral provocation tests were undertaken in hospital, with progressively increasing concentrations starting at 1×10^{-4} of dosage to full dosage contained in one tablet, against a placebo.

Results

In nine patients with confirmed sensitization to tetrazepam on patch testing or oral provocation testing, there were no cross-reactions on patch testing, prick testing, or intradermal testing with other benzodiazepines (Table 1). Moreover, in five cases, oral provocation tests with other benzodiazepines were negative.

Discussion

A literature search of patients suffering from work-related contact allergy to tetrazepam found one case of cross-reactions to other benzodiazepines, but this individual was also exposed to three different benzodiazepines (2).

Another case showed no cross-reaction between benzodiazepines (3). Other literature examples with systemic exposure to tetrazepam (4–11) are summarized with our cases in Table 2. Only one patient (8) of 24 studied developed a positive patch test to diazepam, and there were no positive reactions to other benzodiazepines.

Toxic epidermal necrolysis, possibly caused by tetrazepam, was found in one patient with a history of neutropaenia related to carbamazepine (12), and Wolf et al. (13) suggested that a 'seven-membered organic ring structure with one or two nitrogen heteroatoms (azepine) and a fused benzene ring' was responsible for inducing toxic epidermal necrolysis. If this chemical structure, which is present in both benzodiazepines and carbamazepine, was the responsible moiety, then cross-reactions with tetrazepam and other benzodiazepines would occur frequently. However, they are highly exceptional.

Diazepam is the benzodiazepine that has the most similar chemical structure to that of tetrazepam (Fig. 1). These two molecules only differ by the substituent at position 5

Table 1. Clinical features and test results with different benzodiazepines in nine cases of cutaneous adverse drug reactions caused by tetrazepam

Case number	Sex	Age (year)	Cutaneous adverse drug reactions	Onset after	Drug	PT	pT	IDT	OPT
1	F	54	Maculopapular rash	3 days	Tetrazepam	±	—	nd	+
					Diazepam	—	—	—	nd
2	F	55	Maculopapular rash	12 hr	Tetrazepam	+	nd	nd	nd
					Diazepam	—	—	—	nd
					Bromazepam	—	—	nd	nd
					Lorazepam	—	—	nd	nd
3	F	46	Maculopapular rash	24 hr	Tetrazepam	+	nd	nd	nd
					Diazepam	—	nd	nd	nd
					Bromazepam	—	nd	nd	nd
					Clorazepate	—	nd	nd	nd
4	F	38	Maculopapular rash	5 days	Tetrazepam	+	nd	nd	nd
					Bromazepam	nd	nd	nd	— (self-medication)
5	M	74	Maculopapular rash	3 days	Tetrazepam	+	nd	nd	nd
					Diazepam	—	—	—	nd
					Lorazepam	—	—	nd	—
6	F	48	Maculopapular rash	12 hr	Tetrazepam	+	—	nd	nd
					Diazepam	—	—	—	—
					Lorazepam	—	nd	nd	nd
					Tetrazepam	+	nd	—	—
7	F	43	Maculopapular rash	5 days	Diazepam	—	—	—	—
					Bromazepam	—	nd	nd	nd
					Lorazepam	—	nd	nd	nd
					Oxazepam	—	nd	nd	nd
					Tetrazepam	+	nd	nd	nd
8	F	50	Fixed drug eruption	3 weeks	Diazepam	—	—	—	—
					Bromazepam	—	nd	nd	nd
					Tetrazepam	+	nd	nd	nd
9	F	67	Stevens Johnson syndrome	9 days	Diazepam	—	—	—	nd
					Tetrazepam	+	nd	nd	nd

IDT, intradermal test; nd, not done; pT, prick test; PT, patch test with tetrazepam in 10% pet. (33 negative controls).

Table 2. Cross-reactions between benzodiazepines in patients sensitized to tetrazepam from the literature

Cases	Clinical features	Sensitization to tetrazepam proven by	Drug skin tests with diazepam	OPT with diazepam	Other investigations with benzodiazepines
Kampgen et al. (8)					
Case 1	Maculopapular rash	PT+	PT+	nd	nd
Case 2	Erythematous rash	PT+	PT–	nd	nd
Pirker et al. (4)					
Case 2	Stevens Johnson syndrome	PT+	PT–	–	
Case 4	Maculopapular rash	PT±, OPT+	PT–	–	
Ortega et al. (9)					
1 Case	Maculopapular rash	PT+, OPT+	PT–, pT–	–	PT–: bromazepam, OPT–: bromazepam
Quinones et al. (7)					
1 Case	Photodermatitis	PhotopatchT+, OPT+	PT–, PhotoPT–	nd	
Tomb et al. (5)					
1 Case	Maculopapular rash	PT+	PT–	nd	OPT–: lorazepam, bromazepam; PT–: lorazepam, bromazepam, nitrazepam, flunitrazepam, clobazam, oxazepam, clorazepate
Blanco et al. (10)					
Case 1	Urticarial rash	PT+, OPT+	?	–	OPT–: bromazepam
Case 2	Maculopapular rash	PT+, OPT+	?	–	OPT–: bromazepam
Case 3	Generalized erythema	PT+, OPT+	?	–	OPT–: bromazepam
Del Pozo et al. (11)					
Case 1	Maculopapular rash	PT+ 1%	PT–, pT–, IDT–	–	
Case 2	Maculopapular rash, DRESS?	PT+ 1%	PT–, pT–, IDT–	–	
Case 3	Maculopapular rash	PT+ 1%	PT–, pT–, IDT–	–	
Case 4	Maculopapular rash	PT+ 1%	PT–, pT–, IDT–	–	OPT–: lorazepam
Case 5	Vesicular eruption and mucosal involvement	PT+ 1%	PT–, pT–, IDT–	nd	

–, negative results; +, positive results; DRESS, drug reaction with eosinophilia and systemic symptoms; IDT, intradermal test; nd, not done; OPT, oral provocation test; pT, prick test; PT, patch test.

on the diazepam ring, which is cyclohexene in tetrazepam and phenyl in diazepam (14). Sensitization to tetrazepam could be related to the

'half-chair' conformation of the cyclohexene substituent (14) as all the other benzodiazepines have planar conformations.

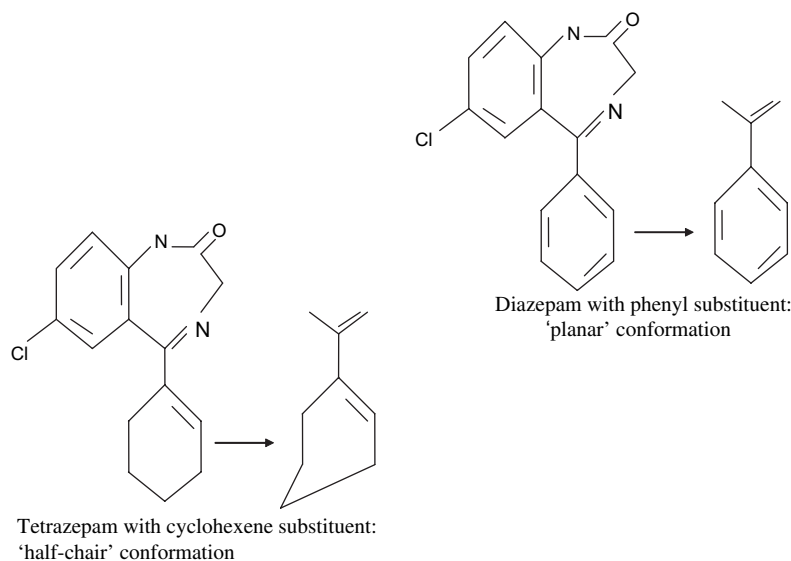


Fig. 1. Chemical structures of tetrazepam and diazepam.

Considering the structural differences of these molecules, two hypotheses are proposed. First, the T-cell receptor recognizing the conformation of the tetrazepam cyclohexene half-chair does not recognize the planar conformations (phenyl or pyridinyl) of other benzodiazepines. The second hypothesis is that the cyclohexene half-chair is less chemically stable than the planar substituents of other benzodiazepines. Nucleophilic attacks could more easily occur on the cyclohexene, inducing a higher risk of haptenization of tetrazepam and enhancing its sensitization ability (15).

This half-chair conformation that does not exist in other benzodiazepines could explain the absence of cross-reactions between tetrazepam and other benzodiazepines. This hypothesis requires further studies in order to be confirmed on a larger population, but in patients with a cutaneous adverse drug reaction caused by tetrazepam, if patch tests are negative with diazepam, it seems possible to

allow the prescription of all benzodiazepines except tetrazepam.

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