Eczematous dermatitis caused by tetrazepam

To the Editor,

Benzodiazepines are a group of psychoactive drugs whose core chemical structure is the fusion of a benzene ring and a diazepine ring. They are widely used as anaesthetics, hypnotics, anxiolytics, anticonvulsants, and muscle relaxants. In general, benzodiazepines are safe. The most common adverse reactions are neurological and gastrointestinal disorders and skin manifestations are rare.[1,2]

We present the case of a 79-year-old man referred to our department because one month before he had presented a muscular contracture and he started treatment with ibuprofen 600 mg each eight hours and tetrazepam 50 mg per day. After four days taking both drugs simultaneously, he complained of widespread itchy micropapular rash. He stopped using the drugs and was admitted to the emergency room of our hospital, where he was treated with oral antihistamines and oral corticosteroids. The symptoms resolved completely after two weeks with scaling. The patient denied personal or familial history of atopy.

Histological analysis of a punch biopsy of affected skin showed parakeratosis of stratum corneum with vacuolar degeneration and diskeratinocytes, and isolated eosinophils in superficial dermis with no other inflammatory components (Fig. 1). Those findings suggest an eczematous dermatitis caused by drug.

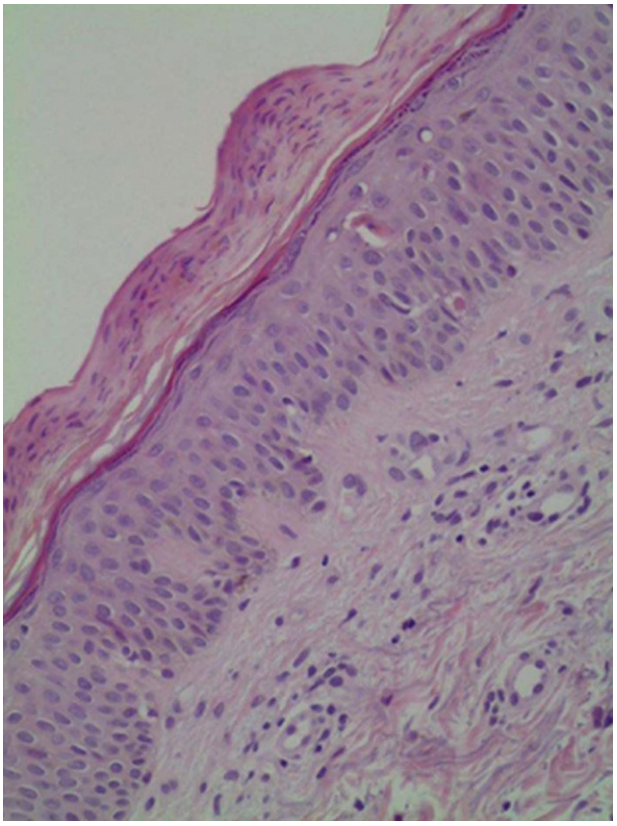

Figure 1 Biopsy of affected skin showed parakeratosis of stratum corneum with vacuolar degeneration and isolated eosinophils in superficial dermis.

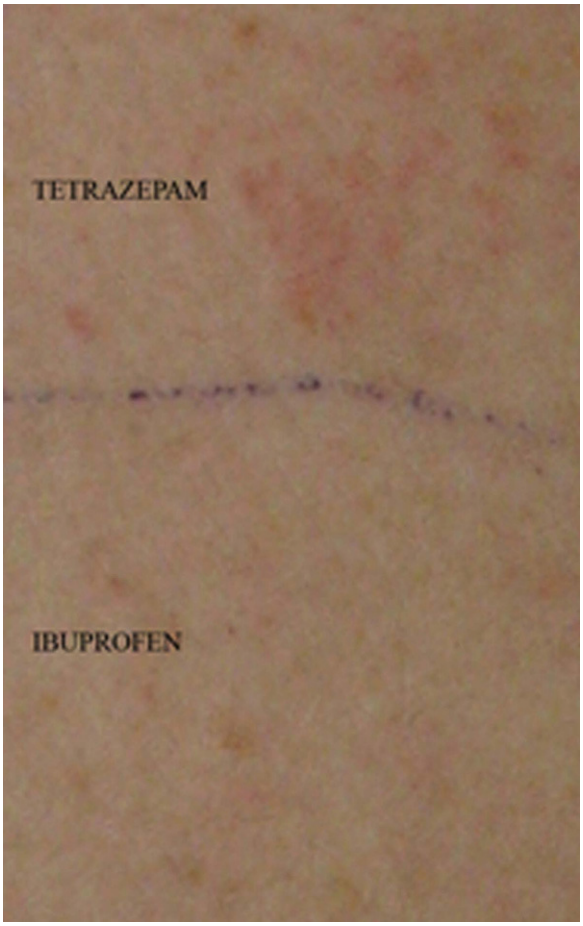

Figure 2 Positive patch test to tetrazepam.

Patch tests were performed with the standard series (by True Test®, Mekos Laboratories ApS, Hillerod, Denmark) and with ibuprofen, tetrazepam, diazepam, clonazepam, midazolam, bromazepam, lorazepam, and lormetazepam (5% petrolatum). They were read at 48 and 96 h and were applied to the skin on his upper back. Patch testing with tetrazepam (+++) was positive (Fig. 2), showing a negative result to all the standard series and to the rest of the drugs tested.

The patient gave his consent for challenge tests. A single-blind placebo-controlled drug challenge performed with 600 mg ibuprofen was negative.

To investigate a possible cross-reactivity between benzodiazepines, we also performed oral challenge on different days with diazepam 5 mg, lorazepam 5 mg, and midazolam 7.5 mg with negative result. Therefore, we recommended the use of those drugs for future treatments.

Skin reactions caused by tetrazepam are unusual, but maculopapular exanthema,[2,3] systemic dermatitis,[1] fixed drug eruption, urticaria,[3] erythematous rash,[4] photodermatitis reactions,[4] contact dermatitis,[5,6] leukocytoclastic vasculitis, toxic epidermal necrolysis, generalised pustulosis,[2] erythema multiforme,[7] and Stevens–Johnson[6,8] syndrome have been reported in association with tetrazepam. No cases of chronic eczematous dermatitis have been described.

Epicutaneous patch testing is a useful tool to confirm tetrazepam allergy.[2,9] In our case, tetrazepam patch test

was positive but the rest of tested benzodiazepines were negative.

Previous reports[2] suggest that there is no cross-reactivity among benzodiazepines. Diazepam is the most similar benzodiazepine to tetrazepam, the only difference between them is the presence at position 5 on the diazepine ring of phenyl in diazepam and clohexen in tetrazepam, and this cyclohexene conformation could explain tetrazepam sensitisation.[9] Our patient also tolerated oral administration of diazepam and other benzodiazepines. Due to the biopsy result and the positive patch test, an oral challenge with tetrazepam was not performed.

We have reported a type IV hypersensitivity reaction confirmed by biopsy as an unusual chronic eczematous reaction caused by tetrazepam with probed tolerance to other benzodiazepines.

References

1. Sanchez Morillas L, Laguna-Martínez JJ, Reaño-Martos M, Rojo-Andrés E, Gómez-Tembleque Úbeda P. Systemic dermatitis due to tetrazepam. J Invest Allergol Clin Immunol. 2008;18:404–6.
2. Bellón T, Barranco P, Padial A, Tapia B, Morel E, Alves-Ferreira J, et al. Acute generalized exanthematous pustulosis due to tetrazepam. J Invest Allergol Clin Immunol. 2008;18:119–22.
3. Pirker C, Misic A, Brinkmeier T, Frosch PJ. Tetrazepam drug sensitivity – usefulness of the patch test. Contact Dermatitis. 2002;47:135–8.
4. Ortiz-Frutos FJ, Alonso J, Hergueta JP, Quintana I, Iglesias L. Tetrazepam: an allergen with several clinical expressions. Contact Dermatitis. 1995;33:63–5.
5. Garcia-Bravo B, Rodriguez-Pichardo A, Camacho F. Contact dermatitis from diazepoxides. Contact Dermatitis. 1994;30:40.
6. Del Pozo MD, Blasco A, Lobera T. Tetrazepam allergy. Allergy. 1999;November (54):1226–7.
7. Cabrerizo Ballesteros S, Méndez Alcalde JD, Sánchez Alonso A. Erythema multiforme to tetrazepam. J Invest Allergol Clin Immunol. 2007;17:205–6.
8. Sánchez I, García-Abujeta JL, Fernández L, Rodríguez F, Quiñones D, Duque S, et al. Stevens–Johnson syndrome from tetrazepam. Allergol Immunopathol. 1998;26:55–7.
9. Barbaud A, Trechot P, Reichert-Penetrat S, Granel F, Schmutz JL. The usefulness of patch testing on the previously most severely affected site in a cutaneous adverse drug reaction to tetrazepam. Contact Dermatitis. 2001;44:259–60.

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Based on a patient: Dermographism should be routinely investigated before every provocation test

To the Editor,

Drug provocation tests (DPTs) are widely considered to be the gold standard to establish or exclude the diagnosis of drug allergy or intolerance.[1] However, some causes such as self infliction, psychological or dermatological problems may lead to false-positive results when performing DPTs.[1] Hereby, we report a child who admitted to our clinic with suspicion of drug allergy and was consequently diagnosed as symptomatic dermographism.

A 12-year-old boy was admitted to our outpatient department because of suspected drug allergy. He suffered from itching, hives, swelling of eyelids, nausea, malaise, dizziness and dyspnoea within 30 min after taking 100 mg acetylsalicylic acid (aspirin®) perorally, 2 years ago. He had similar complaints, within half an hour after 500 mg of metamizole sodium, and 15 min after 500 mg acetaminophen 1 year and 4 months ago, respectively. He was admitted to the emergency room and diagnosed as anaphylaxis in all three incidents. There was no family or personal history of drug allergy or atopy. Open drug provocation tests in order to obtain an alternative analgesic drug were performed on different days. His physical examination and pulmonary function tests were within normal limits before each DPT.

The drug doses in provocation tests were initially adjusted as 1/8 of the patient's ordinary doses and doubled after every 30 min. The procedure was suspended for at least 1 week between two DPTs. Initially, a DPT with ibuprofen was performed. However, the test was terminated when a few urticarial plaques on his trunk occurred within 20 min after the first dose. Additionally, he suffered from itching, nausea and malaise. His blood pressure and oxygen saturation remained within normal range and he had no angio-oedema. One and 2 weeks later, DPTs were performed with meloxicam and nimesulide, respectively. In both DPT, a few linear urticarial plaques were seen on his trunk following the first dose. Thereafter, symptomatic dermographism was established with a blunt object pressed along his forearm which caused hyperaemia, oedema and itching within 10 min. Finally a DPT with placebo was performed and once again urticaria plaques occurred on his trunk following scratching and itching. Consequently, a DPT with benzydamine was performed as preventing physical stimuli that may trigger the symptomatic dermographism and no reaction was seen.

Non-steroidal anti-inflammatory drugs (NSAIDs) have been reported to be the second most common cause of drug hypersensitivity reactions in childhood.[2] There were