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Skin reactions to carbamazepine

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Key words: carbamazepine; erythrodermia; patch test; T cells; toxic epidermal necrolysis.

Abbreviations. CBZ: carbamazepine; EEM: erythema exsudativum multiforme; TEN: toxic epidermal necrolysis.

● CARBAMAZEPINE (CBZ) is an important drug used mainly in the treatment of epilepsy, paroxysmal trigeminal neuralgia, and affective disorders. Skin eruptions caused by CBZ occur in 2-4% of the patients on this therapy and include pruritic and erythematous rashes, urticaria, photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, and toxic epidermal necrolysis

(TEN) (1). Patch tests with CBZ 1% and 5% pet. seem to be useful for diagnostic confirmation purposes in patients with generalized maculopapular hypersensitivity reactions to CBZ (2). A double bond between positions 10 and 11 of the azepine ring of CBZ seems to be critical for skin reactivity. This bond is lost in CBZ metabolites and in its analog oxcarbazepine, which usually does not cross-react with CBZ (3).

Two patients with different skin reactions to carbamazepine are described. Thirteen days after starting CBZ therapy, patient no. 1 (age 36; female) developed a pruritic erythematous maculopapular eruption with some target lesions on the extremities characteristic of erythema exsudativum multiforme (EEM). The lesions progressed to TEN with 50% epidermolysis, accompanied by oral and genital ulcers. Patient no. 2 (age 47; female) developed maculopapular exanthema with erythrodermia about 91 days after starting CBZ therapy. In both patients, CBZ therapy was discontinued, and systemic corticosteroids were initiated.

A skin cell suspension obtained from lesional skin was prepared by enzymatic digestion, by the method of Sager et al. (4). To select for CBZ-specific T cells, the suspension was cocultured with 10^6 irradiated (20 Gy) peripheral blood-derived mononuclear cells in culture medium (RPMI 1640; Gibco, Grand Island, NY, USA) supplemented with 10% human AB serum (Bloedbank, Utrecht, The Netherlands), and IL-2 and IL-4 (both 50 U/ml; Novartis Research Institute, Vienna, Austria)

and CBZ (Tegretol®). T-cell cultures were phenotypically characterized by flow cytometry in order to assess relative expressions of CD4 and CD8. Specificity for CBZ was examined in lymphocyte stimulation tests in which, in triplicates, 40×10^3 T cells were cocultured with equal numbers of autologous, irradiated (40 Gy), EBV-transformed B cells and increasing concentrations of CBZ. ^3H -labeled thymidine incorporation was the measure of T-cell proliferation.

In patient no. 1, the T-cell culture consisted of CD8⁺ T cells mostly (94%). No CBZ specificity was detected in this culture (Fig. 1A). Patient no. 1 had a negative patch test to CBZ, a fact which may be explained by the exclusive presence of CD8⁺ T cells. Indeed, Friedmann et al. previously reported the predominant presence of CD8⁺ T cells in the lesional skin of drug-induced EM/TEN by immunohistochemistry (5). These authors did not detect specificity for CBZ in blood-derived T cells. In patient no. 2, the T cells cultured with CBZ were nearly all CD4⁺ (98%) and showed specificity for CBZ (Fig. 1B). Patient no. 2 had a positive patch test reaction to CBZ after 48 h, suggesting a type IV, cell-mediated skin reaction.

We hypothesize that the way a drug is presented as an antigen is reflected in the type of skin reaction induced by that drug: activation of CD8⁺ T cells (cytotoxicity) in TEN, and CD4⁺ T cells (delayed-type reaction) in erythrodermia.

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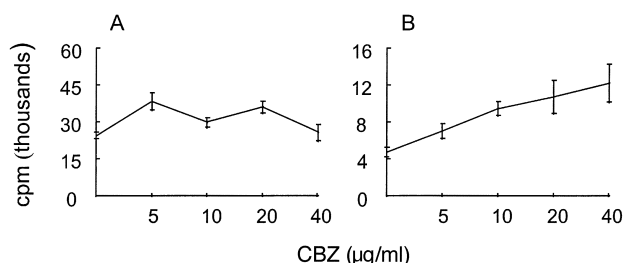


Figure 1. A) No CBZ concentration-dependent proliferation of polyclonal T-cell line derived from lesional skin of patient no. 1. B) Polyclonal T-cell line from patient no. 2 shows increased proliferation with higher concentrations of CBZ. Data are depicted as means of triplicates $\pm$ SEM.

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