Interferon-γ Production in the Peripheral Lymphocytes of a Patient with Carbamazepine Hypersensitivity Syndrome

Sir,

We report here on a patient who developed carbamazepine (CBZ) hypersensitivity syndrome while taking CBZ. To prove hypersensitivity to CBZ, we investigated interferon-γ (IFN-γ) release by peripheral blood mononuclear cells in response to stimulation with CBZ. IFN-γ production in response to stimulation with CBZ was observed in a patient with CBZ hypersensitivity syndrome. These results indicate the presence of CBZ-specific T-cell reactivity in CBZ hypersensitivity syndrome.

CASE REPORT

A 12-year-old boy with epilepsy was started on CBZ. Four weeks later he developed a maculopapular rash over his face, chest and lower extremities. The condition subsided after discontinuing CBZ. One week later, he was again given CBZ and the widespread maculopapular eruptions reappeared with high fever (39.0°C). The skin eruptions progressed to erythroderma. A physical examination on hospital admission revealed tender inguinal and cervical lymphadenopathy. Initial laboratory results included: white blood cell count 26.5×10^9/l with 20% eosinophilia and 4% atypical lymphocytes, aspartate aminotransferase (AST; GOT) 95 IU/l, alanine aminotransferase (ALT; GPT) 188 IU/l, lactate dehydrogenase (LDH) 1,089 IU/l. Antibodies for Epstein Barr virus, cytomegalovirus, hepatitis B and mycoplasma were non-diagnostic. CBZ hypersensitivity syndrome was thereby suspected and this drug was discontinued. Treatment with 60 mg/day of prednisolone was administered and tapered as the clinical symptoms improved. A patch test, performed with 10% and 30% CBZ in white Vaseline®, was positive. The findings of an *in vitro* lymphocyte transformation test were negative. The patient's peripheral blood mononuclear cells, suspended in RPMI medium with 10% human serum (1×10^6/ml), were cultured with or without CBZ (25 μg/ml) for 72 h. One subject who had no drug eruptions when taking CBZ, served as a control source of peripheral blood mononuclear cells. Cell-free supernatants were collected and the activity of IFN-γ in the culture supernatant was measured with an EIA test kit (Medgenix, Brussels, Belgium). When peripheral blood mononuclear cells from the patient were incubated with CBZ, a significantly high level of IFN-γ was detected, in contrast to that from the control subject (Table I). These results indicate that IFN-γ was released by CBZ-specific T-cells from the patient with CBZ hypersensitivity syndrome.

Table I. *IFN-γ production by peripheral blood mononuclear cells (PBMC)*

Source of PBMC	Cultured with CBZ	IFN-γ (IU/ml)
Patient	+	6.0
	−	0.8
Control	+	0.6
	−	0.9

CBZ = carbamazepine.

DISCUSSION

In our case, the presence of atypical lymphocytes, eosinophilia and IFN-γ producing T-cell indicates an immunological basis for the hypersensitive syndrome. Mauri-Hellweg et al. (1) have shown the drug-induced cytokine production of peripheral blood mononuclear cells in patients with hypersensitivity syndrome and the involvement of drug-specific T-cells in hypersensitivity syndrome, which correlated with our results. IFN-γ plays a role in the effector phase of the delayed-type hypersensitivity reaction (2). Our findings suggest that CBZ hypersensitivity syndrome may thus be partially associated with the delayed-type hypersensitivity response to CBZ.

Hypersensitivity syndrome develops usually between 1 week and 3 months after starting therapy. Patients often complain of headache, nausea, general malaise and arthralgias. Symptoms such as fever, skin eruption and lymphadenopathy are invariably present (3). The peripheral blood usually shows leukocytosis, eosinophilia and sometimes the presence of atypical lymphocytes. Liver involvement is also common. These clinical features of hypersensitivity syndrome resemble those of infectious mononucleosis. Many drugs may cause allergic reactions via T-cell activation, but such reactions do not always develop into hypersensitivity syndrome. The immuogenicity of drugs may therefore depend on their ability to bind to proteins. CBZ is not reactive *per se*, but might become immunogenic after intracellular metabolization into reactive intermediates (4).

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