

Patch testing with carbamazepine and its main metabolite carbamazepine epoxide in cutaneous adverse drug reactions to carbamazepine

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The value of skin tests in the diagnosis of adverse drug reactions (ADRs) has been limited. Lack of knowledge as to the nature of drug allergens has contributed to these limitations. Several reports have addressed the roles of metabolites in cutaneous ADRs and skin testing. We evaluated the role of a carbamazepine (CBZ) metabolite on the results obtained from patch tests, using CBZ and its main metabolite 10,11-epoxide of CBZ (CBZ-epoxide), on 13 patients with CBZ-induced drug eruptions and 39 controls with no CBZ-induced cutaneous ADRs. 10 of the 13 patients showed a positive reaction, and 2 of the 10 patients had a reaction to the CBZ-epoxide only and 1 to both CBZ and CBZ-epoxide. None of the 39 controls displayed any reactions to either CBZ or CBZ-epoxide. Patch testing of suspected drugs, as well as their available metabolites, would be helpful in improving the results.

Key words: carbamazepine; carbamazepine epoxide; cutaneous adverse reactions; patch testing technique; positive patch test reactions. © Blackwell Munksgaard, 2003.

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Skin testing is becoming popular in the diagnosis of adverse drug reactions (ADRs) and for the identification of causative drugs. The type of cutaneous ADRs, and nature of the drugs responsible, may influence skin test results. The type of the reaction may be the result of the pathomechanisms of cutaneous ADRs. Although these mechanisms are unclear, an understanding of these types of reaction would be helpful in determining appropriate skin testing methods. However, the value of skin tests has been limited. The lack of accurate information on appropriate concentrations, or proper vehicles for testing the antigens, has contributed to these limitations. One of the most important contributing factors is lack of knowledge as to the nature of drug allergens.

Drugs usually have a low molecular weight, and are required to complex with tissue macromolecules in order to be complete antigens. As most drugs are inert, they need to be activated through metabolic processes (1–2). Drugs are metabolized in 2 phases: in phase I, functionalization processes are involved, where the metabolites

retain pharmacological activity. In phase II, conjugation processes take place, and the metabolites lose pharmacological activity. Most drugs are metabolized in the liver, where there are many metabolic enzymes. Certain metabolic enzymes have been found in the skin (3–4), suggesting that the same metabolites may be formed during percutaneous transfer of certain drugs. If these metabolites from the percutaneous route were the same as those from systemic administration, a favourable skin test result would be expected.

Several reports have addressed the roles of metabolites in cutaneous ADRs and skin testing. A principle metabolite of cyclophosphamide, but not cyclophosphamide itself, evoked immediate positive skin test results in cyclophosphamide-induced urticaria (5) and late-onset allergic reaction (6). Co-incubation of the drug with human liver microsomes, as a source of metabolic enzymes, yielded a positive lymphocyte transformation test in chlorazepate-induced generalized exanthema (7).

Antiepileptic drugs are one of the most common causes of cutaneous ADRs, and

carbamazepine (CBZ) is a popular antiepileptic drug. We evaluated the role of a CBZ metabolite on the results obtained from patch tests, using CBZ and its main metabolite 10,11-epoxide of CBZ (epoxy-CBZ or CBZ-epoxide), on 13 patients with CBZ-induced drug eruptions and 39 controls without CBZ-induced cutaneous ADRs.

Subjects and Methods

13 neurological patients, having taken antiepileptic drugs including CBZ, displayed maculopapular cutaneous eruptions. These included 6 males and 7 females, with an average age of 54 years, ranging from 15 to 74.

As neurological controls, we used 39 subjects also having taken antiepileptic drugs including CBZ, but never having experienced any cutaneous eruptions. These included 19 males and 20 females, with an average age of 42.9 years, ranging from 12 to 78.

CBZ was prepared as a 10% dispersion in a white petrolatum base. A metabolite, CBZ-epoxide (C4206, Sigma, St Louis, MO, USA), was dissolved in ethanol at a concentration of 1 µg/ml. These preparations were used to conduct patch tests on the 13 patients and 39 controls. The results were read on days 2 and 4.

Results

10 of the 13 patients showed a positive patch test reaction. 7 had a reaction to CBZ only, 2 to CBZ-epoxide only, and 1 had a reaction to both (Table 1). None of the 39 controls displayed any reactions to either CBZ or CBZ-epoxide.

Discussion

The success of skin testing in cutaneous ADRs (CADRs) varies according to the drug being tested and the clinical features of the eruption. A high rate of positive results has been obtained from CBZ-induced cutaneous ADRs, with no great dependence on the clinical features (8). Our patients had a maculopapular type of reaction. 10 of the 13 patients with CBZ-induced cutaneous ADRs reacted positively, mirroring the high positive rates of other reports, but 2 of these 10 reacted to the main metabolite CBZ-epoxide but not to CBZ, and 1 other reacted to both. The nature of the antigen is still unknown. Positive reactions to CBZ-epoxide do not necessarily mean that it is an antigen. If CBZ-epoxide were an antigen, it would not explain why some patients reacted only to CBZ. However, the concentration of CBZ-epoxide may have been too low, or the patients may have

Table 1. Profile of patients and patch test results

Patient No.	Sex/Age	Type of reactions	Patch test results*	
			CBZ	Epoxy-CBZ
1	M/56	maculopapular	+	–
2	M/63	maculopapular	+	–
3	F/15	maculopapular	+	–
4	F/42	maculopapular	+	–
5	F/63	maculopapular	+	–
6	F/64	maculopapular	+	–
7	F/74	maculopapular	+	–
8	M/60	maculopapular	+	+
9	M/41	maculopapular	–	+
10	F/49	maculopapular	–	+
11	M/30	maculopapular	–	–
12	M/73	maculopapular	–	–
13	F/72	maculopapular	–	–

*Reading was taken after day 2 and day 4 according to the interpretation key of the International Contact Dermatitis Research Group.

developed an enzyme for metabolizing CBZ-epoxide into another metabolite.

CBZ undergoes almost complete biotransformation in humans (9–10). In this biotransformation, the epoxide pathway is quantitatively the most important. The first actually tangible product of this pathway is CBZ-epoxide, which is chemically stable (11) and is commercially available. The peak plasma concentrations of CBZ, 4–8 µg/ml, are reached within 1–2 hr of its administration at doses between 6 and 8 mg/kg (12), whereas the peak plasma concentrations of the CBZ-epoxide have been found to be approximately 1/3 of this (13). The concentration used for patch testing CBZ-epoxide was determined from the metabolism of CBZ. None of the 39 neurological controls showed any reactions to 1 µg/ml of CBZ-epoxide in ethanol, so, maybe higher concentrations would be more appropriate for patch testing.

The cytochrome P450 (CYP) isozymes, CYP2C8 and CYP3A4, catalyze the 10, 11-oxidation of CBZ, with CYP3A4 being the more important of the two (14). The liver contains plenty of these enzymes, and biotransformation takes place primarily in the liver. However, these enzymes have also been detected in human skin, indicating that the skin might participate in the biotransformation. The levels of CYP expression in the skin have displayed marked inter-individual variation (15, 16), which may explain the differences in the results observed between individuals on patch testing. The patients not reacting to patch testing may express no, or only negligible amounts of, CYP3A4 and CYP2C8 in their skin. They may produce CBZ-epoxide

through metabolism in the liver, but not in the skin, causing a difference in metabolites between systemic and percutaneous administration. Patch testing of suspected drugs, as well as available metabolites, would be useful in improving the results.

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