CONTACT DERMATITIS TO PHENOTHIAZINE DRUGS*

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Since the advent of use of phenothiazine derivatives as "tranquilizing" drugs, physicians have become aware of the occurrence of severe contact dermatitis in response to administration or handling of certain members of this chemical group (1-3). In addition, clinical observations (4) of the course of jaundice in patients taking oral doses of tranquilizers of this group strongly suggest that other side reactions, notably chlorpromazine hepatitis, may well be allergic manifestations. Hepatitis, as well as agranulocytosis, has been accompanied by skin reactions, and the course of the liver sensitization and desensitization, studied in a group of patients on a protracted course of chlorpromazine therapy, seems to indicate that a similar mechanism of drug sensitivity is involved (5). A peculiar type of retinal toxicity, which also seems to have an allergic basis, has been reported with a phenothiazine drug (6).

In this paper we report on a patient in whom skin sensitization developed after exposure to an experimental phenothiazine derivative. Several other analogues were examined by patch testing in order to pinpoint the structural component to which this patient was sensitive. Results seem to indicate a rather specific structure-activity relationship between chlorpromazine and its analogues in causing this cross-reaction.

CASE HISTORY

A 31 year-old white woman laboratory worker was engaged in handling a new phenothiazine derivative, piperidylchlorophenothiazine hydrochloride (NP-207), during a pharmacological experiment (7). After three weeks of daily contact with the drug, the patient developed erythema and pruritus of the hands that progressed to a severe eczematous eruption covering the palmar and dorsal surfaces of the fingers and hands up to the wrists. The lesions persisted and gradually improved during a ten-week period of treatment and avoidance of contact with the drug.

Nine months later the patient inadvertently handled a number of phenothiazine drugs, including NP-207, and immediate itching, erythema, and scaling of the hands ensued and persisted for one month (Fig. 1). After this rash subsided, patch tests were performed on the forearms, using solutions of NP-207, chlorpromazine (Thorazine), prochlorperazine (Compazine), and perphenazine (Trilafon), soaked in small filter paper squares and applied to the skin for 24 hours. All reactions were positive (Fig. 2). One month later patch tests were repeated, using the same compounds and many others in varying concentrations (Table I). Again the tests were repeated, applying the drugs for 48 hours, and this time the test sites were exposed to two hours of intense summer sunlight 48 hours after removal of the patches.

After four testings, the patient became strongly positive to promethazine (Phenergan), indicating new sensitization to this agent. Two water-insoluble compounds, phenothiazine itself and chlorphenothiazine, were applied in crystalline form and elicited primary irritant reactions, which were atypical in duration and character. Those tests that had been negative did not become positive after exposure to sunlight. Two control subjects who were patch tested under the same experimental conditions with the same drugs did not develop positive reactions to any of them.

DISCUSSION AND COMMENT

Our studies of the skin reactions of this patient to various phenothiazine derivatives indicate that compounds containing a chlorine atom in the 2-position of the phenothiazine nucleus elicit positive skin reactions, while those without this particular substituent lack skin sensitizing ability. No reactions developed to compounds having a hydrogen, and acetyl radical, or a grouping such as—CF₃ (in triflupromazine or Vesprin) in that position. The chemistry of the side chain, the feature by which the numerous chlorpromazine analogues differ, did not modify the skin reaction. Promazine and chlorpromazine with identical side chains, differ only in the chlorine atom in question, and in this pair of drugs only the latter produced...
Fig. 1. Scaling of hands following contact with a phenothiazine drug

Fig. 2. Reactions to patch tests using indicated drugs
TABLE I

Drugs used for patch testing and reactions

<table>
<thead>
<tr>
<th>NAME</th>
<th>X=</th>
<th>R=</th>
<th>CONC. MCG/ML</th>
<th>SKIN REACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>MP-207 THORAZINE</td>
<td>Cl</td>
<td>-H</td>
<td>5</td>
<td>++++</td>
</tr>
<tr>
<td>THORAZINE</td>
<td>Cl</td>
<td>-CIClN-CICl</td>
<td>5</td>
<td>++++</td>
</tr>
<tr>
<td>PROMETHAZINE</td>
<td>Cl</td>
<td>-O-(CH2)3-NHCl</td>
<td>5</td>
<td>++++</td>
</tr>
<tr>
<td>TAILIFON</td>
<td>Cl</td>
<td>-H</td>
<td>5</td>
<td>++++</td>
</tr>
<tr>
<td>PYLONAZINE</td>
<td>Cl</td>
<td>-O-(CH2)6-NHCl</td>
<td>5</td>
<td>++++</td>
</tr>
<tr>
<td>DAPRAL THIOPANAZINE</td>
<td>H</td>
<td>-CH2Cl</td>
<td>10</td>
<td>O</td>
</tr>
<tr>
<td>VESPRAZINE</td>
<td>CF3</td>
<td>-O-CH2CH2N-CH3</td>
<td>5</td>
<td>O</td>
</tr>
<tr>
<td>PAROXILAZINE</td>
<td>H</td>
<td>-CH2Cl</td>
<td>5</td>
<td>O</td>
</tr>
<tr>
<td>PHENERGAN PROMETHAZINE</td>
<td>H</td>
<td>-CH2Cl</td>
<td>5</td>
<td>O</td>
</tr>
<tr>
<td>PHENOTHIAZINE</td>
<td>H</td>
<td>NO SIDE CHAIN</td>
<td>CRYSTALS</td>
<td></td>
</tr>
<tr>
<td>2-Chlorethienothiazine</td>
<td>Cl</td>
<td>NO SIDE CHAIN</td>
<td>CRYSTALS</td>
<td></td>
</tr>
</tbody>
</table>

A skin reaction. It is probable that the side chain need not be present, for the presence or absence of activity seems to be a function of the molecular structure; this point merits further investigation (13). Cross-sensitivity between various phenothiazine derivatives, such as promethazine and chlorpromazine, has been reported by Sidi, Hincky, and Gervais (3). Other investigators found no reactions with other phenothiazine derivatives lacking the chlorine atom (Diparcol and Parsidol) in patients who had positive patch tests to chlorpromazine (8).

Intense pruritus and severe sunburn after exposure to sunlight has been observed in patients receiving large oral doses of chlorpromazine (9, 10). We were unable to demonstrate photo-cross sensitivity between promethazine and chlorpromazine or to any other phenothiazine derivatives (3, 11). These phototoxic reactions probably would not be elicited in our experimental work on this patient, since at no time had she ingested any of the drugs; photosensitivity to phenothiazine derivatives is probably induced by ingestion, not by external contact (10-12).

SUMMARY AND CONCLUSIONS

In a subject previously sensitized to a phenothiazine derivative containing a chlorine atom in the ring, positive skin reactions were elicited by patch testing only with compounds having a chlorine in the 2-position. Other atoms or radicals gave negative reactions. The structure of the side chain did not seem to be a critical factor in causing contact (allergic) sensitization. Exposure to strong mid-day sunlight did not bring out any latent reactions and did not seem to affect the severity of the skin reaction.

The experimental data suggest a possible structure-activity relationship, which may be a factor in the development of allergic skin reactions following contact with certain phenothiazine derivatives. Furthermore, sensitization of this type may be related to other side reactions whose manifestations strongly suggest an allergic basis for this reaction.

REFERENCES