

CROSS-SENSITIZATION BETWEEN SYNTHETIC PRIMIN AND RELATED QUINONES

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The allergen in *Primula obconica* has recently been identified (8), and patch tests with 25 μ g of a dilution of 0.004 per cent gave positive reaction in all patients clinically sensitive to the plant (4). Although patch tests with paper chromatograms suggested that two allergens might be present in *Primula obconica* (3), gas chromatography of an ether extract of primula showed one peak only, identical with that found by gas chromatography of primin (1). The extreme degree of sensitivity to primin (2-methoxy-6-n-pentyl-p-benzoquinone) (Fig. 1) indicates that this is the major allergen of the plant.

Several other plants and woods contain allergenic quinones (7, 9). Some of these might be assumed to show cross-sensitivity to primin. This assumption is supported by our previous findings of a striking coincidence between positive reactions to *Primula obconica* leaf and rosewood extract (5).

In the first instance we extended the study to comprise several quinones of a structure closely related to primin with a view to establishing the pattern of cross-sensitivity.

Material and Methods

The initial study was performed on 20 volunteer patients, whose sensitivity to primin

had previously been established by patch tests at the departments of two of us (N.H. & S.F.).

Patch tests were performed with Al-test¹ prepared according to methods previously published (6). 25 μ g of ether solutions were pipetted onto the filter paper discs. Patches were left to dry, wrapped in aluminium foil and kept in a refrigerator until used (1). The patches were fastened by Leukoplast,² all tests being performed on the upper back.

Some of the patients were known to be highly sensitive to primin, and in these initial tests were performed with low concentrations to avoid severe reactions. The patients were also tested with six chemically related quinones synthesized by one of us (H.S.). As the molecular weights of the chemicals varied, the same molar concentration was used for testing, viz. 0.00048 mol./lit., calculated from primin 1:10,000. In Table 1 this concentration is designated by C. Some of the initial tests gave negative reactions. If possible they were repeated with a ten times higher concentration (10 C).

The patients were also tested with methyl-p-benzoquinone,³ 1 per cent in petrolatum, and with p-benzoquinone,³ 1 per cent in petrolatum. The latter substance has previ-

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² Beiersdorf AG, Hamburg, Federal Republic of Germany.

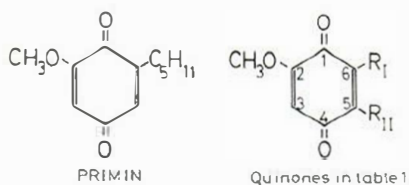
³ Schuchardt, München.

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ously been included in standard patch tests in Lund.

Hydroquinone monobenzyl ether 0.2 per cent in a rubber base has for many years been included in the standard patch test at the Finsen Institute. Positive reactions are usually unexplained, and a possible cross-sensitivity to primin was therefore considered.

Results

The results appear in Table 1.

Exceptionally, patients are only sensitive to primin as such, but usually the sensitivity extends to homologous substances with longer or shorter side-chains (Fig. 1). Maximum sensitivity was found to primin. This appeared particularly from the results of testing in patients with a low degree of sensitivity. The response was less intense if the length of the side-chain exceeded five carbon atoms or was shorter than that of primin. Most patients reacted to the 6-methyl and the 6-ethyl derivatives of 2-methoxyquinone, but only in high concentrations.

Sometimes sensitivity also extended to quinones with a side-chain in 5-position, but this was only observed in patients with a strong sensitivity to primin.

Methyl-p-benzoquinone and p-benzoquinone gave negative reactions throughout.

At the University Clinic of Lund p-benzoquinone has previously given negative reactions in 1196 consecutive patients tested, of whom many must have been sensitive to *Primula obconica* (1), which was not included in the standard series at that time.

Hydroquinone monobenzyl ether and primula have both been included in the standard patch tests at the Finsen Institute. Among 95 consecutive patients with posi-

tive reactions to *Primula obconica* two had positive reactions to hydroquinone monobenzyl ether. Among 70 consecutive patients with positive reactions to hydroquinone monobenzyl ether, eight had positive reactions to primula. These figures do not support an assumption of cross-sensitivity between the two substances.

Comments

Sensitivity to primin usually extends to other quinones with a shorter or longer side-chain although the degree of sensitivity decreases by changes in the molecular structure. The results obtained suggest that the optimal requirements for eliciting reactions in patients sensitized by *Primula obconica* is 2-methoxy-p-quinone with a side-chain in the 6-position comprising 5 carbon atoms. Either a longer or a shorter side-chain gave negative reactions in some persons.

Persons strongly sensitive to primin also reacted to substances with a side-chain comprising 5 or 6 carbon atoms in the 5-position. Judged by the number of positive reactors and by the strength of reactions, substances with side-chains in the 6-position are, however, stronger allergens.

The optimal length and position of the side-chain for inducing sensitization may be related to immunological factors or to the cutaneous penetration of the chemicals.

The capacity to form a full-antigen by combining with a protein may be dependent on the steric configuration of the molecule. Thus, an alkyl chain in 5-position can diminish the reactivity of the carbonyl group in the 4-position by steric hindrance. On the other hand the alkyl chain is an electron-donor substituent and increases the oxidation potential of the carbonyl group, *i.e.* the capacity to react.

Compounds having a short side-chain are more water-soluble, while lipid solubility increases with the length of the side-chain. The weak reactions to the substances with one, two or three carbon atoms in the 6-position may be due to low lipid solubility. A side-chain with four or with six carbon atoms gave a weaker reaction than primin with a side-chain with five carbon atoms.

Table 1. Patch test reactions to primin and related quinones in 20 patients

| R ₁ ** | CH ₃ | | C ₂ H ₅ | | C ₃ H ₇ | | C ₄ H ₉ | | C ₅ H ₁₁ *** | | C ₆ H ₁₃ | | H | |
|--------------------|-----------------|------|-------------------------------|------|-------------------------------|------|-------------------------------|------|------------------------------------|------|--------------------------------|------|------|------|
| | H | 10×C | H | 10×C | H | 10×C | H | 10×C | H | 10×C | H | 10×C | H | 10×C |
| R ₁₁ ** | H | | H | | H | | H | | H | | H | | H | |
| Conc. **** | 10×C | C | 10×C | C | 10×C | C | 10×C | C | 10×C | C | 10×C | C | 10×C | C |
| Case No. 1 | + | | + | | + | | + | | + | | + | | + | |
| 2 | - | | + | | + | | + | | + | | + | | + | |
| 3 | + | | + | | + | | + | | + | | + | | + | |
| 4 | + | | + | | + | | + | | + | | + | | + | |
| 5 | + | | + | | + | | + | | + | | + | | + | |
| 6 | + | | + | | + | | + | | + | | + | | + | |
| 7 | + | | + | | + | | + | | + | | + | | + | |
| 8 | - | | + | | + | | + | | + | | + | | + | |
| 9 | + | | + | | + | | + | | + | | + | | + | |
| 10 | - | | + | | + | | + | | + | | + | | + | |
| 11 | - | | + | | + | | + | | + | | + | | + | |
| 12 | + | | + | | + | | + | | + | | + | | + | |
| 13 | - | | + | | + | | + | | + | | + | | + | |
| 14 | + | | + | | + | | + | | + | | + | | + | |
| 15 | - | | + | | + | | + | | + | | + | | + | |
| 16 | - | | + | | + | | + | | + | | + | | + | |
| 17 | - | | + | | + | | + | | + | | + | | + | |
| 18 | - | | + | | + | | + | | + | | + | | + | |
| 19 | + | | + | | + | | + | | + | | + | | + | |
| 20 | - | | + | | + | | + | | + | | + | | + | |

Reactions in

controls:

Negative

Questionable

25

15

6

10

9

11

12

* 1/4 C. ** See Fig. 1. *** primin. **** Conc.: C = 0.00048 mol./lit.

On the basis of the present study it cannot be decided whether the relative lipid-water solubility of primin is optimal for cutaneous penetration, or whether the length of the side-chain reflects the structure of the antibody as suggested by Baer *et al.* (2) in their study of poison ivy catechols.

SUMMARY

Twenty patients sensitive to allergen in *Primula obconica*—primin—(2-methoxy-6-n-pentyl-p-benzoquinone) were tested with quinones chemically related to it in order to establish the cross-sensitivity pattern. In most cases the sensitivity extended to quinones with longer or shorter side-chains in 6-position as compared to primin. But these gave generally weaker reactions. Sensitivity also extended to quinones with a side-chain in 5-position, but only in patients with a strong sensitivity to primin. Thus, maximum sensitivity was found to primin. The capacity to elicit patch test reactions in primula sensitive patients may depend on the steric configuration of the molecule or on the lipid/water-solubility.

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