

Quinine and Quinidine Photoproducts Can Be Identical

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Quinine and its d-isomer quinidine can both cause contact allergy as well as photoallergy. Contact allergic cross-reactions between quinine and quinidine are uncommon. In allergic photosensitization the two isomers cross-react, suggesting the possibility that quinine and quinidine after UV exposure are converted to one or more common sensitizing photoproducts. Solutions of quinine and quinidine at 0.1% in ethanol 99.5% were exposed to UVA for 14 h (total dose 201.6 J/cm²). Using thin-layer chromatography, we identified 8 and 6 photoproducts from irradiated quinine and quinidine, respectively. Five of these photoproducts were seen in both chromatograms. An identical pattern with four photoproducts was found for both irradiated solutions when these were subjected to analysis in a high-performance liquid chromatography system. This study indicates that photoproducts from irradiated quinine and quinidine can be identical. This would explain the differences in the cross-reactivity pattern between contact and photocontact sensitization clinically. **Key words:** HPLC; photoallergy; TLC; UV irradiation.

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The two quinoline methanols quinine and its d-isomer quinidine are diastereoisomers (Fig. 1). Both have been reported to cause contact allergy (1, 2) and photoallergy following topical (3, 4) as well as systemic administration (5–7). Three reports of occupational quinidine contact sensitivity (7–9) revealed positive patch tests to quinidine. Tests with the isomer were negative in two of the reports (8, 9). One report of occupational quinine contact sensitivity demonstrated positive patch tests to quinine, whereas patch testing with quinidine was negative (4). The isomers do not cross-react in epicutaneous testing. In general, levorotatory compounds (*i.e.* quinine) do not cross-react with dextrorotatory isomers (*i.e.* quinidine) (10). Not only patient data but also animal studies are in agreement with this. In guinea pig sensitization experiments, animals sensitized to either quinine or quinidine did not react to the respective isomer (9).

Topical contact with quinine in combination with UV exposure may produce photosensitivity. In 1975, Johnson et al. (3) described an industrial chemist who had a positive photopatch test to quinine. Tests on control subjects were negative.

Systemic administration of quinine, a drug used in the treatment of recumbency cramps, may cause photosensitivity. Ljunggren & Sjövall (5) reported a woman on oral quinine presenting with a photodistributed dermatitis, where phototesting revealed a lowered UVA threshold while the patient was on the drug. The UVA and UVB thresholds were normal after quinine therapy was stopped.

Photosensitivity to quinidine following internal use was first

described in 1942 (6). It was not until 1983 that a patient was described (11), who developed, during oral quinidine therapy, a photodistributed eczema, where photopatch testing with quinidine was positive.

In a study using albino mice, photoallergy to either quinine or quinidine could be induced after systemic administration, and at challenge, positive reactions were elicited equally well with either of the two isomers (12). Recently we described a patient with photosensitivity from systemic quinine, who showed cross-reactions to quinidine on photoepicutaneous testing (13). These observations suggest the possibility that quinine and quinidine are both converted to one or more common sensitizing photoproducts after UV exposure. In order to test this hypothesis, we performed *in vitro* UV irradiation experiments with both compounds and studied the photoproducts using thin-layer chromatography (TLC) and high-performance liquid chromatography (HPLC).

MATERIAL AND METHODS

Chemicals

Quinine hydrochloride was purchased from ACO Läkemedel AB, Solna, Sweden, and quinidine hydrochloride from Sigma, St Louis, Mo, USA. No further purification was undertaken.

Ultraviolet radiation

UVA was obtained from a bank of 8 fluorescent tubes (Philips TL 20W/09N) with an emission peak around 360 nm. The irradiance at the level of the quartz cuvettes was 4.0 mW/cm² measured with a PUVA-meter (Waldmann AG, Schweningen, Germany). To eliminate the UVB a 15-mm glass pane was inserted between the tubes and the cuvettes.

Solutions of quinine and quinidine at 0.1% (w/v) in ethanol 99.5% (w/v) were exposed to UVA for 14 h, giving a total dose of 201.6 J/cm². Non-irradiated control solutions were covered in aluminum foil and placed in front of the UVA panel during the whole exposure. The temperature in the control solutions did not differ from the irradiated samples.

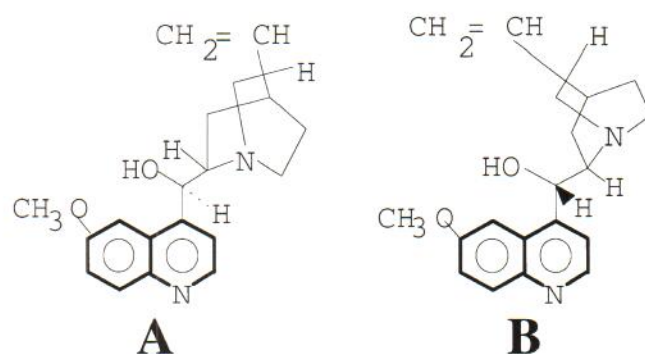


Fig. 1. The structures of the diastereoisomers quinine (A) and quinidine (B).

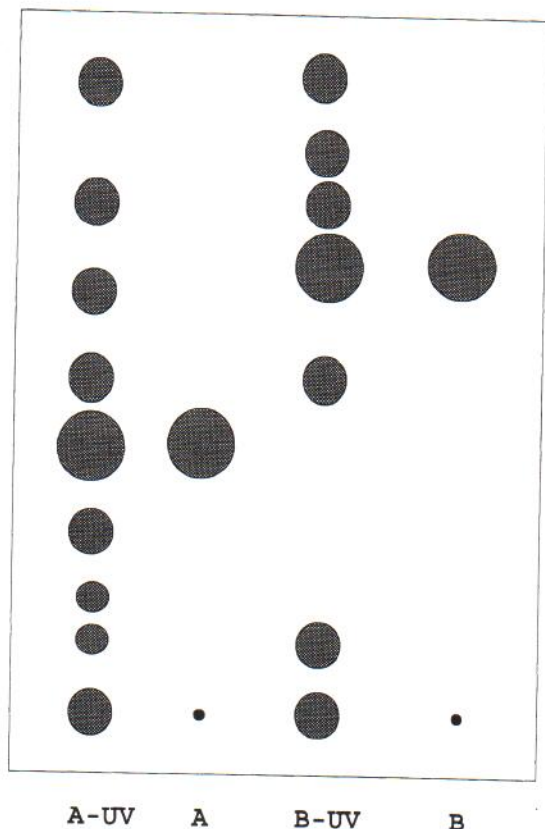


Fig. 2. Thin-layer chromatogram of non-irradiated quinine (A) and quinidine (B) and irradiated quinine (A-UV) and quinidine (B-UV).

Thin-layer chromatography

Precoated silica gel plates, 5 × 10 cm (DC-Fertig platten Kiesel-gel F-254; Merck, Darmstadt, Germany), were used. The solvent system used was petroleum ether/diethylamine/acetone 15:6:6 v/v/v. All solvents were of analytical grade.

Twenty μ l of each of the 4 solutions (2 non-irradiated, 2 irradiated) were applied to silica gel plates, and after elution the plates were inspected during exposure to 360 nm ultraviolet radiation.

High-performance liquid chromatography

An HPLC system was used comprising an LDC Constametric III pump fitted with a Rheodyne loop injector and an LDC Spectro Monitor III variable UV-detector. The volume of the loop was 10 μ l. The column was a 5 × 200 mm Li-Chroma column packed with Nucleosil C₁₈ 5 μ m particles. The flow rate was 1 ml/min. All solvents were of HPLC grade. Methanol/water (NH₃ 0.5% w/v) 90/10 v/v as mobile phase permitted separation of irradiated and non-irradiated quinine and quinidine. The wavelength chosen for detection was 330 nm, as quinine and quinidine have absorption maxima around this wavelength. Each substance was dissolved in the mobile phase at a concentration of 0.001% (w/v) and aliquots were injected into the column.

RESULTS

When the TLC technique was used, quinine and quinidine in the non-irradiated control solutions separated well, yielding single spots. When the irradiated substances were eluted on the plates, photoproducts of both quinine and quinidine were detected as separate spots (Fig. 2).

For quinine, 8 additional spots were found and the corre-

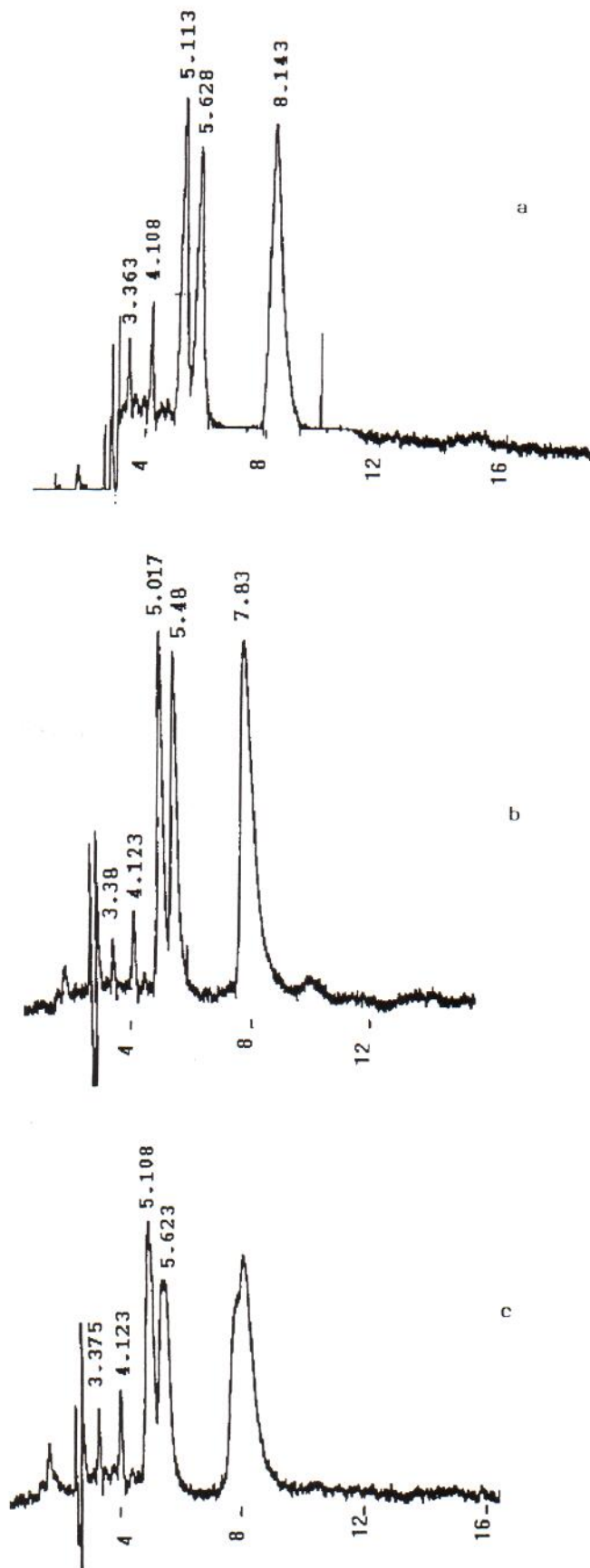


Fig. 3. High-performance liquid chromatogram of (a) irradiated quinine solution with quinine (retention time 8.1 min) and 4 photoproducts; (b) irradiated quinidine solution with quinidine (retention time 7.8 min) and 4 photoproducts; and (c) a 1:1 mixture of irradiated solutions of quinine and quinidine with a double peak with retention times around 8 min (quinidine, quinine) and 4 photoproducts.

sponding figure for quinidine was 6. Five of the photoproducts were seen in both solutions of irradiated quinine and quinidine.

In the HPLC system non-irradiated quinine and quinidine were separated with retention times of 8.1 and 7.8 minutes, respectively. Both in irradiated quinine and quinidine solutions 4 photoproducts were detected. The photoproducts of quinine had the same retention times as the photoproducts of quinidine, and when a 1:1 mixture of irradiated solutions of quinine and quinidine was injected into the system, only 4 photoproducts with the same retention times as for the photoproducts of quinine and quinidine were detected (Fig. 3).

DISCUSSION

The chemicals investigated were of high purity, since only one spot and one peak was demonstrated for each substance, when quinine and quinidine were investigated with TLC and HPLC, respectively. This study shows that photoproducts are generated in UVA-irradiated ethanol solutions of quinine and quinidine. Furthermore, most of the photoproducts seen on the TLC plates and all photoproducts seen on the HPLC chromatogram seem to be identical. However, conclusions as to identity cannot be drawn with certainty from the results of TLC and HPLC investigations. For such a conclusion, separation of the photoproducts and identification of these products by an investigative system that identifies optical isomers is needed. Theoretically, photoproducts of quinine and quinidine can be isomers or they can be identical. Different reactions, e.g. oxidation of the hydroxy group, can lead to several identical products. Photoreactions can also give fragmentation of the molecules, leading to a mixture of identical and isomeric fragments. Identical photoproducts are not separable in any investigative system. The photoproducts of quinine and quinidine were not separable, which means that they can be identical. However, the shorter the retention time is, the harder it is to separate chemically closely related substances, i.e. isomeric forms, and all photoproducts of quinine and quinidine had shorter retention times than quinine and quinidine in the HPLC system. Therefore, the identical peaks on the HPLC chromatogram (Fig. 3) can represent either the same or isomeric photoproducts.

The appearance of the photoproducts seen on the TLC plates was different from that of the photoproducts in the HPLC

chromatogram, since the TLC photoproducts had both shorter and longer retention times than both quinine and quinidine. Common photoproducts were found also among those with longer retention times, which could mean that the photoproducts are identical.

These results indicate that common photoproducts are generated. That this may be clinically relevant is suggested by the findings in our patient on oral quinine, who was positive to both isomers when photopatch-tested (13). In addition, the results of experimental photosensitization in mice (12) correlate well with this hypothesis.

One implication of our study is that if a patient is photoallergic to quinine, he is also photoallergic to quinidine and should avoid both drugs.

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