

Quinine and Quinidine Cross-react after Systemic Photosensitization in the Mouse

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Using a protocol for induction of photoallergy in the mouse after systemic administration, quinine was shown to be just as potent a photosensitizer as its d-isomer, quinidine. The dose-response curves for the two isomers followed a similar course both for induction and elicitation. Cross-reaction experiments, where induction and challenge were performed with different isomers, indicated that quinine and quinidine cross-react. Traces of the isomer as a contaminant in the test compound are not likely to account for this cross-reactivity. For practical purposes, photosensitization to one of these two quinoline methanol isomers seems to exclude the future use of the other.

(Accepted September 25, 1989.)

Acta Derm Venereol (Stockh) 1990; 70: 204-207.

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Quinine, a drug belonging to the group of quinoline methanols, is used in medicine for such different purposes as in the treatment of chloroquine-resistant malaria and in recumbency cramps. The d-isomer of quinine, quinidine, is a potent cardiac antiarrhythmic agent.

Allergic contact sensitivity to quinine has been reported in association with chemical contraceptives for local application and hair preparations containing quinine (1). In one report a patient with allergic contact sensitivity and a chronic photosensitivity dermatitis was described (2). An outbreak of dermatitis in a quinine-processing factory was suggested to be caused by an irritant contact reaction (3). There are also reports of other non-eczematous types of cutaneous reactions to quinine, such as bullous reaction of the palms (4), purpura, and toxic epidermal necrolysis (5, 6). In the latter two reports the reaction was provoked by a trace of quinine contained in beverages.

Quinine has also been said to induce photoreactions. Lichen planus in a photodistribution following the oral use of has been documented (7, 8, 9). Contact photosensitivity is reported experimentally in the

guinea pig (10), and clinically (11). Systemic photosensitivity has been reported clinically, and the underlying mechanism suggested to be either phototoxic (7) or photoallergic (12). Phototoxicity was not demonstrated in vivo (13) but in some in vitro systems (7, 13) in recent studies.

Photoallergy following the systemic administration of quinidine in the mouse was recently demonstrated (14, 15). In the present work the same technique was used to study the photoallergic potential of quinine, as well as its cross-reactivity with quinidine.

MATERIALS AND METHODS

Mice

Groups of 5-8 female NMRI albino mice, weighing 24-30 g were used. The mice used in each individual experiment were delivered at the same time from Anticimex, Sollentuna, Sweden. All mice were housed in identical cages and had unlimited access to food and water.

Chemicals

Quinine hydrochloride was obtained from ACO Läkemedel AB, Solna, Sweden, and quinidine chloride from Sigma, St Louis, Mo, U.S.A. No further purification was undertaken, since analysis of samples of both drugs showed a purity of more than 99% and 98%, respectively. The analysis were performed by ACO, Sweden (both drugs) and Sigma, U.S.A. (quinidine only) using thin-layer chromatography. Cyclophosphamide was purchased from Lääkefarmos, Turku, Finland.

Ultraviolet radiation

The UVB source consisted of two fluorescent sunlamp tubes (Westinghouse Sunlamp FS40, 40 W) emitting continuously from 280 to 380 nm with an emission peak at 312 nm. The irradiance at the level of the animals was measured with a photometer (Waldmann AG, Schwenningen, GFR) and was 0.7 mW/cm² within UVB. UVA was obtained from two fluorescent blacklight tubes (Philips TLA 40 W/08) with an emission peak around 360 nm. The irradiance was 1.6 mW/cm² as measured with a PUVA-meter (Waldmann AG).

Immunoadjuvant

To enhance the immunological reaction, mice were given 150 mg/kg cyclophosphamide into the intraperitoneal space 2 days prior to photosensitization. Immediately before injection, cyclophosphamide was dissolved in sterile normal saline.

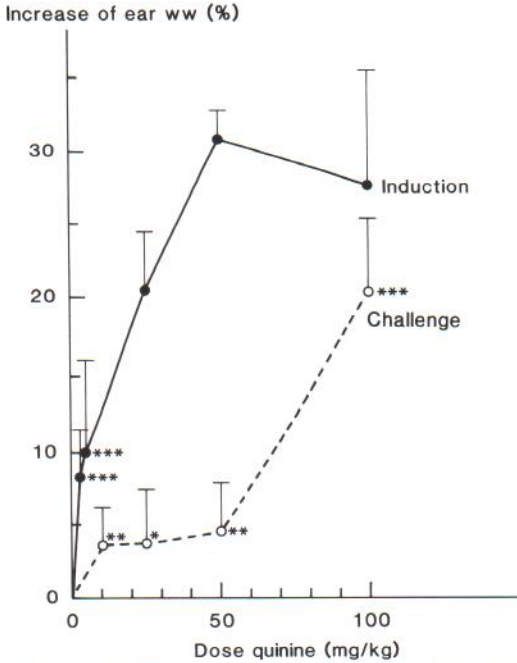


Fig. 1. Dose-response curves for induction (constant challenge dose 100 mg/kg) and challenge (constant induction dose 100 mg/kg) in systemic photoallergy to quinine in the mouse. Reaction measured as relative wet weight (ww%) increase over controls. Range bars indicate SD. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Photosensitization

The procedure for photosensitization has been described in detail in a previous report (14). On day 0, 150 mg/kg cyclophosphamide, dissolved in normal saline to a total volume of 0.5 ml, was injected intraperitoneally (i.p.). On day 2 approximately 4 cm² of ventral skin was shaved. The mice were then injected i.p. with either quinine or quinidine in doses ranging from 0.1 to 100 mg/kg. After one hour in the dark the animals were anesthetized with pentothal sodium, 80 mg/kg, by i.p. injection. The mice were then placed in plastic tubes for fixation and exposed to UVB 0.1 J/cm² followed by UVA 5.0 J/cm², given to the shaved ventral skin. During this procedure the ears were shielded from light inside the plastic tubes. On day 3 the exposure to drug and UV was repeated, but the mice were not reshaved.

A control group, designed to exclude phototoxicity, following the same procedure except for the omission of UV irradiation, was included in all experiments. Baseline ear thickness was measured under anesthesia with a micrometer (NSK Digital, Japan).

Photochallenge

Quinine or quinidine in doses from 10 to 100 mg/kg was administered i.p. to photosensitized and control mice on day 7. After being kept in the dark for one hour the mice were anesthetized with pentothal sodium and placed in the fixation device. The left ear, facing the UV lamp, was exposed

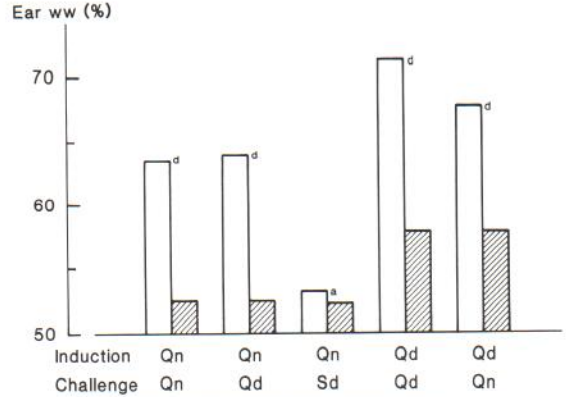


Fig. 2. Cross-reaction experiments in systemic photoallergy to quinine (Qn) and quinidine (Qd) in the mouse. Relative ear wet weight (ww%) 24 h after challenge in experimental group (□) and controls (▨). Sulphanilamide = Sd. a, NS; b, $p < 0.05$; c, $p < 0.01$; d, $p < 0.001$. All induction and challenge doses, 100 mg/kg.

to UVA 5.0 J/cm² while the right ear was shielded from UV radiation. UVA in a dose of 5.0 J/cm² did not provoke an inflammatory reaction in the absence of drug.

Evaluation

Evaluation was made on day 8, using two different methods. Increased ear thickness was measured with the micrometer. By excising both ears after sacrifice and weighing them before and after drying in an oven for one hour at 110°C, the relative wet weight could be estimated. Here the results are presented as ear wet weight, since this proved to be the more sensitive evaluation technique (15).

Statistics

Student's *t*-test was used for the statistical analysis.

RESULTS

Photoallergy to quinine could be induced by i.p. administration of doses down to 2.5 mg/kg (the lowest dose tested in the dose-response study). The maximum wet weight increase of ear tissue was seen with 50 mg/kg, and no further increase in response could be registered by doubling the induction dose (Fig. 1). With a constant induction dose of 100 mg/kg of quinine, challenge doses as low as 10 mg/kg were sufficient to elicit a statistically significant ear reaction ($p < 0.01$). The response could be increased however by increasing the challenge dose up to 100 mg/kg (Fig. 1). A phototoxic reaction could be excluded, since there was no ear edema in the group of control mice. No differences were noted between the wet weights of the right (UV-shielded) ear in the different groups of mice (data not shown).

Table I. Induction of systemic photoallergy to low doses (mg/kg) of quinine (Qn) and quinidine (Qd) in the mouse.

Doses in parentheses indicate sham induction with drug but without UV exposure (phototoxicity controls). Reaction measured as relative ear wet weight (WW%) 24 h after challenge.

Induction		Challenge		WW%	SD±	p
Qn	Qd	Qn	Qd			
10		100		63.7	2.07	
10			100	61.1	3.36	NS
0.1		100		60.4	2.27	
(100)		100		57.1	1.50	<0.01
	10		100	63.1	1.89	
	10	100		61.4	1.85	NS
	0.1		100	59.1	3.15	
	(100)		100	57.2	2.53	NS

To study whether quinine and quinidine cross-react, induction was performed with one isomer and challenge with the other. The results of these experiments are shown in Fig. 2. In all experiments, induction and challenge, the dose of quinine, quinidine and sulphanilamide was 100 mg/kg. The two quinoline isomers were shown to cross-react. No statistically significant differences could be obtained between experiments where one isomer was given for induction and the other for challenge, or in experiments where the same isomer was given for both induction and challenge. Sulphanilamide, structurally unrelated to quinine, did not elicit a statistically significant reaction in quinine-photosensitized animals, thereby demonstrating the specificity of the reaction.

To elucidate whether a very low dose of quinine or quinidine, theoretically present as a contaminant in the other preparation, could induce photoallergy, experiments with induction doses of only 0.1 mg/kg were performed. This amount corresponds to a less than 1% contamination of quinine in the quinidine preparation, and vice versa. With quinine, this small amount of drug was sufficient for a significant, though weak reaction, at challenge, whereas this was not the case with quinidine (Table I).

DISCUSSION

Quinidine, the d-isomer of quinine, was recently shown to have photoallergic properties when admin-

istered systemically in the mouse (15). In this study, using quinine, we obtained dose-response curves for induction and elicitation which were quite similar to those for quinidine. Recently, a similar dose-response pattern with a steep induction curve reaching a plateau, and a less steep curve for challenge, was reported for photocontact allergy to TCSA in the mouse (16). In our study, a statistically significant reaction could be obtained with a dose of 10 mg/kg at challenge, and with doses below that at induction (Fig. 1). The successful induction of photoallergy to quinine after systemic administration in this study gives support to the assumption that the photosensitivity reaction to oral quinine recently described (12) was due to a photoallergic mechanism.

Our observation that quinine and quinidine cross-react seems perhaps not surprising in view of the structural similarity between the two drugs. However, 3 patients with occupational contact dermatitis due to quinidine were recently described (17, 18), and in these patients patch tests with quinine hydrochloride were negative. The authors also induced experimental contact sensitivity to quinidine and quinine in the guinea pig, and found that only 3 out of 20 animals sensitive to quinidine also reacted to quinine. None of 20 animals contact sensitive to quinine reacted to quinidine (18).

By studying enantiomeric compounds, Benezra et al. (19) were able to show that allergic contact dermatitis is essentially enantiospecific. Quinine and quinidine are diastereomers rather than enantiomers, however, and the exact antigenic site on the molecule is not known.

The cross-reactions noted in this study may have been due to a true chemical cross-reactivity, or to a photoproduct of quinine and quinidine forming a common hapten. A third possibility would be that a small amount of one compound may be present as a contaminant in the other. Thin-layer chromatography studies performed by the manufacturers on the actual batches used for the experiments showed this amount to be in the order of 1% or less. Although in one of our experiments an induction dose as low as 0.1 mg/kg of quinine was sufficient to cause a reaction at challenge, the reaction was weak. A similar dose of quinidine did not induce a significant reaction (Table I). If the cross-reactivity pattern observed were due to contamination of the test compound, the challenge reactions obtained with the other isomer would be expected to be consistently weaker. This was not the case, and there was no statistical difference between

reactions elicited with the induction compound and the other isomer. We therefore consider it unlikely that the elicitation reactions obtained with the isomer not used for induction are due to contamination.

In view of previous negative cross-sensitivity studies on patients as well as experimental data (17, 18), the hypothesis that quinine and quinidine are both converted to a common photohapten following irradiation is perhaps the most likely one. The nature of the photoproducts of quinine and quinidine remains to be investigated.

Quinine and quinidine are listed among potentially photosensitizing drugs, and there are clinical reports of photosensitivity following the use of both (7, 20). In this study, the two drugs were shown to have the same potential to cause photosensitivity. According to official Swedish statistics (21) quinidine is a more frequent cause of photosensitivity than quinine, but this difference may be due to causes other than the photosensitizing potential, such as dosage conditions and frequency of prescription.

For practical purposes, photosensitization to one of these two quinoline methanol isomers seems to exclude the future use of the other.

ACKNOWLEDGEMENTS

This work was supported by grants from the Edvard Weiland Foundation and the Finsen Foundation. The skilful technical assistance of Mrs Karin Lundberg is gratefully acknowledged.

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