

DIGITALIS ALLERGY WITH DEMONSTRABLE ANTIBODY

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THIS is a report of a case of hypersensitivity to digitalis, manifested by urticaria, angioedema, and the formation of bullae in the skin, and in which was demonstrated direct specific immediate wheal-type skin reactions and passive transfer of specific reagins.

CASE REPORT

A 53-year-old Negro had noted dyspnea, fatigue, and swelling of his lower extremities for about three months when he consulted his family physician. Tincture of digitalis, 10 drops three times daily, had been prescribed, which he had taken from Nov. 8, 1952, until his admission to Hines Veterans Administration Hospital in January, 1953. There had been very little subjective relief during this treatment.

Physical examination at that time revealed bilateral crepitant râles at the bases of both lungs and mild edema of the feet. Treatment with rest, a low salt diet, and ammonium chloride provided excellent benefit, and on discharge he was asymptomatic.

On his return home, the patient again started taking tincture of digitalis. Twenty-four hours after initiating this medication, he noted urticaria of both arms, which progressed in another day to severe tense angioedema and numerous large bullae, so that he returned to the hospital presenting a brawny edema of both forearms covered with severe vesiculation of the skin. He was treated with cold soaks, Pyribenzamine, and ephedrine. No digitalis was given at this time. In five days the lesions had subsided markedly. On the sixth day he developed severe angioedema of the neck resembling a cellulitis, and during the next two days intermittent generalized urticaria. A history of using an ointment containing iodine was elicited, but a patch test with this substance was negative. By the tenth hospital day all skin lesions had completely disappeared.

On the fourteenth hospital day the patient showed some signs of frank cardiac insufficiency. The venous pressure was found to be 14 cm. of water, and the Decholin circulation time was 31 seconds. Accordingly, he was started on digitoxin by mouth. Four days later he developed urticaria and angioedema of the left upper extremity. After this had subsided he had intracutaneous tests on the right forearm with Decholin and digitoxin, with the latter giving a large immediate wheal reaction. Two days later the right forearm and arm became massively swollen and the skin covered with numerous large blebs. All medication was now stopped and in five days the swelling had completely disappeared.

Ten days later he again showed signs of myocardial failure and oral digitoxin therapy was started. Within three days he again developed severe swelling and vesiculation of the skin of his left arm. Digitoxin was stopped and the lesions gradually subsided. A few weeks later, direct skin testing was attempted with various digitalis preparations, and that night he developed a swelling on the back of his neck, plus edema of the left arm. A week later, after intracutaneous testing of the right forearm, he developed angioedema and bullae of the entire right arm. Two weeks later the left arm was used for additional intracutaneous tests with digitalis and in three days the entire left arm erupted severely with swelling and bullae. Since his discharge, at which time he was warned against the use of any digitalis preparations, he has remained free of urticaria, and has remained comfortable by restricting his activity and staying on a low salt diet.

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A review of the results of skin testing in this patient, summarized in Table I, showed positive immediate wheal reactions for digitoxin, lanatoside C, and Digilanid, questionable reactions to the whole digitalis leaf, and negative reactions for squill glycoside, ouabain, and strophanthin. Identical tests on three control subjects were all negative. Passive transfer was positive for digitoxin on two recipients with negative controls. Lanatoside C gave a positive passive transfer in one of two test subjects; but transfers for the whole leaf, ouabain, and strophanthin were negative.

Fluid aspirated from the bullae and used for passive transfer gave results similar to those of passive transfer with serum, positive reactions being elicited with digitoxin and lanatoside C, and negative reactions with squill and the whole leaf.

Serum from another patient thoroughly digitalized with whole leaf was used as a testing substance. The direct immediate skin reaction in our patient was positive, as was a passive transfer to a recipient, and controls in each test were negative.

TABLE I

	DIRECT		SERUM PASSIVE TRANSFER				BULLA PASS. TRANS.	
	PATIENT	CONTR.	TRANSFER #1 P. T. CONTR.	TRANSFER #2 P. T. CONTR.			P. T.	CONTR.
Digitalis leaf (Digilusin)	±	0	0	0	0	0	0	0
Digitoxin (Crytostigin)	+	0	+	0	+	0	+	0
Lanatoside C (Cedilanid)	+	0	+	0	0	0	+	0
Ouabain	0	0	0	0	0	0	0	0
Strophanthin	0	0	0	0	0	0		
Squill glycoside (Scillaren B)	0	0	0	0				
Lanatosides A, B&C (Digilanid)	+	0	+	0				
Serum of P. T. Digitalized with whole leaf	+	0	+	0				

DISCUSSION

Acquired sensitivity to digitalis must be rare because of the paucity of such reports. It was recognized early, however, for Morrow¹ in 1887 mentioned several cases, and quoted Behrand and Traube as having described others. In 1940 Cohen and Brodsky² reported a case of urticaria produced by tincture of digitalis in which the patch test was negative. Early in 1953 Wolfe and Geiger³ also reported a case of urticaria produced by digitalis. They tried six different preparations, namely, digitalis whole leaf, digitoxin, Digoxin, Digilanid, lanatoside C, and squill glycoside and were able to reproduce the urticaria with all these drugs. They suggested that the allergic response could be attributed to the cyclopentenophenanthrene nucleus which is common to all of these cardiotonic glycosides, since these digitalis derivatives are actually from three different species, *Digitalis purpurea*, *Digitalis lanata*, and the squill, *Urginea Maritima*. Skin testing in their patient was reported as negative.

In our patient sensitivity was acquired from tincture of digitalis. Digi-toxin, a crystalline derivative of whole leaf likewise gave manifestations of systemic reaction when given orally or when injected into the skin. In so far as we can determine, there are no previous reports of digitalis sensitivity associated with positive skin tests. The skin reactions were elicited regularly only with the pure glycosides. While the whole leaf itself failed to demonstrate specific antibody convincingly, serum from a patient saturated with the whole leaf did react directly and by passive transfer. It might be inferred that there is conjugation of some fraction of the drug with a body protein which is the specific complete antigen, and this explains the failure to demonstrate reagin for the whole leaf with the same preciseness as that for substances derived from it. The three- to five-day incubation period from the time of administration, either by ingestion or when injected into the skin, to the period of systemic reactivity might also be explained on this basis.

SUMMARY

A case of allergy to digitalis is presented which reacted with a severe urticarial response, and which demonstrated specific skin-sensitizing antibody to digitalis glycosides.

REFERENCES

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