

MEPHENESIN (TOLSEROL) SENSITIVITY WITH DEMONSTRABLE SKIN-SENSITIZING ANTIBODY IN THE SERUM

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ATTEMPTS to demonstrate a whealing type of skin reaction or the presence of skin-sensitizing antibodies in the serum of patients who have had an allergic reaction to drugs of a simple chemical nature have been unsuccessful for the most part. Sherman and Cooke¹ obtained positive passive transfer reactions to sulfadiazine and sulfapyridine in sites sensitized with the serum of a patient who had experienced a severe reaction to sulfadiazine. Ingestion of sulfadiazine resulted in reactions of passively sensitized sites in forty to ninety minutes.

Recently we have seen a patient with a severe immediate reaction to Tolserol (mephenesin) and we have been able, by passive transfer, to demonstrate skin-sensitizing antibodies to this drug.

Tolserol†^{2, 3} (3-ortho-toloxyl-1,2-propanediol) is a central nervous system depressant used in anxiety states and neuromuscular disorders. It has its main site of action on the midbrain, brain stem, at the level of the thalamus, and in the spinal cord probably at the internuncial neurons. The drug is rapidly absorbed when given orally and is detoxified by the liver as B (ortho-toloxyl) lactic acid. It exerts muscle-relaxing properties with little effect on the blood pressure or respiration. Untoward reactions described include circumoral anesthesia, flushing of the face, nausea, vomiting, dizziness, diplopia, blurring of vision, pruritus, tinnitus, and horizontal and vertical nystagmus. Intravascular hemolysis, hemoglobinuria, and fatal anuria have occurred. Red cell casts and protein in the urine following the use of the drug have been reported in the literature.³ We were unable to find any reports of an acute anaphylactoid reaction to mephenesin.

CASE REPORT

A 41-year-old white married woman was admitted to Milwaukee County General Hospital for the first time on July 24, 1956, following an acute drug reaction. She had been seen that morning in the outpatient department because of left-sided neck pain of two weeks' duration. Examination revealed moderate spasm with tenderness of the left sternocleidomastoid muscle, as well as an edematous, injected pharynx. Tablets of aspirin-phenacetin-caffeine (APC), Tolserol, and tetracycline were prescribed. After she reached

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home, she took one of each of these medications. Approximately twenty minutes later, she experienced diaphoresis and circumoral and upper extremity numbness, with tingling and tightness of the chest. She was taken immediately to Johnston Emergency Hospital where she received supportive therapy, with a prompt recovery. She then was transferred to the medical service at the Milwaukee County General Hospital.

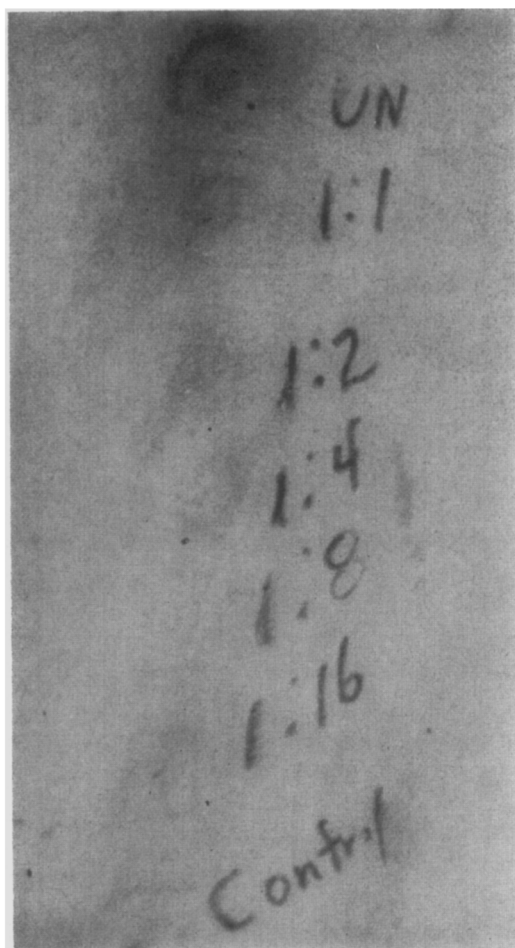


Fig. 1.—Whealing reaction in passively sensitized skin sites (subject A) thirty minutes after ingestion of 500 mg. mephenesin (Tolserol). An appreciable reaction occurred through a 1:16 serum dilution.

In 1952 she had had a hysterectomy because of a fibroid tumor of the uterus. Chronic cholecystitis with cholelithiasis was also diagnosed at that time. There was no history of any previous drug reactions or allergic disorders.

The physical examination revealed a well-developed, well-nourished, somewhat apprehensive white woman who did not appear acutely ill. Blood pressure was 120/80; pulse, 80; respirations, 18. The head showed no abnormalities. Minimal spasm and tenderness of the left sternocleidomastoid muscle was noted. Examination of the heart, lungs, abdomen, pelvis, rectum, extremities, skin, reflexes, and sensorium showed no abnormalities.

TABLE I. PASSIVE TRANSFER REACTIONS OBTAINED WITH SERUM TAKEN ON DAY OF SECOND REACTION

DILUTION OF SERUM	FIRST-DAY SERUM			
	TEST SUBJECTS			
	A	B	C	D
Undiluted	4+	3+	0	3+
1:1	3+	2+	0	0
1:4	2+	1+	0	0
1:8	1+	0	0	0
1:16	1+	0	0	0
Control	0	0	0	0

Chest x-ray was normal. The hemoglobin was 13 grams; white blood count was 11,700, with a differential of 13 stabs, 51 segmented polymorphonuclears, 30 lymphocytes, 5 monocytes, 1 basophil and no eosinophils. A Wassermann test was negative. The urine, blood, nonprotein nitrogen, and fasting blood sugar were all normal. Routine cutaneous and intracutaneous tests with inhalants and food allergens were negative.

The resident on the service believed clinical trial by readministration of the drugs in question to be justified. Accordingly, one APC tablet was given on the patient's second hospital day, and one capsule of tetracycline was given on the third day without reaction. On the fourth hospital day, she was given 250 mg. of Tolserol orally. Within thirty minutes, circumoral angioedema was apparent and she complained of numbness and tingling of the upper extremities and tightness of the chest. At this time, some inspiratory and expiratory wheezing was audible. There was a precipitous fall in blood pressure from 110/70 mm. to 50 mm. systolic pressure and this time her diastolic pressure could not be determined. She was given 50 mg. of Benadryl intravenously at once, and intravenous administration of one ampule of l-Arterenol and 100 mg. of hydrocortisone diluted in one liter of 5 per cent glucose in water was started also. Within a few minutes, the angioedema had lessened markedly. One hour later all symptoms had disappeared and only a few urticarial lesions remained. A direct cutaneous test with 1 per cent aqueous mephenesin solution was negative.

Twenty cubic centimeters of blood was drawn at this time and sterile serum was prepared. Ring precipitin tests with this serum and a 10 per cent ethyl alcohol solution of Tolserol were negative. Additional samples of serum were obtained from the patient after intervals of ten and thirty days. Each serum was serially diluted with normal saline. Skin sites were prepared on the backs of four nonsensitive persons by intradermal injections of 0.1 ml. of undiluted serum and 1:1, 1:4, 1:8, and 1:16 dilutions. Control sites were prepared with normal serum from both A and B type bloods. Forty-eight hours later, 500 mg. of Tolserol was given orally to each of four sensitized subjects.

TABLE II. PASSIVE TRANSFER REACTIONS OBTAINED WITH SERA TAKEN AFTER RECOVERY

DILUTION OF SERUM	TEN-DAY SERUM		THIRTY-DAY SERUM	
	TEST SUBJECTS		TEST SUBJECTS	
	A	E	F	G
Undiluted	+	0	+	0
1:1	0	0	0	0
Control	0	0	0	0

A marked whealing reaction occurred within ninety minutes after ingestion of the drug in sites sensitized with undiluted serum in three of the four test subjects. In two subjects the reaction was apparent within thirty minutes. In one subject (A), an appreciable reaction occurred in sites sensitized with serum through a 1:16 dilution (Fig. 1); another subject (B) showed reactions through a 1:4 dilution; another (D) had a detectable reaction only in the undiluted serum site. One subject, a large, obese man (C), had

no detectable reaction in any site. Serum obtained ten days after the initial drug reaction was used to sensitize sites in two subjects, one of whom (A) had shown reactions after ingestion of Tolserol in the first experiment. A positive reaction was again obtained in subject A in the undiluted serum site; no reaction was detected in the other subject (E). One of two additional subjects sensitized with undiluted serum obtained thirty days after the initial drug reaction reacted in the site sensitized with undiluted serum after ingestion of the test dose of Tolserol (Table II).

SUMMARY

Skin sites were sensitized in normal recipients with serum obtained from a patient immediately after an allergic reaction to ingested Tolserol. Positive reactions occurred within thirty to ninety minutes in the sensitized skin sites of three of the four subjects tested by ingestion of a challenging dose of 500 mg. of Tolserol. Some skin-sensitizing activity could still be demonstrated in serum withdrawn thirty days after the patient's reaction to Tolserol.

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