HYPERSENSITIVITY FOLLOWING INGESTION OF HYDROXYZINE (ATARAX) IN A MEPROBAMATE-SENSITIVE PATIENT

ARMAND E. COHEN, M.D.,* AND NORMAN K. COHEN, M.D.,** LOUISVILLE, KY.

UNTOWARD reactions to meprobamate are being reported with increasing frequency,[1-7] but in a review of the literature we were unable to find a single case of severe hypersensitive reaction to hydroxyzine hydrochloride. In fact, the side effects from this drug have been reported as infrequent and mild,[8] and the Council on Pharmacy and Chemistry of the American Medical Association has reported the drug as having a low toxicity.[9]

CASE REPORT

A 39-year-old man, while apparently recovering from a dermatosis caused by meprobamate, received hydroxyzine as substitute therapy and experienced an acute serumlike reaction shortly thereafter. He had taken meprobamate without incident from 1956 until July, 1957. The drug was discontinued thereafter until Sept. 10, 1957, when he resumed his usual dose of 400 mg. three times daily. The medication was again stopped on Sept. 15, 1957, because of the appearance of a macular erythematous discrete rash which was said to have extended over the entire body. The patient was seen on Sept. 16, 1957, complaining of a mild sore throat. The pharynx was injected, and Erythrocin was prescribed for the infection. At this time a slight macular rash but no angioedema was noted, and 25 mg. tablets of hydroxyzine were prescribed as a substitute for the meprobamate. The patient did not take the hydroxyzine until the early morning of Sept. 18, 1957, following which he stated that a slight macular nonpruritic rash was noted. The second dose was taken four hours later and was followed shortly thereafter by tightness in the chest, difficult breathing, and later a generalized rash and swelling of the face, feet, and hands. He was admitted to the hospital and immediately was given 0.5 c.c. of epinephrine subcutaneously, and an intravenous infusion of 5 per cent glucose containing 25 mg. of ACTH was started. Benadryl, 50 mg. four times daily, and chloral hydrate at bedtime and as needed were ordered.

The admission temperature was 101° F.; the pulse was 100; and the blood pressure was 115/70. Aside from marked dyspnea, a bright red rash over the entire body, angioedema, and painful arthralgia of the wrists and ankles, the physical examination was not remarkable. The blood count showed white blood cells, 14,900; neutrophils, 82; monocytes, 3; lymphocytes, 15; hemoglobin, 14.5 grams; and hematocrit, 50 volume per cent. The urine gravity was 1.020; microscopically, 4 to 7 red blood cells and 0 to 4 white blood cells per high-power field and occasional granular casts were reported. The nonprotein nitrogen was 26.66 mg., and the cephalin flocculation at the end of forty-eight hours was reported as 3 plus. Only one additional injection of epinephrine was required for relief of the dyspnea some twelve hours after the initial dose.

On the second day of hospitalization the rash appeared maculopapular; the skin of the inner thighs and scrotum was a bright magenta color and itched intensely. Despite the low-grade fever, starch baths followed by application of oil emulsion were ordered. The intravenous infusion of ACTH in glucose was repeated.

The patient showed progressive improvement and was discharged from the hospital on the fourth day after admission. Subsequently there was no return of his symptoms.

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*Associate Professor of Medicine, School of Medicine, University of Louisville.
**Instructor in Medicine, School of Medicine, University of Louisville.

There was no personal history of allergy except for a migraine syndrome, and the only suggestion of an allergic family history was that a brother was said to have migraine and a grandfather had eczema.

Apparently the patient had not had any previous episodes of drug sensitivity, although a review of his record (available to 1950) showed that he had received a number of drugs with sensitizing potentiality. These drugs included barbital, Dilantin, salicylates, Syntropan, codeine, amphetamine, aspirin, belladonna, ergotamine tartrate, phenacetin, nicotinic acid, Co-Elorine, and salicylamide.

COMMENT

The advent of the so-called tranquilizing agents has not only begun a new era in psychopharmacology but likewise has introduced a group of drugs which may pose problems for the dermato-allergist and others interested in these pharmaceutics.

It is hardly surprising that instances of untoward reaction to meprobamate had been reported, considering the popularity of the drug and the quantity which is being used. However, it was not thought that meprobamate had great sensitizing possibilities. Berger[10] stated: "It is not to be expected that a compound of such simple aliphatic structure without either ring structures or unsaturated linkages will induce hypersensitizations as often as more complex compounds."

Berger[11] divides the more important tranquilizers into four groups:

1. Compounds derived from phenothiazine, the more popular being chlorpromazine (Thorazine), promazine (Sparine), mepazine (Pacatal), procloperazine (Compazine), and NP-207 (Kinross-Wright, 1956). Likewise in this group are the antihistamine, promethazine (Phenergan); phenothiazine, an anthelmintic largely discarded because it sometimes caused blood dyscrasias and toxic hepatitis; and the antiparkinsonian agents, diethazine (Diparcol) and ethopropazine (Parsidol).

2. Reserpine and related alkaloids, such as deserpidine and rescinnamine.

3. Compounds derived from diphenylmethane: azacyclonal (Frenquel), benactyzine (Suavitil), and hydroxyzine (Atarax). Likewise closely related are the antispasmodic adiphenine (Trasentine); the antiemetic, meclizine (Bonamine); and the antihistaminic, chlorcyclizine (Perazil).

4. Compounds derived from substitute propanediols, such as meprobamate (Equanil and Miltown), mephenesin (Tolserol and Mephate), and 2-substituted, 4-hydroxymethyl, 1,3-dioxolanes, such as Glyketal and Dimethylane.

In view of the reports[8, 9, 12] of the almost complete absence of toxic or hypersensitive reaction to hydroxyzine, it is with some trepidation that we present this case which suggests such probability. The possibility that this patient's anaphylactic-like reaction following the ingestion of hydroxyzine represented a delayed serum type of reaction to a meprobamate hapten does not seem likely. The possibility that meprobamate, although not chemically closely related, could sensitize a patient to hydroxyzine is to be considered

The desirability that this patient again be given hydroxyzine to determine whether or not sensitivity to the drug is present is recognized. So far we have been unable to gain his consent to take even a small amount of the drug under controlled conditions.

It is to be hoped that after a more prolonged, repeated, and generally greater quantitative experience with hydroxyzine the present opinion of the relative freedom from toxicity or antigencity of the drug may be preserved.

SUMMARY

A case of apparent hypersensitivity to hydroxyzine hydrochloride (Atarax) in a 39-year-old white man known to be allergic to meprobamate is presented. The patient had shown no previous allergic manifestations, although he did suffer from migraine, as did one of his brothers, and his grandfather was said to have had eczema.

Meprobamate and hydroxyzine are not closely related chemically, but the possibility of related sensitizing properties is considered. No cases of hypersensitivity to hydroxyzine have been previously reported, and the drug has been considered relatively free from toxic or antigenic properties.

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