

PREVENTION OF REACTIONS IN INTRAVENOUS UROGRAPHY

S. WILLIAM SIMON, M.D.,* HENRY I. BERMAN, M.D.,** AND

SAUL A. ROSENBLUM, M.D., DAYTON, OHIO

IN DISCUSSING a method to lessen penicillin reactions, one of us (S.W.S.) suggested that antihistaminic drugs could be combined with other preparations which occasionally cause reactions and thereby abolish or definitely reduce their incidence.¹² About the same time Getzoff³ introduced his method of reducing reactions to intravenous Diodrast (the diethanolamine salt of 3, 5—diiodo—4—pyridone—N—acetic acid) by giving the patient orally 50-200 mg. of Pyribenzamine (N, N—dimethyl—N¹ benzyl—N¹ (Alpha-pyridyl)—ethylene diamine). In 1951 Olsson⁸ added 20 mg. of Benadryl (2—[Benzhydryloxy]—N, N—dimethylethylamine Hydrochloride) to each 20 ml. of Diodrast solution, and in 1953 Moore and Sanders⁵ tried 20 mg. of Benadryl and later 6 mg. Thenfadil (2—[(2—Dimethylaminoethyl)—3—thenylamino] pyridine) with each 30 ml. of Diodrast solution.

The dangers of injecting intravenous contrast materials are real, and at least twelve deaths had been reported in the literature up to 1949. The “milder” reactions consist of chills, flush, arm pain, nausea, vomiting, and urticaria. Of these “milder” reactions, nausea, vomiting, and urticaria are considered allergic and the others as vasomotor phenomena. The more severe reactions consist of edema of the eyelids, laryngospasm, bronchospasm (asthma), vertigo, pallor of the skin, syncope, cyanosis, and other evidences of shock. Of these, edema of the eyelids, laryngospasm, bronchospasm, vertigo, and shock may be considered allergic or anaphylactoid. It is beyond the scope of this paper to consider any but the allergic reactions which should be reduced by antihistamines. Vasomotor reactions will not be noted as they are unaffected.

All drugs used as contrast media in urography are iodide salts and probably the iodine acts as a haptene although the speed of some reactions in extremely sensitive patients causes one to wonder. Sherman^{10, 11} doubts the value of scratch or patch tests to nonprotein drugs. Alyea and Haines¹ reported four times as many reactions in patients with previously noted positive intradermal tests as in those with negative. Our experiences with the intradermal and eye sensitivity tests have only served to emphasize their futility and unreliability. We do agree with these authors, however, that patients with a history of allergy are much more likely to react to the contrast media than those without such a history.

Many papers have appeared comparing the percentage and severity of reactions using the various drugs. As we are not extolling the efficacy or

Received for publication Jan. 25, 1954.

*Chief, Allergy Clinic, Brown General Hospital, V.A.C.

**Chief, Urology Service, Brown General Hospital, V.A.C.

paucity of reactions of any of the drugs used as contrast media, we have added together the figures for each drug in the production of side reactions and sensitivity symptoms. To arrive at the percentage of patients exhibiting these various signs, the figures of several authors are given for each symptom, and then these are averaged to arrive at a control percentage (Table I). It is noted that in almost 5,700 patients given contrast media over 17 per cent developed some type of allergic reaction to the drug used.

The comparative figures as reported by Ollson and Moore and Sanders adding an antihistamine to the contrast drug are given in Table II. In 726 patients given Diodrast and Benadryl or Thenfadil, the average reaction rate was 9.7 per cent.

Our series of 530 patients was composed of both outpatients and those in the hospital. With Diodrast the 35 per cent solution was used, 20 ml. being given to patients under 150 pounds, 25 ml. from 150 to 175 pounds, and 30 ml. if over 175 pounds. The Chlor-Trimeton* (1—para-chlorophenyl—1—[2—pyridyl]—3—dimethylaminopropane) maleate solution, which contained 5 mg. of the drug in each 2.5 ml., was withdrawn from 10 ml. rubber-capped vials and mixed in the syringe with the Diodrast; 5 mg. were used with 20 ml. of Diodrast and 6 mg. with 25 or 30 ml.

TABLE I. PERCENTAGE OF REACTION SYMPTOMS (CONTROLS)

NAME	NO. OF PATIENTS	HISTORY OF ALLERGY	NAUSEA	VOMITING	URTICARIA	DIZZINESS	SNEEZING, ASTHMA, WHEEZING	UNCONSCIOUSNESS	ALL SYMPTOMS	CONTRAST MEDIA USED
Nesbit and Lapidés ⁶	1,281		10.7	3.5	2.03	1.4	0.13		17.8	Urokon, Diodrast and Neo-Iopax
Robbins, Colby, Sosman and Eyler ⁹	2,952	8.5	9.0	4.7	0.65		0.75	0.03	15.1	Urokon and Diodrast
Nesbit and Nesbit ⁷	1,000		12.0	4.0	1.0	0.0			17.0	Urokon
Olsson ⁸	500		15.0	4.0	1.0		3.8	0.2	24.0	Diodrast
Moore and Sanders ⁵	111		23.4	5.4	9.9		6.3		45.0	Diodrast
Total or Average	5,694	8.5	10.6	4.2	1.2	0.8	1.0	0.1	17.3	

Likewise, in those patients receiving 50 per cent Neo-Iopax (the disodium salt of N—methyl—3, 5—diiodo-chelidamic acid) the amount of solution used and of antihistamine added were the same as with Diodrast.

*Chlor-Trimeton used in this series was furnished through the courtesy of the Schering Corporation, Bloomfield, N. J.

TABLE II. PERCENTAGE OF REACTION SYMPTOMS WITH ANTIHISTAMINE ADDED
(FROM LITERATURE)

AUTHORS AND DRUG USED	NO. OF PATIENTS	NAUSEA	VOMITING	URTI- CARIA	RESPIRA- TORY SYMPTOMS	ALL SYMPTOMS	CONTRAST MEDIUM USED
Olsson (Benadryl) ⁸	500	4.6	0.4	0.8	0.4	6.0	Diodrast
Moore and Sanders ⁵ (Benadryl)	110	16.3	1.8	3.6	2.7	24.4	Diodrast
Moore and Sanders ⁵ (Thenfafil)	116	12.1		0.9	0.9	13.9	Diodrast
Total or Average	726	7.3	0.54	1.2	1.3	9.7	

Those patients who were given 30 per cent Urokon Sodium (the sodium salt of 3 acetyl-amino—2, 4, 6—triiodobenzoic acid) all received 25 ml. mixed with 6 mg. of Chlor-Trimeton regardless of weight or history of allergy. It should be added, however, that the patients in the Diodrast or Neo-Iopax series who had either a history of allergy or previous reaction to iodides or contrast media usually were given 10 mg. of Chlor-Trimeton.

The results are noted in Table III which in summary gave an over-all reaction rate of 7.1 per cent. However, each type of reaction is considered separately, and if one patient developed nausea, vomiting and urticaria, the three symptoms were added to the total.

All reactions were mild and generally subsided quickly without added medication. However, epinephrine was always kept handy and 0.5 ml. was given on three occasions and intravenous Benadryl on two, in each case after the use of Urokon which also produced all of the delayed reactions. As the patients receiving Urokon were without exception outpatients while all of the others were hospitalized, this, too, must be taken into consideration.

TABLE III. RESULTS WITH CHLOR-TRIMETON ADDED TO CONTRAST MEDIA

DRUG	NO. OF PATIENTS	HISTORY OF ALLERGY	NAU- SEA	VOMIT- ING	URTI- CARIA	SNEEZ- ING	ASTHMA, WHEEZ- ING	UNCON- SCIOUS- NESS	DELAYED REACTION
Urokon 30 per cent	85	3	5	2	0	0	2	0	12
Neo-Iopax 50 per cent	303	19	8	2	0	0	1	0	0
Diodrast 35 per cent	142	17	12	0	2	3	1	0	0
Totals	530	39	25	4	2	3	4	0	12
Percentage of total		7.3	4.7	0.7	0.3	0.6	0.7	0	2.2

7.1 per cent of patients had reaction.

Case histories of three patients each of whom had a peculiar problem follow:

CASE 1.—A 42-year-old paraplegic physician gave a history of a severe reaction to two previous attempts at intravenous urography. He did not know which drugs were used at those times but with each developed much apprehension, nausea, vomiting, and unconsciousness. The skin and eye tests previous to injection were negative. Due to these previous reactions we added 5 ml. or 10 mg. of Chlor-Trimeton maleate to 20 ml. of Diodrast. The patient experienced transient mild arm pain and a slight face flush lasting less

than thirty seconds but no other reaction of any type. Three months later several needles were placed in his back to locate ganglia for paravertebral block and some Diodrast solution was introduced with each needle in order to locate them by x-ray. A very small amount of the contrast medium was used, but the patient developed severe nausea, vomiting, and mental confusion immediately following the injection and the procedure had to be stopped. Later, the Diodrast was used in the same way but with Chlor-Trimeton added and the study was completed without difficulty. A repeat intravenous pyelogram was made some months later using Neo-Iopax and Chlor-Trimeton. The patient experienced no untoward symptoms.

CASE 2.—A 24-year-old white man was hospitalized for the treatment of a ureteral calculus and pyelonephritis. An intravenous urographic study was attempted using Diodrast following a negative dermal test. After about 5 ml. had been injected the patient complained of burning of his chest, arms, and legs, and shortly thereafter developed urticaria on these parts. There was no previous history of allergy. A urographic study was completed later by using Neo-Iopax to which 5 mg. of Chlor-Trimeton had been added.

CASE 3.—A 60-year-old white man with a long history of chronic bronchial asthma was given the intravenous injection of Neo-Iopax with 5 mg. of Chlor-Trimeton added without producing any reaction or of aggravating the pre-existing bronchial asthma.

DISCUSSION

It is obvious from a comparison of the figures given in the studies of various authors that wide discrepancy exists. Where both Olsson and Moore and Sanders used Benadryl with Diodrast, the Americans Moore and Sanders had four times as many reactions as the Swedes. Perhaps the latter are hardier, but the more likely explanation lies in the way the injections are given and the interpretation of the reactions. In our experience, the following factors will reduce vasomotor reactions and possibly nausea and vomiting: (1) Warm solution to body temperature before injecting. (2) Inject 1 ml. of solution slowly, then wait approximately one minute to determine individual tolerance following which the remainder of the solution is injected quite rapidly. (3) Use smallest needle consistent with intravenous injection—probably 22 gauge.

We have made our comparisons using the symptoms in the control series which are least controversial and most likely to be on an allergic basis. It is questionable if nausea and vomiting are allergic symptoms, but as they are reduced in all series by the use of antihistamines, they are included. Vasomotor symptoms such as chills, fever, flushing, arm pain, and dizziness are not included because they are caused many times by merely drawing blood and apparently are not reduced by using the antihistamines. The respiratory symptoms consist of sneezing, laryngospasm, bronchospasm, or asthma, and it is felt that these are definitely due to allergy. Unconsciousness, when it occurs, is a severe, generalized, anaphylactoid reaction.

Delayed reactions are harder to explain. All of ours took place in outpatients and were possibly aggravated by apprehension. The formation of a conjugated antigen takes just as long in the hospital as outside.

In spite of Getzoff's³ good results using premedication with oral antihistamines, several authors feel that this procedure does not materially reduce reactions.^{2, 6}

One of us (S.W.S.) has devoted much time to the prevention of reactions from penicillin by adding an antihistamine to the diluent. The opinion is expressed that there is an optimum dose for each antihistaminic drug, somewhere below the toxic dose, which will protect the most sensitive patient.^{13, 14} However, some patients may either have or develop a refractoriness to certain antihistamines⁴ so the ideal result of no reactions will never be reached. We are continuing our studies but with increased dose of Chlor-Trimeton (10 mg.). This amount was very effective in materially reducing reactions in blood transfusions.¹⁵

SUMMARY

A total of 530 intravenous urographic examinations were made using various contrast media to which were added from 5 to 10 mg. of Chlor-Trimeton. While vasomotor reactions were not influenced, the allergic reactions of nausea, vomiting, urticaria, sneezing, wheezing, and syncope were reduced from a control level of 17.3 per cent to 7.1 per cent.

REFERENCES

1. Alyea, E. P., and Haines, C. E.: Intradermal Test for Sensitivity to Iodopyracet Injection or "Diodrast," *J. A. M. A.* **135**: 25, 1947.
2. Crepea, S. B., Allanson, J. C., and Delambre, L.: Failure of Antihistamine Drugs to Inhibit Diodrast Reactions, *New York J. Med.* **49**: 2556, 1949.
3. Getzoff, Paul H.: Use of Antihistamine Drug Prophylaxis Against Diodrast Reactions, *J. Urol.* **65**: 1139, 1951.
4. Monash, S.: Development of Tolerance of Skin Towards Anti-histaminic Drugs, *Urol. & Cutan. Rev.* **54**: 722, 1950.
5. Moore, T. D., and Sanders, N.: Reaction to Urographic Agents With and Without Antihistamines, *J. Urol.* **70**: 538, 1953.
6. Nesbit, R. M., and Lapides, J.: Observations on Urokon, *Univ. Michigan M. Bull.* **16**: 37, 1950.
7. Nesbit, R. M., and Nesbit, T. E.: Experiences With High Concentration Urokon for Pyelography, *Univ. Michigan M. Bull.* **18**: 225, 1952.
8. Olsson, O.: Antihistaminic Drugs for Inhibiting Untoward Reactions to Injections of Contrast Medium, *Acta radiol.* **35**: 65, 1951.
9. Robbins, L. L., Colby, F. H., Sosman, J. L., and Eyler, W. R.: Excretory Urography: A Clinical Trial of a New Contrast Medium, *Radiology* **56**: 684, 1951.
10. Sherman, W. B.: Drug Allergy, *Am. J. Med.* **3**: 586, 1947.
11. Sherman, W. B.: Drug Allergy, *J. A. M. A.* **140**: 447, 1949.
12. Simon, S. W.: Hypo-Allergic Penicillin, *Ann. Allergy* **8**: 194, 1950.
13. Simon, S. W.: Hypo-Allergic Penicillin IV. Chlor-Trimeton-Penicillin, *Ann. Allergy* **10**: 187, 1952.
14. Simon, S. W.: Hypo-Allergic Penicillin V. Pyribenzamine-Penicillin, *Ann. Allergy* **11**: 218, 1953.
15. Simon, S. W., and Eckman, W. B.: The Use of Chlor-Trimeton in the Prevention of Transfusion Reactions, *Ann. Allergy*. To be published.