

The effect of premedication with chlorpheniramine on reactions to methylglucamine iodipamide

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In 1,830 cholangiographic examinations in which methylglucamine iodipamide was given at the Mayo Clinic, premedication with chlorpheniramine, in doses of 6 to 10 mg. given intramuscularly 5 minutes prior to intravenous injection of the contrast medium, reduced the incidence of reactions to 6 per cent from the rate of 24 per cent in 854 such examinations without antihistaminic premedication. Methylglucamine iodipamide can and does produce toxic and anaphylactoid reactions as well as hypotension if given too rapidly. Studies of blood concentrations of histamine in 10 cases failed to substantiate the idea that methylglucamine iodipamide may be a histamine releaser, except in one case in which a reaction occurred. There the concentration of histamine increased to twice as much as that found before the injection. Adding epinephrine (in two tested quantities) to the chlorpheniramine for injection seemed not to enhance the effects of chlorpheniramine, but rather added annoying side effects. Premedication with an antihistaminic drug, though definitely helpful, does not appear to be the complete answer to the prevention of reactions following injection of contrast medium for cholangiography, but we do recommend its use for lessening these reactions.

Antihistaminic drugs have been used with varying success to prevent reactions after intravenous administration of contrast media for urographic examinations and after blood transfusions. However, except for the recent article of Johnson and Wise,¹ few reports and little statistical information are available on their use with biliary contrast media, which is the subject of this paper.

Among the many accounts of efforts to decrease reactions to urographic media and transfusion, Frankel and Weidner² reported in 1953 that the addition

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of chlorpheniramine* to each unit of blood transfused decreased the frequency and severity of allergic and pyrogenic reactions from 3.5 per cent in the controls to 0.3 per cent in the test group.

In 1954, Simon, Berman, and Rosenblum³ reported on the addition of 5 to 10 mg. of chlorpheniramine to various contrast media that were given intravenously for urographic examinations. Vasomotor reactions were not affected, but the allergic reactions of nausea, urticaria, sneezing, wheezing, and syncope were reduced from the control level of 17.3 per cent to 7.1 per cent. The authors suggested that, because some patients may have or may develop refractoriness to certain antihistamines, the ideal goal of no reactions will never be reached.

Sanger,⁴ reporting further observations, countered the fear of many that delayed reactions would follow addition of antihistamines to injectable mixtures by saying that after 7 years' experience with more than 1,000 cases he had yet to see in any patient "a delayed anaphylactic or toxic reaction . . . except . . . transient dizziness or sleepiness." He concluded that antihistamines have a place in preventing reactions and that a history of allergy is not a contraindication to urography if antihistamines are added to the injection medium.

The disagreement as to the effectiveness of antihistamines may be due in part to difference in the routes of administration (oral, intramuscular, intravenous, or subcutaneous) and in part to variation in the time of administration (before, during, or after injection of the contrast medium). We believe that antihistaminic drugs are likely to be most effective if given prior to the injection of contrast media, and in this respect we agree with the conclusions of Nesbit⁵ from his work with urographic media. We also believe that the speed of injection of biliary contrast media has a marked influence on the number of patients showing a reaction.

PHARMACOLOGIC ASPECTS OF METHYLGLUCAMINE IODIPAMIDE

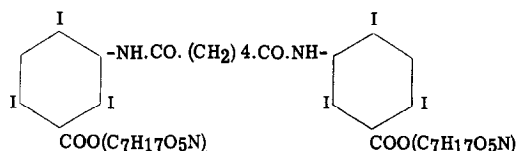
In the field of biliary visualization, marked progress has been made since the introduction in 1953 of iodipamide methylglucamine†—now meglumine iodipamide, U.S.P. This compound has an iodine content of 24.96 per cent in a 52 per cent solution. The total iodine content in 20 ml. (the usual dose) is 4.99 Gm. and the molecular weight is 1,584. The chemical structure is shown in Fig. 1.

Being an iodine compound, methylglucamine iodipamide can and does produce toxic and anaphylactoid reactions. However, it passes promptly through the liver after intravenous injection; and there is also some visualization of the kidneys which indicates prompt excretion by the kidneys. Studies by Billion and associates,⁶ using iodipamide-¹³¹I, revealed 10 per cent of the dose in urine and 70 per cent in feces in the first 48 hours after injection, with practically no reabsorption from the intestines. These authors gave the ratio of biliary clearance rate to renal clearance rate as 3.5:1 in a group of cases of mixed pathologic conditions, and greater under physiologic conditions.

Edling and Helander⁷ reported a pronounced repression of renal opacifica-

*Chlor-Trimeton, Schering Corporation, Bloomfield, N. J.

†Cholografin, E. R. Squibb & Sons, New York, N. Y.

**Fig. 1**

Iodipamide methylglucamine (the methylglucamine salt of *N,N'*-adipyl-bis) (3-amino-2, 4, 6, triiodobenzoic acid).

tion and enhancement of biliary opacification when para-aminohippuric acid or benzathine penicillin G (Penditan, the penicillin G salt of *N,N'*-dibenzylethylenediamine), or both, were given with the iodipamide.

Wise,⁸ from experience with methylglucamine iodipamide in two series, reported reaction rates of 20 per cent and 11.3 per cent, but no fatal reactions. He regarded slowness of injection as the most important factor in preventing reactions, since a definite increase in incidence, but not necessarily in severity of reactions (nausea and vomiting), followed rapid injection. In a recent controlled study, however, he and Johnson¹ were convinced that antihistaminic premedication is worthwhile.

Recently, the effect of iodipamide and other contrast media on erythrocytes and the vascular system has been under study. Lindgren and Saltzman⁹ found that iodipamide given intravenously to cats caused a moderate fall in blood pressure and produced vasodilator effects, even though peripheral blood flow was little affected by such administration. They found also that responses diminished with repetition of doses, thus suggesting a tachyphylactic response or depletion of histamine. Lindgren and associates¹⁰ in 1964 reported that iodipamide increased erythrocyte aggregation in 15 of 25 patients, as determined by microscopic study of conjunctiva, and decreased erythrocyte sedimentation in 7 of 12 cases studied. They stated that their results "give only partial support to the hypothesis that erythrocyte aggregation caused by intravenous contrast media may explain some of the circulatory side effects that obviously accompany these compounds." They also demonstrated increased right ventricular pressure in cats after injection.

Bernstein and associates¹¹ in 1964, after intravenous injection of iodipamide into dogs, found increased plasma viscosity and density, increased whole blood and apparent erythrocyte viscosity, decreased diameter and difficulties in packing of erythrocytes, and inconstant but occasionally severe hemolysis.

Methylglucamine iodipamide differs from urographic media in that it must not be given rapidly. Ten minutes is the recommended time course for injection of iodipamide, in contrast with 3½ minutes or less for urographic media.

MATERIAL AND METHODS

Our study was undertaken to determine whether chlorpheniramine would decrease the number of reactions to methylglucamine iodipamide given for cholangiography. It encompasses 2,684 examinations in which iodipamide was given at the Mayo Clinic from April 18, 1956, through 1963. The 854 examina-

tions for which iodipamide was given without any premedication dated from April 18, 1956, through Nov. 6, 1958, and served as controls. Our attempt to lessen reactions by administration of chlorpheniramine before injection of iodipamide was begun on Nov. 10, 1958.

If there was a history of sensitivity to iodides or of any constitutional reaction, cholangiography was not attempted. Of possible reactions, only nausea, vomiting, chills, fever or flushing, and hives were studied. Each time any of these conditions occurred, it was listed as a separate reaction. There was no fatal anaphylactoid reaction. Blood pressures were measured when reactions occurred, but records were not kept except in a series of 27 cases. In general, blood pressure was decreased significantly during reactions.

Since the effect of chlorpheniramine given prior to cholangiography was about the same whether it was administered intravenously or intramuscularly, and since the intramuscular injection seemed more expedient, this latter procedure was adopted. We found that mixing the chlorpheniramine and the methylglucamine iodipamide in the syringe was likely to produce precipitation, and therefore we gave the two solutions separately. The contrast medium was at room temperature when injected.

The dose of chlorpheniramine varied from 6 to 10 mg. on the 1,830 occasions of its use. Five minutes after it had been injected intramuscularly, a 1.0 ml. test dose of methylglucamine iodipamide was given intravenously. If there was any untoward reaction to the test dose of iodipamide, the procedure was cancelled. If the test interval of 3 to 5 minutes passed uneventfully, intravenous administration of the remaining 19 ml. of methylglucamine iodipamide was begun and continued over the next 8 to 10 minutes.

Several related studies were incorporated. In 1962, thinking that if some of the reactions had an allergic basis the addition of epinephrine to chlorpheniramine might help synergistically to prevent reactions, we gave the epinephrine intramuscularly, mixed with the chlorpheniramine. The idea was based on some animal experiments in which Dr. H. E. Essex of this clinic and one of us (G. A. P.), working with a substance of the type described by Delezenne and Ledebt,¹² which produces anaphylaxis in dogs and rabbits, had found that chlorpheniramine and epinephrine together seemed a more effective preventive than either alone.

The effect on blood pressure of injecting 20 ml. of methylglucamine iodipamide at the recommended rate was studied in 20 patients. To test the idea that iodipamide might release histamine, blood histamine levels were determined^{13, 14} before and after injection of iodipamide in 10 patients. Since some investigators believe that reactions are more likely to occur in allergic patients than in others, we checked this possibility by carefully reviewing the records of 50 of our patients with reactions for a history of allergy.

RESULTS

Reactions in control period

In the control period (April 18, 1956, to Nov. 6, 1958) 204 reactions followed the 854 examinations. Seventy reactions consisted of nausea, 37 of vomit-

ing, 25 of chilliness, 30 of fever or flushing, and 42 of hives. The fever was not necessarily a true febrile response, but was the description used by the patient for his general feeling. More than one type of reaction followed some tests. The over-all incidence of reactions was 24 per cent (Table I).

Effect of chlorpheniramine on reactions

From Nov. 10, 1958, when premedication was begun, we gave chlorpheniramine in a dose of 10 mg. to 13 patients. We used this dosage only 13 times because some of the patients became so drowsy that their walking was affected. On November 22, therefore, we reduced the dosage to 6 mg.; but with that, the incidence of reactions to iodipamide was too high. So on Jan. 1, 1959, we adopted a compromise dosage of 8 mg. Table II shows the results in 1,318 examinations done by the end of 1963. The over-all incidence of reactions was only 4 per cent.

Effect of epinephrine

When we gave epinephrine intramuscularly in the amount of 0.1 ml. of 1:1,000 solution with 8 mg. of chlorpheniramine to patients who later received methylglucamine iodipamide, the reaction rate increased so much that we had to reduce the amount of epinephrine by half (0.5 ml. of 1:10,000). Even with this modified dosage, the reaction rate remained high on 136 examinations; and symptoms such as nausea, vomiting, chilliness, nervousness, and trembling were so prominent that we discontinued the use of epinephrine. Giving the drugs intramuscularly had increased the reaction rate to approximately 10 per cent (Table III).

Blood pressure

The usual dose of 20 ml. of methylglucamine iodipamide given intravenously in 10 minutes decreased the systolic blood pressure by an average of 12 mm. Hg and the diastolic pressure by an average of 7 mm. in 20 of the 27 patients in whom blood pressure was studied. There was no change in the blood pressure of the other seven patients. It is apparent from this small series that, even when

Table I. *Reactions to methylglucamine iodipamide given without chlorpheniramine premedication (control group), April, 1956, to November, 1958*

	1956 (4/18 to 12/31)	1957	1958 (1/3 to 11/6)	Total
Total examinations	225	304	325	854
<i>Reactions</i>				
Nausea	16	25	29	70
Vomiting	8	12	17	37
Chills	9	5	11	25
Fever or flushing	10	9	11	30
Hives	10 (4%)	14 (5%)	18 (6%)	42 (5%)
Total*	53 (24%)	65 (21%)	86 (26%)	204 (24%)

*In some examinations, reactions were multiple.

Table II. Reactions to methylglucamine iodipamide given with chlorpheniramine premedication, November, 1958, to December, 1961

	1958		1959	1960	1961	Total
	11/10 to 11/21	11/22 to 12/31				
Total examinations	13	30	437	411	427	1,318
Chlorpheniramine, mg.	10	6	8	8	8	6-10
<i>Reactions</i>						
Nausea	0	2	2	11	7	22
Vomiting	0	1	1	0	2	4
Chills	0	1	1	1	3	6
Fever or flushing	1	1	1	3	6	12
Hives	0	0	0	4 (1%)	6 (1%)	10 (1%)
Total	1 (< 1%)	5 (16%)	5 (1%)	19 (5%)	24 (6%)	54 (4%)

Table III. Reactions to methylglucamine iodipamide given after chlorpheniramine premedication with and without epinephrine, 1962-1963

	1962			1963
	Epinephrine		No epinephrine	No epinephrine
	0.1 ml. of 1:1,000	0.5 ml. of 1:10,000		
Total examinations	29	136	412	347*
Chlorpheniramine, mg.	8	8		8
<i>Reactions</i>				
Nausea	2	5	No accurate rec-	6
Vomiting	1	4	ord. Similar to	8
Chills	1	0	1961	4
Fever or flushing	0	1		7
Nervousness, trembling	+	+		
Hives	0	3 (2%)		6 (2%)
Total reactions	4 (14%)	13 (10%)		31* (9%)

*Five reactions occurred on fast injection.

Table IV. Histamine concentrations* in blood (in micrograms per milliliter) in 10 patients before and after injection of methylglucamine iodipamide without chlorpheniramine premedication

Before	After	Difference
0.017	0.013	-0.04
0.033	0.036	+0.003
0.030	0.032	+0.002
0.027	0.029	+0.002
0.013	0.027	+0.014†
0.080	0.080	0
0.040	0.040	0
0.080	0.020	-0.06
0.080	0.050	-0.030
0.070	0.070	0

*Determined by modified method^{13, 14} of Barsoun and Gaddum.

†Reaction occurred in this case.

injected at a slow rate, methylglucamine iodipamide is able to produce some lowering of the blood pressure.

Blood histamine levels

Among the ten patients tested for blood concentration of histamine before and after injection of iodipamide, a decrease was found in three, an increase in four, and no change in three (Table IV). In the one patient who had a reaction, the amount of histamine originally present in the bloodstream was doubled after the injection.

Effect of a history of allergy

We found that 13 of 50 patients with reactions whose records were studied for a history of allergy did have a history of hay fever, asthma, vasomotor rhinitis, urticaria, allergic blepharitis, or drug allergy (Table V). Besides allergy, 2 of the 13 patients also had migraine. Six of these 13 had undergone liver-function tests with sulfobromophthalein (Bromsulphalein), 5 with normal results and one with dye retention, grade 1. One patient who was intolerant to morphine and oxytetracycline (Terramycin) underwent five cholangiographic examinations (one T-tube, one operative, and three regular intravenous). In this patient the retention of dye in the liver-function test was 12 per cent (grade 1); but she was only slightly nauseated after the second intravenous cholangiogram

Table V. *History of clinical allergy in 50 cases of reactions to methylglucamine iodipamide*

<i>Prior history</i>	<i>Patients</i>	<i>Reactions</i>
Positive for allergy	13*	
Hay fever, asthma	2	Hives, pruritus
Vasomotor rhinitis, urticaria	1	Fever, flushing
Allergic blepharitis, vasomotor rhinitis	1	Pain in back resembling gallbladder attack
Urticaria	1	Hives, chills
Drug allergy		
Penicillin	4	Hives
Sulfa	2	Facial swelling, flushing
Other drugs	2	Miscellaneous
Negative for allergy	37	None

*Two patients had migraine also.

Table VI. *Summary of reactions to methylglucamine iodipamide*

<i>Circumstances</i>	<i>Examinations</i>	<i>Reactions</i>
Without chlorpheniramine, 4/18/56 to 11/6/58	854	204 (24%)
With chlorpheniramine	1,830	102 (6%)
6-10 mg., 11/11/58 to 12/31/61	1,318	54 (4%)
8 mg.; plus epinephrine, 0.1 ml. of 1:1,000 or 0.5 ml. of 1:10,000; 1962*	165	17 (10%)
8 mg., 1963	347	31 (9%)

*Records of reactions not complete for 412 additional cases in 1962.

and had no reaction to the others. There was no evidence to suggest that repeated cholangiography caused sensitization.

The reactions to methylglucamine iodipamide are summarized in Table VI.

TYPES OF REACTIONS: REPORT OF 6 CASES

Case 1

A 49-year-old woman who was seen in 1963 had reddening and swelling of the left eye (chemosis) 25 minutes after the intravenous injection of iodipamide, despite premedication with 8 mg. of chlorpheniramine given intramuscularly 5 minutes before the injection of iodipamide. The patient was allergic to penicillin, had been extremely nervous for 3 or 4 years, and had neurodermatitis.

Case 2

A woman seen in October, 1960, had a severe anaphylactic reaction within 5 minutes of completion of an intravenous injection of iodipamide with 10 mg. of diphenhydramine (Benadryl) administered over a period of 8 to 10 minutes. She had flushing, tingling in the arms and feet and around her mouth, nausea, and felt as if she were going to sneeze but could not. She felt weak and ill. Blood pressure decreased to 80/?. She had no cough or wheeze. She recovered promptly after administration of epinephrine. She had not had any drug reactions or allergic disease. In 1938, she had experienced a state of marked anxiety.

Case 3

A physician, seen in 1961, had had electroshock therapy 30 times. For 1½ years he had treated himself with steroids and whiskey for urticaria. He was sensitive to gallbladder dye and castor oil. Hypotension followed administration of iodipamide.

Case 4

A patient seen in 1962 gave a history of hay fever due to pollens of trees, grasses, and weeds, sensitivity to procaine which caused local swelling, and sensitivity to opiates which produced nausea and vomiting. On a test of liver function the day before cholangiography, the forearm had reddened within 5 to 10 minutes above the site of injection of sulfobromophthalein. Next she had undergone excretory urography with diphenhydramine given intramuscularly as premedication, and there had been no reaction to the contrast medium. On the following day, the forearm was still red from the injection of sulfobromophthalein. Chlorpheniramine, 10 mg. was given before the intravenous injection of iodipamide. A few minor hives developed over the neck and trunk with mild itching, and the patient felt like sneezing but did not do so. She also had erythema of the neck and face. She was given 0.3 ml. of 1:1,000 solution of epinephrine followed by 6 mg. of dexchlorpheniramine maleate (Polaramine).

Case 5

A 46 year-old man had irritable bowel syndrome and neurosis. Despite premedication with 6 mg. of chlorpheniramine, he reacted to iodipamide by marked erythema of the upper half of the trunk and urticaria in the lower half, with pruritus and trembling of the lower extremities. An additional 6 mg. of chlorpheniramine was given after the injection, with diphenhydramine, 10 mg. plus epinephrine, 0.6 ml. in 1:1,000 solution, followed by another 12 mg. of chlorpheniramine and 1 Amesec pulvule (130 mg. aminophylline, 25 mg. ephedrine, 25 mg. amobarbital). The reaction disappeared in 3 hours. There was no previous history of allergy in the patient or his family.

Case 6

A woman had had migraine-tension headaches, hyperventilation with tetany, marked anxiety-tension state, and allergy to penicillin and sulfonamides. An allergic reaction followed injection of iodipamide, and an injection of outdated epinephrine gave no relief. Fresh epineph-

rine, 0.35 ml. of 1:1,000 solution and 1 Tedral tablet (130 mg. theophylline, 24 mg. ephedrine, 8 mg. phenobarbital) were effective. No details of the reaction were recorded. There was no history of allergy in the patient or her family.

COMMENT

We believe it is logical to give the antihistaminic drug before the contrast medium, rather than in the same injection. But although such premedication helps to reduce reactions to the intravenous injection of methylglucamine iodipamide, it does not appear to be all that is needed. Perhaps such hypertonic iodide solutions release other chemical mediators besides histamine—such as serotonin, bradykinin, acetylcholine, and slow-reacting substance A (SRS-A)—for which the antihistaminic drugs are not antagonists. Or, further, histamine release by iodipamide may be difficult to antagonize because of the intimate association of the released amine and histamine receptors at reactive sites. There also may be an inadequate concentration of the antihistamine at such sites. Unbound, freely circulating histamine would not necessarily be an indication of this level of tissue histamine activity.

Why epinephrine did not give beneficial effects is difficult to explain. Perhaps the vasoconstriction immobilized the chlorpheniramine when the two were given together. Furthermore, chlorpheniramine has vasoconstrictive effects of its own, as has been shown by Abramson and associates.¹⁵ In view of the side effects mentioned, however, epinephrine probably is best reserved for those occasions when allergic reactions occur, with administration then to be prompt and parenteral.

We believe that the strongest single factor contributing to reaction from methylglucamine iodipamide was the speed of injection. Although the incidence of reactions in 1963, even with use of chlorpheniramine, was high (Table III), review of the records has shown that 5 of the 31 episodes occurred during examinations performed by one physician who gave the injections of iodipamide rapidly and always in less time than the recommended 10 minutes. Apparently he believed that the speed of injection had little to do with the incidence of reactions because in urologic experience he had given contrast media rapidly.

The difference between these compounds must be emphasized. We agree with Wise that methylglucamine iodipamide should not be given rapidly, and the recommended time for injecting it is 10 minutes—a contrast to the 1½ minutes in which urographic media can be given without affecting the blood pressure. In dogs, as we have verified repeatedly, rapid injection of methylglucamine iodipamide produces hypotension, tachycardia, cardiac irregularities, and even retching.

The changes in blood concentrations of histamine after reactions suggest a need of further investigation in cases where reactions have occurred.

The finding that 13 (approximately 25 per cent) of our 50 patients who had reactions and were investigated for history of allergy did have some kind of allergy recorded is a reinforcement of the general impression that the allergic patient is more likely to have a drug reaction.

SUMMARY

In 1,830 cholangiographic examinations in which methylglucamine iodipamide was given at the Mayo Clinic, premedication with chlorpheniramine in doses of 6 to 10 mg. given intramuscularly 5 minutes prior to intravenous injection of the contrast medium reduced the incidence of reactions to 6 per cent from the rate of 24 per cent in 854 such examinations without antihistaminic premedication.

Methylglucamine iodipamide can and does produce toxic and anaphylactoid reactions as well as hypotension if given too rapidly.

Studies of blood concentrations of histamine in 10 cases failed to substantiate the idea that methylglucamine iodipamide may be a histamine releaser, except in one case in which a reaction occurred. In this case the concentration increased to twice as much as before the injection.

Adding epinephrine (in two tested quantities) to the chlorpheniramine for injection seemed not to enhance the effects of chlorpheniramine but added annoying side effects.

Premedication with an antihistaminic drug, though definitely helpful, does not appear to be the complete answer to the prevention of reactions following injection of contrast medium for cholangiography, but we do recommend its use for lessening these reactions.

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