

Prophylactic antihistamines in the management of radiographic contrast reactions

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Summary

Two hundred and twenty consecutive patients, referred for intravenous pyelography, were assessed for adverse reactions. The effect of prophylactic antihistamines was evaluated. Patients were divided randomly into control, saline or chlorpheniramine treated groups. Changes in serum total haemolytic complement (CH_{50}) and immune complexes (IC) at times 0, 1, 5, 10 and 20 min after injection of radiocontrast material were assayed. Forty-two of the 220 patients suffered reactions, classified clinically into allergic and non-allergic types.

There was no difference in the incidence of allergic reactions between control and saline groups. However, significantly less ($P < 0.05$) allergic reactions were noted in the antihistamine pre-treatment group. Depressed CH_{50} occurred in forty-three, of eighty-eight patients tested and persisted for at least 20 min in twenty-two. There was no correlation between CH_{50} depressions and clinical symptoms. The IC remained unchanged throughout. In conclusion, prophylactic antihistamines may diminish the incidence of allergic reactions. Complement activation occurs in a large number of patients, unrelated to symptomatology, and does not appear to be the only factor responsible for adverse reactions.

Introduction

Intravenous pyelography is a common method of investigation for a number of medical problems. The injection of radiographic contrast material may elicit a variety of reactions related to the skin, respiratory, gastro-intestinal, cardiovascular, genito-urinary and central nervous systems. The mechanisms of adverse reactions to contrast material are largely unknown, and the management of such problems, either prophylactically or in response to previous reactivity, has been poorly understood. Hypersensitivity mechanisms have been postulated, but never proven, to be important

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(Arroyave, Bhat & Crown, 1976; Arroyave, Schatz & Simon, 1979; Brasch & Caldwell, 1976; Cogen *et al.*, 1979).

In order to prevent adverse reactions to radiographic material, antihistamines have been used in a variety of ways (Fischer & Doust, 1972; Gates & Ceccarelli, 1972; Gorevic & Kaplan, 1979). It is uncertain whether antihistamines do indeed provide some protection against adverse reactions (Fischer & Doust, 1972; Gates & Ceccarelli, 1972; Gorevic & Kaplan, 1979).

The purpose of our study was two-fold: first, to determine whether antihistamines can prevent adverse reactions in patients undergoing intravenous pyelography and, secondly, to clarify a possible mechanism of reaction, assaying changes in serum total haemolytic complement and circulating immune complexes.

Materials and methods

Two hundred and twenty consecutive patients, referred for intravenous pyelography for a variety of reasons, were assessed. Patients taking antihistamines were excluded from the study, but the remainder were randomly divided into three groups. Each patient was interrogated and told that all questions asked were part of a routine procedure prior to intravenous pyelography. The first group received no pre-medication. The second group received a subcutaneous injection of saline, and the third, 10 mg of chlorpheniramine, subcutaneously. Each injection was given approximately 15 min prior to injection of contrast medium, which was administered rapidly over 30 s. Blood samples were subsequently withdrawn 1, 5, 10 and 20 min after the injection. All reactions were then recorded by the attending radiologist.

Serum samples were stored at -70°C until assayed together at the completion of the study. Serum haemolytic complement was determined, using the method of Kent and Fife (1963). Circulating immune complexes were detected using a C1q-binding assay, as described by Zubler *et al.* (1976).

Results

Forty-two of the 220 patients had a reaction (Table 1). All could be classified as mild or minimal. There were nineteen, fifteen, and eight reactions in groups one, two and three respectively. The difference between the chlorpheniramine-treated group and either the saline, or control groups was significant at the $P < 0.05$ level. There was no statistical difference between saline, and control groups. Reactions were further sub-divided into non-allergic and allergic. Allergic reactions included hives and

Table 1. Reactions of 220 patients receiving radiographic contrast material for intravenous pyelography

Treatment groups	No. of patients	No. of reactions		Allergic reactions		Gastro-intestinal reactions		Other	
		No.	%	No.	%	No.	%	No.	%
Control	71	19	27	10	14	7	10	2	3
Saline	71	15	21	5	7	9	13	1	1
Chlorpheniramine	78	8	10	1	1	4	5	3	4

generalized pruritis. No respiratory or cardiovascular symptoms were detected. Non-allergic reactions were predominantly gastro-intestinal, manifested mainly by nausea and occasional vomiting. There were a few non-specific, mild, unclassifiable adverse effects.

There was no significant difference between the control, and saline groups for any reaction. There was a significant difference ($P < 0.05$) between the chlorpheniramine-treated group and either the saline, or control groups for allergic reactions. There was no significant difference for gastro-intestinal reactions.

Laboratory evaluation

Normal serum haemolytic complement values were between 120 and 180 haemolytic units. A change of 20 units was considered significant. The first eighty-eight patients were evaluated for changes in serum complement during the intravenous pyelography. Forty-three patients showed a decrease in haemolytic complement 1 min after infusion, which gradually returned towards normal over the next 20 min (Table 2). However, twenty-two patients showed a persistently depressed haemolytic complement 20 min after infusion (Table 2). Only one patient had a depressed CH_{50} at 20 min without a prior depression noted at 1 min. Neither baseline complement levels, nor depressions at 20 min correlated with symptoms (Table 3). The distribution of complement depressions revealed a higher incidence of changes in both the saline, and chlorpheniramine-treated groups, compared to the control patients. At 20 min, 21% of patients who had reactions showed complement consumption, 35% of patients, having no

Table 2. Changes in serum haemolytic complement (CH_{50}) during intravenous pyelography

Group	No.	Change in CH_{50} (1 min)		Change in CH_{50} (20 min)	
		No.	%	No.	%
Control	25	5	20	3	12
Saline	25	15	60	8	32
Chlorpheniramine	38	23	61	11	29
Total	88	43	49	22	25

Table 3. Changes in serum haemolytic complement (CH_{50}) during intravenous pyelography

	Control			Saline			Chlorpheniramine		
	Total	Reaction	No reaction	Total	Reaction	No reaction	Total	Reaction	No reaction
Unchanged CH_{50} (20 min)	22	5	17	17	6	11	27	4	23
Decreased CH_{50} (20 min)	3	1	2	8	2	6	11	1	10

reaction, showed a similar drop. Similar findings were detected with the complement levels at 1 min, but are not shown on the table. There was no observed relationship between the initial complement value and susceptibility to change. Immune complexes showed no change throughout the study.

Discussion

The incidence of radiographic contrast reactions is unknown. One author has suggested an incidence of anaphylactic-like reactions of 1:50 000, but the incidence of mild reactions is not documented (Arroyave *et al.*, 1976; Arroyave *et al.*, 1979; Brasch & Caldwell, 1976; Cogen *et al.*, 1979). The role of antihistamines for prophylaxis of both mild, and severe contrast reactions has been debated (Fischer & Doust, 1972; Gates & Ceccarelli, 1972; Gorevic & Kaplan, 1979; Kelly *et al.*, 1978; Lalli, 1980; Lasser *et al.*, 1979). Although no data have suggested that antihistamines may decrease the number of mild reactions, it has been recognized that pre-treatment with antihistamines may diminish the number of anaphylactic reactions (Kelly *et al.*, 1978; Lalli, 1980; Lasser *et al.*, 1979). However, since the incidence of these reactions is small, significant data are most difficult to obtain.

Our objective was to determine whether antihistamines prevent symptoms related to contrast media injections, and whether the mechanism of this reaction can be elucidated. It was clearly shown that pre-treatment with antihistamines leads to significantly less 'allergic' reactions. These reactions were all mild, but there was a clearly diminished number in the treated group. The other reactions, including gastro-intestinal and neurological manifestations, did not seem to be affected by antihistamine pre-treatment, but include very small numbers only.

The mechanism of radiographic contrast reactions remains unknown. Histamine release appears to be the final, common pathway. A number of mechanisms leading to mediator release have been proposed, but none are entirely acceptable (Cogen *et al.*, 1979; Lieberman & Siegle, 1978; Siegle & Lieberman, 1976). Increased susceptibility of mast cells to hyperosmolar contrast and activation of the alternative pathway of complement would appear to be two likely mechanisms of mediator release (Lieberman & Siegle, 1978; Lieberman & Siegle, 1979; Lieberman, Siegle & Taylor, 1978; Peters, Hodgson & Donovan, 1966; Ring *et al.*, 1978; Ring, Simon & Arroyave, 1978; Sanger, 1959; Schatz *et al.*, 1975; Siegle & Lieberman, 1976). In our study, almost 50% of patients showed some change in serum haemolytic complement, in association with contrast injections. Therefore, activation of complement does occur with contrast injection, but does not correlate with symptomatology.

The rapid depletion of complement occurred within 1 min of injection and returned to normal in most cases within 5 min. Previous studies have documented changes in complement only after a minimum of 3 min, and have probably underestimated the incidence of complement depletion. It is possible that if earlier sampling had been taken in our study, closer to 100% of all patients may have shown some changes in haemolytic complement. These data suggest that the injection of radiographic contrast material commonly leads to complement activation, usually transient in nature, but on occasion long-lasting and unrelated to clinical symptomatology.

Although no definite IgE-mediated reaction has been observed, a number of authors have suggested that serum antibodies may play a role (Arroyave *et al.*, 1976; Arroyave *et al.*, 1979; Brasch & Caldwell, 1976). The injection of foreign material may lead to immune complex formation, with pre-formed antibody and subsequent

basophil degranulation via complement activation. There was no evidence in our study that immune complexes were formed during contrast injection, but this must be interpreted within the limitations of the assay. Only one assay for immune complexes was performed, defining only a sub-population of immune complexes, and we cannot exclude the possibility of other immune complexes being pathogenic for contrast reactions (Simon *et al.*, 1979; Yocum, Heller & Abels, 1978; Zubler *et al.*, 1976).

In summary, it appears that antihistamines may be of some value in the prophylaxis of allergic reactions. This applied to mild reactions only, since no severe reactions were encountered. Major reactions are probably not adequately pre-treated with small doses of antihistamines. The mechanisms of such reactions remain unclear. Although contrast injection appears to activate complement, this does not appear to be related to clinical symptomatology. The demonstration of complement decrease, following contrast reactions, clearly should not lead to the conclusion that complement release is pivotal in the production of these reactions, although the data do not exclude this possibility.

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References

- ARROYAVE, C.M., BHAT, K.N. & CROWN, R. (1976) Activation of the alternative pathway of the complement system ARROYAVE, C.M., SCHATZ, M. & SIMON, R. (1979) Activation of the complement system by radiographic contrast media: studies *in vivo* and *in vitro*. *Journal of Allergy and Clinical Immunology*, **63**, 276.
- BRASCH, R.C. & CALDWELL, J.L. (1976) The allergic theory of radiocontrast agent toxicity: demonstration of antibody activity in sera of patients suffering major radiocontrast agent reactions. *Investigative Radiology*, **11**, 347.
- COGEN, F., NORMAN, M.E., DUNSKY, E., HIRSHFELD, J. & ZWIEMAN, B. (1979) Histamine release and complement changes following injection of contrast media in humans. *Journal of Allergy and Clinical Immunology*, **64**, 299.
- FISCHER, H.W. & DOUST, V.L. (1972) An evaluation of pre-testing in the problem of serious and fatal reactions to excretory urography. *Radiology*, **103**, 497.
- GATES, D.F. & CECCARELLI, F.E. (1972) Benadryl and the IVP reaction. *Journal of Urology*, **10**, 627.
- GOREVIC, P. & KAPLAN, A.P. (1979) Contrast agents and anaphylactic-like reactions. *Journal of Allergy and Clinical Immunology*, **63**, 225.
- KELLY, J.F., PATTERSON, R., LIEBERMAN, P. & MATHISON, S.D. (1978) Radiographic contrast media studies in high-risk patients. *Journal of Allergy and Clinical Immunology*, **62**, 181.
- KENT, J.F. & FIFE, E.H. (1963) Precise standardization of reagent for complement fixation. *American Journal of Tropical Medicine*, **12**, 103.
- LALLI, A.F. (1980) Contrast media reactions: data analysis and hypothesis. *Diagnostic Radiology*, **134**, 1.
- LASSER, E.C., LANG, J.H., LYON, S.D. & HAMBLIN, A.E. (1979) Complement and contrast material reactors. *Journal of Allergy and Clinical Immunology*, **64**, 107.
- LIEBERMAN, P. & SIEGLE, R.L. (1978) A review of untoward reactions to iodinated contrast material. *Journal of Urology*, **119**, 581.
- LIEBERMAN, P. & SIEGLE, R.L. (1979) Complement activation following intravenous contrast material administration. *Journal of Allergy and Clinical Immunology*, **63**, 13.
- LIEBERMAN, P., SIEGLE, R.L. & TAYLOR, W. W. (1978) Anaphylactoid reactions to iodinated contrast material. *Journal of Allergy and Clinical Immunology*, **62**, 174.
- PETERS, G., HODGSON, J.R. & DONOVAN, R.J. (1966) The effect of pre-medication with chlorpheniramine on reactions to methylglucamine iodipamide. *Journal of Allergy*, **38**, 74.

- RING, J., ARROYAVE, C.M., FRIZLER, M.J. & TAN, E.M. (1978) *In vitro* histamine and serotonin release by radiographic contrast media (RCM). *Clinical and Experimental Immunology*, **32**, 106.
- RING, J., SIMON, R.A. & ARROYAVE, C.M. (1978) Increased *in vitro* histamine release by radiographic contrast media in patients with a history of incompatibility. *Clinical and Experimental Immunology*, **34**, 302.
- SANGER, M.D. (1959) Further observations with antihistamines in reducing reactions in intravenous pyelography. *Annals of Allergy*, **17**, 762.
- SCHATZ, M., PATTERSON, R., O'ROURKE, J., NICKELSON, J. & NORTHRUP, C. (1975) The administration of radiocontrast media to patients with a history of previous reaction. *Journal of Allergy and Clinical Immunology*, **55**, 358.
- SIEGLE, R.L. & LIEBERMAN, P. (1976) Measurement of histamine, complement components and immune complexes during patient reactions to iodinated contrast material. *Investigative Radiology*, **11**, 98.
- SIMON, R.A., SCHATZ, M., STEVENSON, D.D., CURRY, N., YASAMOTO, F., PLOW, E., RING, J. & ARROYAVE, C. (1979) Radiographic contrast media infusions—measurement of histamine, complement and fibrin split products and correlation with clinical parameters. *Journal of Allergy and Clinical Immunology*, **63**, 281.
- YOCUM, M.W., HELLER, A.M. & ABELS, R. (1978) Efficacy of intravenous pre-testing and antihistamine prophylaxis in radiocontrast media-sensitive patients. *Journal of Allergy and Clinical Immunology*, **62**, 309.
- ZUBLER, R.H., LANGE, G., LAMBERT, P.H. & MIESCHER, P.A. (1976) Detection of immune complexes in unheated sera by a modified ¹²⁵I C1q binding test. *Journal of Immunology*, **116**, 232.

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