

Adverse Reactions to Intravascular Administration of Contrast Media

ELLIOTT C. LASSER

University of California, San Diego School of Medicine, U.S.A.

Adverse reactions to intravascular administration of contrast media, while low in incidence, merit serious consideration in view of increased utilization of these substances all over the world. Evidence for involvement of soluble mediators, antibody-antigen reactions, psychogenic factors, and the acute activation systems, is reviewed. As a group, the pre-contrast challenge plasmas of reactors are characterized by slightly diminished concentrations of C₁-esterase inhibitor and total hemolytic complement, and by an accelerated rate of conversion of prekallikrein to kallikrein on exposure to contact activators. The role of intravenous pretesting and pretreatment is considered. A rationale for pretreatment with adrenocorticosteroids is presented.

Key words: adverse reactions; C₁-esterase inhibitor; complement system; contrast media.

The overall incidence of adverse reactions to intravascular injections of contrast media is believed to be in the neighborhood of 7 to 8% (1). Of these, perhaps 1 to 2% can be classified as moderate in extent – that is, they required some form of treatment without undue alarm for the patient's safety, and 0.1% can be considered as severe – there was fear for the patient's life, and intensive treatment was necessary. The overall incidence of deaths following contrast reactions is perhaps 1:40,000, but may be as low as 1:12,500 in the age group of 60 years and older (1).

In general, toxic effects resulting from contrast media injections can be considered in two major categories: 1) chemotoxicity; and 2) systemic toxicity. Chemotoxicity may result when injections of high concentrations and/or quantities of contrast media are injected into a vessel supplying an organ or a tissue. Ultimately, chemotoxicity must be a function of the concentration and the application time of the injected material. While the precise etiology of chemo-

toxic effects is still poorly understood, it is believed that major contributing factors are the hyperosmolarity of these triiodinated substituted benzoic acid compounds (9), and the enzyme inhibitory potential of these substances (13). This latter appears to be related principally to the relative hydrophobicity of the individual contrast molecules (16). Systemic toxicity (anaphylactoid, idiosyncratic) can result from the introduction of even very small quantities of contrast material into any vessel in the body.

Major advances in the development of contrast media have been slow to evolve. Initially, inorganic iodides were used and these then progressed to diiodinated organic media, and then progressively from incompletely substituted benzoic acid salts to completely substituted compounds. Recently, there has been a more dramatic progression from triiodinated ionic compounds to triiodinated nonionic media. The intravascular utilization of these latter substances, however, has been sufficiently limited

that one cannot yet directly address the question of adverse reactions. This report, then, will concern itself with the anaphylactoid or idiosyncratic reactions to triiodinated substituted benzoic acid contrast media.

For convenience, one can consider idiosyncratic contrast reactions under four major headings: 1) mediator release; 2) antibody-antigen reactions; 3) psychogenic factors; 4) involvement of acute activation systems (complement, coagulation, kinins, fibrinolysins). Clearly, these categories are not necessarily mutually exclusive.

The *in vitro* incubation of mast cells with contrast media will result in the direct release of histamine (2). This release can be augmented, however, by the presence of normal human serum presumably secondary to the participation of C3 (28). It is also known that contrast injections will result in histamine release in experimental animals (17) and in man (6). Serotonin release occurs on *in vitro* incubation of human platelets with contrast material (28). The contrast media appear to induce complex changes in the interaction among at least three circulating cells: basophils, neutrophils, and platelets. While some correlation appears to exist between the occurrence of reactions and the potential of contrast media to induce histamine release *in vitro*, no direct correlation between the extent of *in vitro* histamine release and the presence or absence of reactions has been noted.

The role of true hypersensitivity or contrast allergy is still unclear. Although the injection of isolated contrast molecules has not been shown to result in the production of antibodies in animals or man, antibodies have been produced in experimental animals against contrast analogs chemically conjugated to proteins (4). On the other hand, anti-contrast medium antibodies have been observed in some patients suffering severe reactions from injections of urographic media (5), and classical antibody-antigen reactions were thought to have occurred in some others (10, 33). While many of the patients identified as having anti-contrast medium antibodies had not previously been injected with contrast media, it was believed that antibodies

had been induced earlier by cross-reacting substances such as halogenated benzene rings found in food additives, pesticides, and herbicides (5). The composition of injectable urographic media is such that one would expect them to be non-reactive chemically and not to function as haptens. The cholangiographic media, however, while also chemically non-reactive, have a general structure which resembles that of other divalent antigens. In the few clinical instances where positive passive cutaneous transfer studies have been carried out utilizing the serum of individuals having had a contrast reaction, the injected material has had the divalent composition (33). In any event, the fact that some patients react adversely immediately after injections of only very small quantities of contrast media suggests that at least for some reactions an IgE mechanism is operative.

Iodide sensitivity *per se* could also account for some contrast reactions. Although the iodine items on these molecules are tightly bound to the benzene rings, free iodide is found in each contrast vial as a consequence of the manufacturing process (14), and some deiodination evidently occurs on salivary excretion of contrast media (31).

A role for psychogenic factors has been suggested by some. Lalli found that the pretreatment of mice with central nervous system depressants significantly affected the LD₅₀ (12). In this study, the mice were given an injection of contrast material that would be equivalent to roughly 9 or 10 times that usually administered for urographic studies in man over a short period of time. At this dosage, a significant breakdown of the blood-brain barrier would be expected, and earlier studies have shown that in this circumstance CNS depressants would give protection (18, 36). There is no doubt that in some individuals the classical vago-vaso mechanisms come into play, and that, in some, anxiety might promote the release of circulating mediators. There is, however, no direct evidence to substantiate the notion that all adverse contrast reactions are related to activation of the limbic portion of the central nervous system.

In recent years, a role for the so-called activa-

tion systems in contrast anaphylactoid reactions has been suggested (19). *In vitro* activation of the complement system occurs on incubation of contrast media with plasma or serum (3, 11, 32). Activation of the complement system has also been noted in both experimental animals (15), and in man (20), following contrast injections. The degree of complement activation is greatest in individuals having anaphylactoid reactions, and is considerably greater than that which could be ascribed simply to circulating concentrations of contrast media. Correspondingly, activation of the coagulation system and elevated fibrinolysins have also been noted in animals and man (21, 22).

A number of components in the activation systems are controlled wholly or in part by the C $\bar{1}$ -esterase inhibitor. The mean concentration of this substance was significantly lower in the pre-contrast challenge serum samples of confirmed reactors when compared with confirmed non-reactors. Particularly low levels were noted in individuals having very severe reactions (23). Furthermore, confirmed reactors have lower mean levels of total hemolytic complement than do confirmed non-reactors (23, 30). Based on these findings, it has been suggested that any factors that might stress the classical pathway of complement activation, resulting in some depletion of the inhibitor, might predispose patients to contrast reactions. In this connection, it has been noted that individuals with collagen diseases and vasculitis have an increased incidence of adverse reactions (34).

Additional evidence for an abnormality in the intrinsic coagulation pathway in reactors can be noted in the fact that reactors have an accelerated rate of conversion of prekallikrein to kallikrein in comparison with confirmed non-reactors (24). In a preliminary retrospective study, the rate of conversion of prekallikrein to kallikrein in individuals with a confirmed contrast material reaction differed appreciably from the rate of conversion in confirmed non-reactors. This study, that involved the incubation of citrated siliconized plasma with a low concentration of dextran sulfate at 0°C over varying periods of time, suggested that assay of the rate of kallikrein formation could be used to iden-

tify reactors with a sensitivity of 88%, a specificity of 82%, and a predictive value of 79%.

Pending the confirmation of the prekallikrein conversion assay, patient screening must remain dependent on appropriate history-taking and intravascular pretesting. Individuals with a previous history of a contrast reaction are approximately 10 times more likely to have a subsequent reaction on contrast injections than are individuals without such a history (1). Intravascular pretesting has usually been accomplished by injection of about 1 ml of the contrast material to be utilized in the clinical study. The general consensus in the literature has been that pretesting is without value, and might even be dangerous in itself (7). Recently, however, it has been shown that the incidence of positive tests in individuals with a previous definite history of contrast material reactions can be increased with safety by utilizing up to 5 ml of contrast media in gradually increasing concentrations (35). In addition, in one study where 375 individuals with a positive pretest were nevertheless given a full bolus of contrast material for the clinical study, the incidence of total reactions was 16 times more common than in individuals with a negative pretest, or those not tested. Furthermore, reactions requiring therapy in this group were 15 times more common (29). These findings suggest that while intravenous pretesting may be an inefficient overall screening method, it nevertheless should be reevaluated as a potential screening mechanism in individuals thought to be at high risk because of appropriate histories. Furthermore, the whole subject of the technique of intravenous pretesting needs to be reexamined.

Is there a role for the pretreatment of patients thought to be at high risk?

Both experimental and clinical evidence suggest that adrenocorticosteroids and/or antihistamines may play a protective role in contrast material reactions. In dog and rabbit models of contrast toxicity, pretreatment with prednisolone in dosages ranging from 1 mg/kg to 30 mg/kg was found to afford considerable protection (25). In man, patients in the high-risk category showed appreciable diminution in the

expected repeat reaction rate after pretreatment with corticosteroids and antihistamines (8). In the animal studies, it was noted that pretreatment with corticosteroids was accompanied by rather marked elevations of the Cl-esterase inhibitor, and of factor XII (26). These were believed to have resulted from steroid-induced blunting of a hypothetical ongoing low-level activation of factor XII-dependent reactants. Blunting such activation would diminish the intensity of reactant-inhibitor complexing, and hence would allow for increments in the concentrations of the individual involved proteins (assuming that metabolic pathways are otherwise undisturbed). In man, a limited study, following the ingestion of a total of 96 mg of prednisolone over a 2-day period, resulted in elevations of factor XII and total prekallikrein, again suggesting the possibility of some blunting of ongoing intrinsic factor activation (27).

Our knowledge of the pathogenesis of anaphylactoid reactions to contrast media is evolving at an accelerating rate. Perhaps the advent of the general intravascular utilization of new and novel non-ionic contrast substances will obviate further concern. In any case, it is clear that we now know a good deal more about the pathogenesis of these reactions than we did 10 years ago, and that we are in a position to begin to develop appropriate measures to both prevent and treat reactions based on this knowledge.

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Address:

Elliott C. Lasser, M.D., Professor of Radiology
UCSD Medical Center
University Hospital
225 Dickinson Street
San Diego
California 92103
U.S.A.

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